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Weaning from mechanical ventilation in people with neuromuscular disease: systematic review

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ABSTRACT

Objective: This systematic review aimed in assessing the effects of different weaning protocols in people with neuromuscular disease (NMD) receiving invasive mechanical ventilation searching for the best one and how different protocols can affect outcomes as weaning success, duration of weaning, intensive care unit and hospital stay and mortality. **Design:** Systematic review. **Data sources:** Electronic databases (MEDLINE, EMBASE, Web of Science and Scopus) were searched from January 2009 up to August 2020. **Eligibility criteria for selecting studies:** Randomized controlled trials (RCT) and quasi-RCTs that evaluated NMD patients (adults and children from 5 years old) in the weaning process managed with a protocol (pressure support ventilation; synchronized intermittent mandatory ventilation; CPAP; "T" piece). **Primary outcome:** Weaning success. **Secondary outcomes:** weaning duration; ICU stay; hospital stay; ICU mortality; complications (pneumothorax, ventilation associated pneumonia). **Data extraction and synthesis:** Two review authors assessed the titles and the abstracts for inclusion independently. **Results**: We found no studies that fulfilled the inclusion criteria. **Conclusions**: The absence of studies about different weaning protocols for NMD patients does not allow concluding the superiority of any specific weaning protocol for patients with NMD or determining the impact of different types of protocols on other outcomes. The result of this review encourages further studies. **PROSPERO registration number:** CRD42019117393.

Keywords: mechanical ventilation; ventilator weaning; neuromuscular disease

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study will help searches to develop new researches about mechanical ventilation weaning in neuromuscular disease patients, trying to identify the best way to deal with it.
- This study has highlighted that neuromuscular patients are usually not managed with conventional protocols for mechanical ventilation weaning.
- No studies were identified about the protocols proposed to be studied in this population.
- No conclusions could be made based on the lack of evidence about the subject searched.

INTRODUCTION

Neuromuscular disease (NMD) can be defined as a chronic and progressive disease, which may present with different clinical characteristics, in which its pattern is based on the location where the injury occurs in a motor unit.[1,2] NMD are characterized by progressive muscular impairment, with difficulty in ambulation, swallowing and ventilation, with progressive reduction of vital capacity and increased work of breathing.[3] These changes lead to the development of acute and chronic respiratory failure, which is an important cause of prolonged ventilatory dependence[4,5], associated with increased healthcare costs.[6]

Three main components may contribute to respiratory failure and the need for mechanical ventilation in these patients: (1) inspiratory muscle weakness; (2) expiratory muscle weakness; (3) upper airway compromise.[7-9] The NMD patients experience this respiratory impairment, in general, by a large proportion of motor units that innervate the respiratory muscles affected.[2]

The majority of critically ill patients admitted to ICU require ventilatory support for acute or chronic respiratory failure,[3] specially the NMD ones.[8,10-12] In addition, the pattern of neuromuscular abnormalities associated with critical illness, defined as ICU-acquired weakness (ICUAW), can lead to prolonged mechanical ventilation, a longer hospital stay and increased ventilation.[4]

The emergence of respiratory symptoms, with progressive hypercapnia, can lead to death from respiratory failure.[3,7] Long-term invasive or non-invasive mechanical ventilation is the main intervention for people who present with acute respiratory acidosis; progressive decline in vital capacity (<10–15 mL/kg); or progressive decline in maximal inspiratory pressure (<20–30 cmH2O).[3,8,13]

Weaning from mechanical ventilation is the process of transition to spontaneous ventilation.[14] In people with NMD, conventional weaning is generally not possible.[15] Weaning difficulty may occur in different populations, such as elderly with prolonged ICU hospitalization, people with chronic respiratory diseases or NMD.[16] Therefore, the decision to progress to extubation is more challenging in this group of people with advanced respiratory muscle weakness, and this can lead to a need for tracheostomy and prolonged mechanical ventilation.[4]

The weaning process may be conducted in different protocols such as the following:

- 'T' piece: in which the patient receives only supplemental oxygen through a T-shaped tube connected to an endotracheal tube (orotracheal or tracheostomy).[14]
- Continuous positive airway pressure (CPAP): the weaning protocol involves using a continuous pressure, equal to the previous positive end-expiratory pressure level used before.[14]
- Pressure support: the use of progressive lower levels of inspiratory pressure support until it reaches 5–8 cmH2O.[14]

Successful weaning is defined as the ability to maintain spontaneous ventilation without the need for reintubation and invasive mechanical ventilation for 48 hours after extubation.[14] For patients with NMD, due to the difficulty of weaning, it may be also defined as the absence of a need for tracheostomy and mechanical ventilation for 5 days after extubation.[4]

Post weaning monitoring should observe whether two of the following findings are present: respiratory acidosis (pH <7.35; PaCO2>45 mm Hg); SpO2<90% or PaO2<60 mm Hg with FiO2>50%; RR >35 rpm; decreased level of consciousness, restlessness or excessive sweating; or signs suggestive of

respiratory muscle fatigue, such as the use of accessory muscles or paradoxical movement of the abdomen, in order to determinate the need to re-establish mechanical ventilation again.[4,14]

Weaning failure from invasive ventilation is frequent in people with NMD due to muscle weakness and gradual hypercapnia.[4] In this way, the non-invasive ventilation, even after weaning failure, is an option. And a future weaning can be conducted when and if clinically possible.[4,16,17] Although this whole process significantly increases health costs with this patient population.

Objectives

The aim of this systematic review was to assess the effects of different weaning protocols in people with NMD receiving invasive mechanical ventilation. Our secondary aim was to assess how the different protocols affect weaning success, duration of weaning, duration of stay in the ICU, duration of hospital stay, ICU mortality and also to assess adverse effects.

METHODS

Protocol and registration

This systematic review was registered on PROSPERO (Registration Number: CRD42019117393. The review authors followed the Cochrane Handbook for Systematic Reviews of Interventions[18] and the PRISMA Statement.[19]

Eligibility criteria for inclusion

Population

Adults (above 16 years old) and children (from 5 to 16 years old) people with a clinical diagnosis of a NMD (muscular dystrophy of any origin including Duchenne muscular dystrophy, amyotrophic lateral sclerosis, congenital myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillian Barré Syndrome, severe inherited neuropathies, metabolic myopathies

(Pompe disease), inflammatory myopathies and mitochondrial diseases) of any gender.

All patients ventilated for at least 48 hours with orotracheal tube or tracheostomy because of acute respiratory failure, and considered by physicians to be ready for weaning according to clinical criteria and weaning parameters. No patients with other respiratory or cardiovascular clinical diagnosis associated were considered, nor patients with mixed NMD diagnosis.

Intervention

The intervention assessed was the process of weaning from mechanical ventilation in people with NMD using a protocol with criteria for deciding if the patient is ready for extubation with 30 min to 2 hours SBT at the end point of the protocol. The following protocols were considered for inclusion:

1. Pressure support ventilation, with gradual reduction of the support pressure.

2. Synchronized intermittent mandatory ventilation, with gradual reduction of respiratory rate and support pressure.

3. CPAP, with gradual reduction of applied pressure.

4. 'T' piece, with progressive increase of spontaneous ventilation time.

Comparison

Any comparison between the different protocols was considered. If the studies classified the weaning based on the outcomes: simple (successful after first attempt of spontaneous breathing trial); difficult (requiring up to three attempts or less than 7 days to reach success; prolonged (requiring more than 7 days to reach success), comparisons would also be considered.

Outcomes

Primary outcome

Weaning success, defined as the ability to maintain spontaneous ventilation without the need for reintubation and invasive mechanical ventilation for 48 hours after extubation.[14]

Secondary outcomes

- Duration of weaning in patients with acute and prolonged mechanical ventilation - defined as the time between the weaning protocol initiation and the moment of extubation.
- Duration of ICU stay in patients with acute and prolonged mechanical ventilation - defined as the time between ICU admission and ICU discharge.
- Duration of hospital stay in patients with acute and prolonged mechanical ventilation - defined as the time between hospital admission and hospital discharge.
- ICU mortality rate in patients with acute and prolonged mechanical ventilation - defined as the mortality rate during ICU stay.
- Incidence of pneumothorax during mechanical ventilation period.
- Incidence of ventilation associated pneumonia.

Study designs

To ensure this evidence synthesis is based upon the highest quality of evidence, we only considered including randomized controlled trials (RCTs) and quasi-RCTs (experimental study with participants subjected to some type of intervention or control group, and with the same outcome of interest measured). There were no restrictions to language in the studies selection.

Search method

Electronic databases were searched from 1st January 2009 up to 31st August 2020: Cochrane Neuromuscular Specialised Register (The Cochrane Library, current issues), MEDLINE, EMBASE, Web of Science and Scopus. We will also searched the United States National Institutes of Health Clinical Trials Registry, ClinicalTrials. gov (ClinicalTrials. gov) and the WHO International Clinical Trials Registry Portal (apps. who. int/ trialsearch/).

Search terms included weer: 'neuromuscular disease' or all other terms compatible with clinical diagnoses of these types of diseases, such as 'muscular dystrophy', 'Duchenne muscular dystrophy', 'amyotrophic lateral sclerosis', 'congenital myasthenia', 'myasthenia gravis', 'congenital myopathy', 'spinal muscular atrophy', 'Guillian Barré Syndrome', 'severe inherited neuropathies', 'metabolic myopathies', 'Pompe disease', 'inflammatory myopathies' and 'mitochondrial diseases' combined with 'mechanical ventilation' or 'artificial respiration' or 'mechanical ventilation weaning' or 'ventilator weaning' or 'respirator weaning' and all the combination between them. The search strategy is available as an online supplementary file.

Study selection

Two review authors (SCBN and IL) performed the search. Two review authors (SCBN and RTC) assessed the titles and the abstracts for inclusion independently and induplicate. When the full text was assessed for eligibility criteria it was performed independently as well, and the authors had an excellent agreement of 99,5%. The disagreements were resolved through consultation of a third review author (IL).

RESULTS

After searching scrutinously all the databases proposed from January 2009 to August 2020 no studies fulfilled the inclusion criteria regarding different weaning protocols on neuromuscular disease patients receiving mechanical

ventilation for respiratory failure. A flowchart shows the detailed process of selection (Fig1).

Fig1. Flowchart showing publication selection.[19]

DISCUSSION

We found no high quality evidence either for or against any of the weaning protocols proposed (PSV, SIMV, CPAP or 'T' piece) in MND patients under mechanical ventilation.

The decision about the ideal time to extubate these patients and wean them from ventilatory support is much harder for the patients that deal with respiratory muscle weakness and chronic ventilatory failure, increasing repeated extubation fails and tracheotomies rates.[17]

According to the studies observed during the search, weaning has been studied and applied to this population in any of the aforementioned types of protocols. But the results are not satisfactory for any of them, with high failure rates in the process anyway.

The search for the best way to promote weaning from mechanical ventilation for the population of patients with NMD has led professionals and researchers to focus on the use of NIV as a way of progressing and continuing weaning from MV.[17,20] This type of approach is justified by the absence of studies with appropriate methodology that identify a better way to conduct weaning in these patients. The combination of NIV with invasive MV has led to a reduction in reintubation rates, despite the increase in the number of patients dependent on this therapy.[17,21] This observation was also described even for prolonged MV patients with NMD.[20]

Although NIV has been described as an excellent alternative for weaning in patients who fail in the conventional conditions for evaluating weaning[21] (protocols proposed for analysis) it seems to be more efficient when installed immediately after MV removal and not after the appearance respiratory failure, when it would be, especially for patients with NMD, associated with a greater probability of failure and the need to return to invasive MV.[17]

Xu et al[22] observed, in a series of cases of infantile and juvenile patients with Pompe disease, that after conducting weaning in CPAP or PSV, the use of NIV immediately after extubation led to an improvement in respiratory muscle strength, with better respiratory conditions after extubation. But the result reported by the authors reinforces that the conventional assessment on weaning does not seem to be sufficient for patients with NMD.

Another important consideration is that respiratory failure in patients with NMD is not only due to impaired respiratory muscle strength, but also due to bulbar dysfunction. Traditional methods of assessing the progression of weaning and extubation have important limitations in determining these changes. Craig et al even conditioned the removal of MV and placement in NIV for progression of the weaning to conventional parameters of spontaneous breathing conditions and also to safe bulbar function.[20]

Lack of evidence of effectiveness, like in this case, is not evidence that the interventions are ineffective, simply means that there were no papers that met the criteria of methodological quality to be evaluated.

Implications for practice

We found no relevant evidence, so we can not make any recommendations about better weaning protocols for neuromuscular disease patients. The guidelines about ventilatory support management for NMD patients should be more explicit and clear about the basis of the recommendations regarding weaning protocols.

Implications for research

Given the high incidence of NMD patients requiring mechanical ventilation for acute or chronic respiratory failure[10,11] there is a lot of space for randomized controlled trials, with high methodological rigor to better define the best weaning protocol in this population to ensure better outcomes, mainly in the weaning success.

CONCLUSION

The absence of studies presenting the proposed inclusion criteria does not allow concluding the superiority of any specific weaning protocol for patients with NMD or determining the impact of different types of protocols on other outcomes such as duration of mechanical ventilation and weaning, duration of ICU or hospital stay, mortality or complications.

The result of this review encourages other authors and researchers to develop specific research and with an adequate methodology in order to seek better answers on weaning protocols in this population.

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CONFLICTS OF INTERESTS

The authors have declared that no competing interests exist.

AUTHOR STATEMENT

Data curation: SCBN; RTC.

Formal analysis: SCBN; RTC.

Methodology: SCBN; RTC; IL.

Resources: VRR; GAFF.

Writing - original draft: SCBN; RTC; GAFF.

Writing – review & editing: SCBN; RTC; IL; VRR; GAFF.

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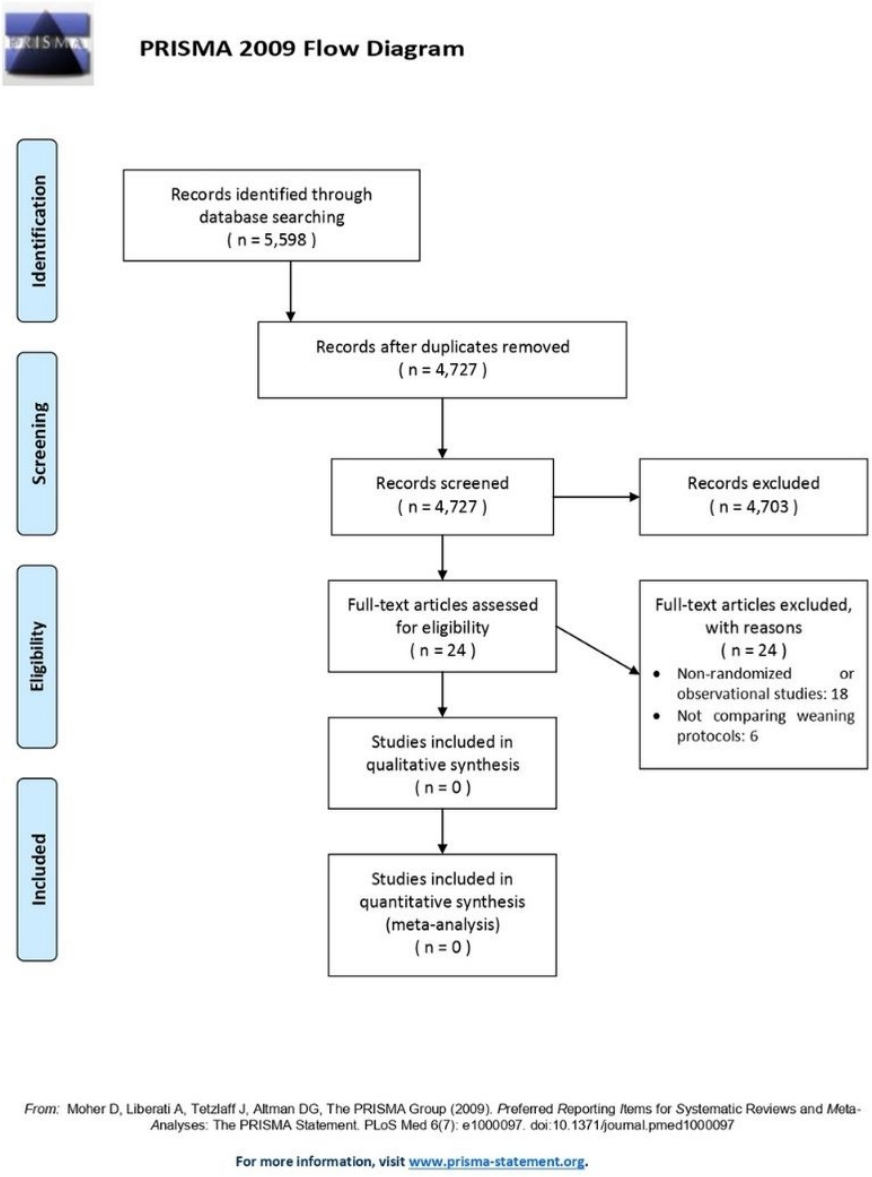

Fig1 - PRISMA Flow Diagram - BMJ Open

215x280mm (96 x 96 DPI)

Open access Protocol

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Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review

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ABSTRACT

Introduction Neuromuscular diseases (NMD) are characterised by progressive muscular impairment. The muscle weakness is directly related to respiratory muscles weakness, causing reduction in vital capacity, especially when associated with mechanical ventilation (MV). Conventional MV weaning in NMD is generally difficult. Weaning process can be conducted in protocols such as: 'T' piece or Pressure Support Ventilaton. Weaning failure is frequent because of muscle weakness. Protocol aim is to assess the effects of different weaning protocols in NMD patients receiving invasive MV in weaning success rate, duration of weaning, intensive care unit (ICU) stay, hospital stay and ICU mortality.

Methods and analysis A search will be carried in the Cochrane Neuromuscular Specialised Register, MEDLINE, EMBASE, Web of Science, Scopus, United States National Institutes of Health Clinical Trials Registry, ClinicalTrials.gov and WHO International Clinical Trial Registry Protal, of randomised controlled trials (RCTs) and quasi-RCTs. Inclusion criteria of individuals are adults (above 16 years old) and children (from 5 to 16 years old), with clinical diagnosis of NMD (muscular dystrophy, amyotrophic lateral sclerosis, congenital myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillian Barré Syndrome, severe inherited neuropathies, metabolic myopathies, inflammatory myopathies, mitochondrial diseases) of any gender. All patients ventilated for at least 48 hours due to respiratory failure and clinically considered ready for weaning. Other respiratory or cardiovascular diagnosis associated will not be included. Intervention assessed will be weaning from MV using a protocol with 30 min to 2 hours of spontaneous breathing trial at the end point. All comparisons of different protocols will be considered.

Ethics and dissemination Formal ethical approval is not required as primary data will not be collected, since it will be a systematic review. All studies included should have ethical committee approval. The results will be disseminated through a peer-reviewed publication and in conferences and congresses or symposia.

PROSPERO registration number CRD42019117393.

Strengths and limitations of this study

- This study will help to identify the best way to conduct mechanical ventilation (MV) weaning in patients with neuromuscular diseases (NMD), improving the outcomes of this population when using MV.
- It will be difficult to find articles that meet the inclusion criteria leading to greater difficulty for statistical analysis.
- There are very different approaches in the weaning process of patients with NMD, and that will bring difficult to compare the protocols.
- Too many NMD will need to be included because of NMD heterogeneity.

INTRODUCTION

Neuromuscular disease (NMD) can be defined as a chronic and progressive disease, which may present with different clinical characteristics, in which its pattern is based on the location where the injury occurs in a motor unit.[1 2] NMD are characterised by progressive muscular impairment, with difficulty in ambulation, swallowing and ventilation, with progressive reduction of vital capacity and increased work of breathing.[3] These changes lead to the development of chronic respiratory insufficiency, which is an important cause of prolonged ventilatory dependence.[4]

Muscle weakness is directly related to weakness of respiratory muscles, especially the diaphragm. Diaphragmatic weakness, often found in patients with NMD causes a reduction in the capacity to generate force, especially when associated with the use of controlled mechanical ventilation.[5]

Intensive care unit (ICU) admission, regardless of the presence of NMD, may be a cause of neuromuscular disorders that lead to muscle impairment.[6] It is estimated that such a condition occurs in up to 62% of critically ill patients in the ICU.[7] The NMD patients experience this respiratory impairment, in general, by a large proportion of motor units that innervate the respiratory muscles affected.[2]

Some risk factors such as use of sedatives, malnutrition, systemic inflammation and prolonged mechanical ventilation may further impair the neuromuscular performance of people admitted to ICU.[8]

The majority of critically ill patients admitted to ICU require ventilatory support for acute or chronic respiratory failure,[3] specially the NMD ones. In addition, the pattern of neuromuscular abnormalities associated with critical illness, defined as ICU-acquired weakness (ICUAW),[4] can lead to prolonged mechanical ventilation, a longer hospital stay and increased ventilation.[4]

The emergence of respiratory symptoms, with progressive hypercapnia, can lead to death from respiratory failure.[3] Long-term invasive or non-invasive mechanical ventilation is the main intervention for people who present with acute respiratory acidosis; progressive decline in vital capacity (<10–15 mL/kg); or progressive decline in maximal inspiratory pressure (<20–30 cmH_2O).[3 9]

Weaning from mechanical ventilation is the process of transition to spontaneous ventilation.[10] In people with NMD, conventional weaning is generally not possible.[11]

Weaning difficulty may occur in different populations, such as elderly with prolonged ICU hospitalisation, people with chronic respiratory diseases or NMD.[12] Therefore, the decision to progress to extubation is more challenging in this group of people with advanced respiratory muscle weakness, and this can lead to a need for tracheostomy and prolonged mechanical ventilation.[4]

Difficult weaning can be defined as the requirement of up to three spontaneous breathing trials (SBT) in a period of no longer than 7 days of mechanical ventilation to achieve extubation.[10 13]

The weaning process may be conducted in different protocols such as the following:

- 'T' piece: in which the patient receives only supplemental oxygen through a T-shaped tube connected to an endotracheal tube (orotracheal or tracheostomy).[10]
- Continuous positive airway pressure (CPAP): the weaning protocol involves using a continuous pressure, equal to the previous positive end-expiratory pressure level used before.[10]
- Pressure support: the use of progressive lower levels of inspiratory pressure support until it reaches 5–8 cmH_2O.[10]

Successful weaning is defined as the ability to maintain spontaneous ventilation without the need for reintubation and invasive mechanical ventilation for 48 hours after extubation.[10] For patients with NMD, due to the difficulty of weaning, it may be also defined as the absence of a need for tracheostomy and mechanical ventilation for 5 days after extubation.[4]

Postweaning monitoring should observe whether two of the following findings are present: respiratory acidosis (pH <7.35; $PaCO_2$ >45 mm Hg); SpO_2 <90% or PaO_2 <60 mm Hg with FiO_2 >50%; RR >35 rpm; decreased level of consciousness, restlessness or excessive sweating; or signs suggestive of respiratory muscle fatigue, such as the use of accessory muscles or paradoxical movement of the abdomen, in order to determinate the need to re-establish mechanical ventilation again.[4 10]

Weaning failure from invasive ventilation is frequent in people with NMD due to muscle weakness and gradual hypercapnia.[4] In this way, the non-invasive ventilation, even after weaning failure, is an option. And a future weaning can be conducted when and if clinically possible.[4 12] Although this whole process significantly increases health costs with this patient population.

Objectives

The aim of this systematic review is to assess the effects of different weaning protocols in people with NMD receiving invasive mechanical ventilation. Our secondary aim is to assess how the different protocols affect weaning success, duration of weaning, duration of stay in the ICU, duration of hospital stay, ICU mortality and also to assess adverse effects.

METHODS

Eligibility criteria

Studies will be selected according to the criteria outlined below.

Study designs

We will include randomised controlled trials (RCTs) and quasi-RCTs (experimental study with participants subjected to some type of intervention or control group, and with the same outcome of interest measured. But in this kind of study, also known as non-randomised trial, populations are subjected to any of the groups using other methods of allocating, usually not truly random). Other study types, such as non-randomised trials, crossover studies and case–control studies will be described in the 'Discussion' section of the review, but they will not be included in the Results section. We will include studies reported as full-text, those published as abstract only and unpublished data. There will be no restrictions as to language.

Participants

We will consider for inclusion adults (above 16 years old) and children (from 5 to 16 years old) people with a clinical diagnosis of a NMD (muscular dystrophy of any origin including Duchenne muscular dystrophy, amyotrophic lateral sclerosis, congenital myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillian Barré Syndrome, severe inherited neuropathies, metabolic myopathies (Pompe disease), inflammatory myopathies and mitochondrial diseases) of any gender.

We will consider all patients ventilated for at least 48 hours with orotracheal tube or tracheostomy because of acute respiratory failure, and considered by physicians to be ready for weaning according to clinical

criteria and weaning parameters. No patients with other respiratory or cardiovascular clinical diagnosis associated will be included, nor patients with mixed NMD diagnosis.

If any subset of participants with NMD is analysed, these patients will be included.

Interventions

The intervention assessed will be the process of weaning from mechanical ventilation in people with NMD using a protocol with criteria for deciding if the patient is ready for extubation with 30 min to 2 hours SBT at the end point of the protocol.

We will consider the following protocols for inclusion.

1. Pressure support ventilation, with gradual reduction of the support pressure.
2. Synchronised intermittent mandatory ventilation, with gradual reduction of respiratory rate and support pressure.
3. CPAP, with gradual reduction of applied pressure.
4. 'T' piece, with progressive increase of spontaneous ventilation time.

Comparators

We will consider any comparisons of the different protocols.

The protocols will also be compared in relation to the classification of weaning outcomes, in order to identify which protocols develop better outcomes.

- Simple—successful after first attempt.
- Difficult—require up to three attempts (or less than 7 days to reach success).
- Prolonged—require more than 7 days to reach success.

Outcomes

Primary outcome

Weaning success is defined as the ability to maintain spontaneous ventilation without the need for reintubation and invasive mechanical ventilation for 48 hours after extubation.[10]

Secondary outcomes

- Duration of weaning in patients with acute and prolonged mechanical ventilation—defined as the time between the weaning protocol initiation and the moment of extubation.
- Duration of ICU stay in patients with acute and prolonged mechanical ventilation—defined as the time between ICU admission and ICU discharge.
- Duration of hospital stay in patients with acute and prolonged mechanical ventilation—defined as the time between hospital admission and hospital discharge.
- ICU mortality rate in patients with acute and prolonged mechanical ventilation—defined as the mortality rate during ICU stay.
- Incidence of pneumothorax during mechanical ventilation period.
- Incidence of ventilation associated pneumonia.

Language

We will include articles reported in English and other languages. There will be no restrictions.

Information sources

Electronic searches

We will search the Cochrane Neuromuscular Specialised Register (The Cochrane Library, current issues), MEDLINE, EMBASE, Web of Science and Scopus. We will scan conference abstracts for relevant studies.

We will also search the United States National Institutes of Health Clinical Trials Registry, ClinicalTrials.gov (ClinicalTrials.gov) and the WHO International Clinical Trials Registry Portal (apps.who.int/trialsearch/).

We will search all databases from January 2009 to December 2019, and we will impose no restriction on language of publication.

We will identify non-randomised studies for inclusion in the discussion from the same search results.

We will search reference lists of all relevant and included trials and review articles for additional references. We will search for errata or retractions of included trials. We will also search relevant manufacturers' websites for trial information. And we will search grey literature, in reports of technical research and projects related to government programme, to identify other studies.

We will contact study authors of included trials to identify additional trials whether published or unpublished.

If no RCTs or quasi-RCTs in this area are not found, the authors will review other well-designed observational studies, where the population (NMD), intervention (mechanical ventilation weaning) and outcome (weaning success) are clearly documented, in the 'Discussion' section of the review. We will identify these (non-randomised studies) via a search in MEDLINE (from inception to the present), EMBASE (from inception to the present), Web of Science (from inception to the present) and Scopus (from inception to the present). This will be done in order to give a comprehensive descriptive narrative of any non-randomised data.

Search strategy

Search terms will include: 'neuromuscular disease' or all other terms compatible with clinical diagnoses of these types of diseases, such as 'muscular dystrophy', 'Duchenne muscular dystrophy', 'amyotrophic lateral sclerosis', 'congenital myasthenia', 'myasthenia gravis', 'congenital myopathy', 'spinal muscular atrophy', 'Guillian Barré Syndrome', 'severe inherited neuropathies', 'metabolic myopathies', 'Pompe disease', 'inflammatory myopathies' and 'mitochondrial diseases' combined with 'mechanical ventilation' or 'artificial respiration' or 'mechanical ventilation weaning' or 'ventilator weaning' or 'respirator weaning' and all the combination between them.

An example of the search strategy is available as a online supplementary file.

Study records

Selection of studies

Two review authors (SCBN and RTC) will independently screen titles and abstracts of all the potential studies retrieved by the search for inclusion and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will retrieve full-text study reports/publications, and two review authors (SCBN and RTC) will independently screen the full text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies.

We will resolve any disagreements through discussion or, if required, through consultation with a third review author (GAFF).

We will report the selection process in sufficient detail to complete a Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data extraction form that we will initially pilot on at least one trial included in the review to collect study characteristics and outcome data. One review author (SCBN) will extract study characteristics from included trials. We will collect information on study design and setting, participant characteristics (including disease severity and age), study eligibility criteria, details of the intervention(s) given, the outcomes assessed, the source of study funding and any conflicts of interest stated by the investigators.

Two review authors (SCBN and RTC) will independently extract outcome data from included trials. We will note in the 'Characteristics of included studies' table if the trials did not report outcome data in a usable way. We will resolve any disagreements by consensus or consult a third review author (GAFF). One review author (SCBN) will transfer data into Review Manager (RevMan) V.5.3.[14] A second review author (RTC) will check the outcome data entries.

The same review author (RTC) 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. To minimise bias in the review process, the review authors will not screen studies for inclusion, extract data, or assess the risk of bias in trials they themselves have authored. In such circumstances, we will involve a third review author (GAFF).

Risk of bias individual studies

Two review authors (SCBN and RTC) will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[15] These authors will resolve disagreements by discussion or by involving another review author (GAFF).

We will assess the risk of bias according to the following domains:

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

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (eg, for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, 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.

If we are able to pool a sufficient number of studies, that is, more than 10 trials,[15] we will create and examine a funnel plot to explore possible small study biases.

Data synthesis

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RR) with corresponding 95% CI and continuous data as mean difference (MD) with 95% CI, or as standardised mean difference with 95% CI 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. This will be identified if there are two or more trials with comparable populations and interventions.

Where a single trial reports multiple trial arms, we will include only the arms relevant to the review question.

All data will be pooled according to age group, dividing them into two groups (adults—over 16 years old, and children—between 5 and 16 years old). After this grouping, the analysis will be done, first, comparing the success rate and failure rate in each of the groups. Subsequently, the data will also be evaluated taking into consideration the weaning outcomes in simple, difficult and prolonged (as described in the types of interventions).

Unit of analysis issues

We do not expect to have any crossover or cluster randomised controlled trials, since weaning is a one-off event and also due to the lack of control group, since all

patients are submitted to the same intervention, which is weaning from mechanical ventilation.

If we are able to find cluster randomised controlled trials with different clusters of different NMD, we will conduct this 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 random-effects results and explore possible causes by prespecified subgroup analysis.

We will be following the rough guide to interpretation outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

- 0%–40%: might not be important;
- 30%–60%: may represent moderate heterogeneity;
- 50%–90%: may represent substantial heterogeneity and
- 75%–100%: considerable heterogeneity.

Data synthesis

If the review includes more than one comparison that 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.
- Weaning success.
- Duration of weaning (time difference between weaning protocol initiation and the moment of extubation moment).
- Duration of ICU stay.
- Duration of hospital stay.
- ICU mortality rate in patients with acute and prolonged mechanical ventilation—defined as the mortality rate during ICU stay.
- Incidence of pneumothorax during mechanical ventilation period.
- Incidence of ventilation associated pneumonia.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence (studies that contribute data for the prespecified outcomes). We will use methods and recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions[15] using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade or upgrade the quality of studies using footnotes, and we will make comments to aid readers' understanding of the review where necessary. Two authors will independently grade the quality of the evidence. They will resolve disagreements by discussion and by consultation with a third review author.

Subgroup analysis and investigation of heterogeneity

- We plan to perform the following subgroup analyses.
- Simple weaning: successful after first attempt.
- Difficult weaning: require up to three attempts.
- Prolonged weaning: require more than 7 days to reach success.
- Children: from 5 to 16 years old.
- Adults: above 16 years old.

We will use both primary and secondary outcome measures in all subgroup analyses. We will use the formal test for subgroup interactions in Review Manager V.5.3.[14]

Sensitivity analysis

We plan to undertake the following sensitivity analyses.

3wRepeat the analysis by excluding studies at high risk of bias (sequence generation, allocation concealment, blinding of personnel, outcome assessment and attrition).

If there are one or more very large trials, we will repeat the analysis by excluding them to examine how much they dominate the results.

Reaching conclusions

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

Patient and public involvement

In the present protocol of systematic review and in the subsequent systematic review, there will be no involvement of patients or public.

The paper proposes to use results previously authorised and published by other authors, without there being any need for patient or public involvement. The research question was developed based on the questions raised by other authors, most of the time according to the clinical difficult and necessity of improving the weaning protocols for this population.

The results of the present study will be published in indexed journal so it can be available for NMD patients, in general, and public, specially health professionals.

CONCLUSION

This systematic review will provide evidence in different weaning protocols that can be applied to the NMD patients, analysing the weaning success rate, leading to extubation. The hypothesis is that one specific protocol has higher success weaning rates.

Where sufficient data are available, we will conduct a meta-analysis to confirm the relationship between the different protocols and duration of weaning, duration of stay in the ICU, duration of hospital stay and ICU mortality. It will also be able to assess adverse effects of weaning protocols that fail to lead to extubation.

Moreover, if the hypothesis is confirmed, the review will clarify the reasons any weaning strategy interfere to higher success weaning rates.

Overall, the review will complement the evidence based on mechanical ventilation weaning for NMD patients.

Contributors SCBN: screen titles, abstracts and full text to identify studies for inclusion or exclusion; extract study characteristics; extract outcome data; transfer data into RevMan; assess risk of bias. RTC: screen titles, abstracts and full text to identify studies for inclusion or exclusion; extract outcome data; check outcome data entries; spot-check study characteristics for accuracy; assess risk of bias. IL: development of the text; statistical analysis and revision of the final text. VRR: development of the text; statistical analysis, revision of the final text. GAFF: discussion about the disagreements the two authors have in any issues; screen studies the other two authors have authored.

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Estratégia de busca para MEDLINE

1 - exp Neuromuscular Diseases/co, di, mo, nu, pa, ph, pp, pc, rh, th [Complications, Diagnosis, Mortality, Nursing, Pathology, Physiology, Physiopathology, Prevention & Control, Rehabilitation, Therapy]
2 - Myotonic Dystrophy/ or Muscular Dystrophy, Duchenne/ or dystrophy.mp. - 46861
3 - muscular dystrophy.mp. or exp Muscular Dystrophies/ - 32736
4 - Myasthenia Gravis/ or myasthenia.mp. - 17216
5 - congenital myasthenia.mp. or exp Myasthenic Syndromes, Congenital/ - 654
6 - myopathy.mp. or *Muscular Diseases/ - 31947
7 - Myopathies, Structural, Congenital/ or congenital myopathy.mp. - 1225
8 - inflammatory myopathy.mp. or *Myositis/ - 7195
9 - metabolic myopathy.mp. or Mitochondrial Myopathies/ - 1972
10 - pompe disease.mp. - 1063
11 - spinal muscular atrophy.mp. or exp Muscular Atrophy, Spinal/ - 6338
12 - Polyradiculoneuropathy/ or exp Guillain-Barre Syndrome/ or guillian barre.mp. or Polyneuropathies/ - 13731
13 - Peripheral Nervous System Diseases/ or severe inherited neuropathy.mp. - 22861
14 - amyotrophic lateral sclerosis.mp. or exp Amyotrophic Lateral Sclerosis/ - 24339
15 - 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 - 270807
16 - Positive-Pressure Respiration/ or Respiration, Artificial/ or Ventilator Weaning/ - 65155
17 - Weaning/ or weaning.mp. - 33982
18 - Airway Extubation/ or spontaneous breathing trial.mp. - 1798
19 - 16 or 17 or 18 - 95029
20 - 15 and 19

Estratégia de busca para EMBASE

#1 - 'neuromuscular disease' OR 'muscular dystrophy' OR myasthenia OR myopathy OR 'glycogen storage disease type 2' OR 'muscle atrophy' OR polyradiculoneuropathy OR 'peripheral neuropathy' OR 'amyotrophic lateral sclerosis' - 159,527
#2 - 'artificial ventilation' OR 'ventilator weaning' OR extubation OR 'spontaneous breathing trial' - 5,215
#3 - #1 AND #2 AND [2009-2020]/py

Estratégia de busca para WEB OF SCIENCE

#1 - Todos os campos: (neuromuscular disease) OR Todos os campos: (muscular dystrophy) OR Todos os campos: (myasthenia) OR Todos os campos: (myopathy) OR Todos os campos: (glycogen storage disease type 2) OR Todos os campos: (muscle atrophy) OR Todos os campos: (polyradiculoneuropathy) OR Todos os campos: (peripheral neuropathy) OR Todos os campos: (amyotrophic lateral sclerosis) Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=2009-2020 - 100.078

#2 - Todos os campos: (artificial ventilation) OR Todos os campos: (ventilator weaning) OR Todos os campos: (extubation) OR Todosos campos: (spontaneous breathing trial) Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=2009-2020 - 9.840

#3 - #1 AND #2 - Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=2009-2020

Estratégia de busca para SCOPUS

('artificial AND ventilation' OR 'ventilator AND weaning' OR extubation OR 'spontaneous AND breathing AND trial') AND ('neuromuscular AND disease' OR 'muscular AND dystrophy' OR myasthenia OR myopathy OR 'glycogen AND storage AND disease AND type AND 2' OR 'muscle AND atrophy' OR polyradiculoneuropathy OR 'peripheral AND neuropathy' OR 'amyotrophic AND lateral AND sclerosis') AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009))

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Sup.2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	N/A
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	N/A
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Weaning from mechanical ventilation in people with neuromuscular disease: a systematic review

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Respiratory medicine
Keywords:	Neuromuscular disease < NEUROLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine), INTENSIVE & CRITICAL CARE

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Weaning from mechanical ventilation in people with neuromuscular disease: a systematic review

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ABSTRACT

Objective: This systematic review aimed in assessing the effects of different weaning protocols in people with neuromuscular disease (NMD) receiving invasive mechanical ventilation, identifying which protocol is the best and how different protocols can affect weaning outcome success, duration of weaning, intensive care unit and hospital stay and mortality. **Design:** Systematic review. **Data sources:** Electronic databases (MEDLINE, EMBASE, Web of Science and Scopus) were searched from January 2009 up to August 2020. **Eligibility criteria for selecting studies:** Randomised controlled trials (RCT) and non-randomised controlled trials that evaluated NMD patients (adults and children from 5 years old) in the weaning process managed with a protocol (pressure support ventilation; synchronized intermittent mandatory ventilation; CPAP; “T” piece). **Primary outcome:** Weaning success. **Secondary outcomes:** weaning duration; intensive care unit (ICU) stay; hospital stay; ICU mortality; complications (pneumothorax, ventilation associated pneumonia). **Data extraction and synthesis:** Two review authors assessed the titles and the

abstracts for inclusion and reviewed the full-texts independently. **Results**: We found no studies that fulfilled the inclusion criteria. **Conclusions**: The absence of studies about different weaning protocols for NMD patients does not allow concluding the superiority of any specific weaning protocol for patients with NMD or determining the impact of different types of protocols on other outcomes. The result of this review encourages further studies. **PROSPERO registration number:** CRD42019117393.

Keywords: mechanical ventilation; ventilator weaning; neuromuscular disease

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Studies on weaning for neuromuscular disease do not consider any specific protocol.
- Non-invasive ventilation is described as a promising resource for neuromuscular disease patients after mechanical ventilation.
- Observational and retrospective studies are the most common for neuromuscular disease patients.
- Neuromuscular individuals needs specific weaning protocols.

INTRODUCTION

Neuromuscular disease (NMD) can be defined as a chronic and progressive disease, which may present with different clinical characteristics, in which its pattern is based on the location where the injury occurs in a motor unit.[1,2] NMD are characterized by progressive muscular impairment, with difficulty in ambulation, swallowing and ventilation, with progressive reduction of vital capacity and increased work of breathing.[3] These changes lead to the development of acute and chronic respiratory failure, which is an important cause of prolonged ventilatory dependence[4,5], associated with increased healthcare costs.[6]

Three main components may contribute to respiratory failure and the need for mechanical ventilation in these patients: (1) inspiratory muscle

weakness; (2) expiratory muscle weakness; (3) upper airway compromise.[7-9] The NMD patients experience this respiratory impairment, in general, by a large proportion of motor units that innervate the respiratory muscles affected.[2]

The majority of critically ill patients admitted to ICU require ventilatory support for acute or chronic respiratory failure,[3] specially the NMD ones.[8,10-12] In addition, the pattern of neuromuscular abnormalities associated with critical illness, defined as ICU-acquired weakness (ICUAW), can lead to prolonged mechanical ventilation, a longer hospital stay and increased ventilation.[4]

The emergence of respiratory symptoms, with progressive hypercapnia, can lead to death from respiratory failure.[3,7] Long-term invasive or non-invasive mechanical ventilation is the main intervention for people who present with acute respiratory acidosis; progressive decline in vital capacity (<10–15 mL/kg); or progressive decline in maximal inspiratory pressure (<20–30 cmH_2O).[3,8,13]

Weaning from mechanical ventilation is the process of transition to spontaneous ventilation.[14] In people with NMD, conventional weaning is generally not possible.[15] Weaning difficulty may occur in different populations, such as older people with prolonged ICU hospitalization, people with chronic respiratory diseases or NMD.[16] Therefore, the decision to progress to extubation is more challenging in this group of people with advanced respiratory muscle weakness, and this can lead to a need for tracheostomy and prolonged mechanical ventilation.[4]

The weaning process may be conducted in different protocols such as the following:

- 'T' piece: in which the patient receives only supplemental oxygen through a T-shaped tube connected to an endotracheal tube (orotracheal or tracheostomy).[14]
- Continuous positive airway pressure (CPAP): the weaning protocol involves using a continuous pressure, equal to the previous positive end-expiratory pressure level used before.[14]
- Pressure support: the use of progressive lower levels of inspiratory pressure support until it reaches 5–8 cmH_2O.[14] This protocol is the most used and described one.

Successful weaning is defined as the ability to maintain spontaneous ventilation without the need for reintubation and invasive mechanical ventilation for 48 hours after extubation.[14] For patients with NMD, due to the difficulty of weaning, it may be also defined as the absence of a need for tracheostomy and mechanical ventilation for 5 days after extubation.[4]

Post weaning monitoring should observe whether two of the following findings are present: respiratory acidosis (pH <7.35; $PaCO_2$>45 mmHg); SpO_2<90% or PaO_2<60 mmHg with FiO_2>50%; RR >35 rpm; decreased level of consciousness, restlessness or excessive sweating; or signs suggestive of respiratory muscle fatigue, such as the use of accessory muscles or paradoxical movement of the abdomen, in order to determinate the need to re-establish mechanical ventilation again.[4,14]

Weaning failure from invasive ventilation is frequent in people with NMD due to muscle weakness and gradual hypercapnia.[4] In this way, non-invasive ventilation, even after weaning failure, is an option. Furthermore, a future weaning can be conducted when and if clinically possible.[4,16] Although this whole process significantly increases health costs with this patient population.

Objectives

The aim of this systematic review was to assess the effects of different weaning protocols in people with NMD receiving invasive mechanical ventilation. Our secondary aim was to assess how the different protocols affect weaning success, duration of weaning, duration of stay in the ICU, duration of hospital stay, ICU mortality and also to assess adverse effects.

METHODS

Protocol and registration

This systematic review was registered on PROSPERO (Registration Number: CRD42019117393. The review authors followed the Cochrane Handbook for Systematic Reviews of Interventions[17] and the PRISMA

Statement.[18] The protocol for the systematic review was previously published on BMJ Open.[19]

Eligibility criteria for inclusion

Population

Adults (above 16 years old) and children (from 5 to 16 years old) with a clinical diagnosis of a NMD (muscular dystrophy of any origin including Duchenne muscular dystrophy, amyotrophic lateral sclerosis, congenital myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillian Barré Syndrome, severe inherited neuropathies, metabolic myopathies (Pompe disease), inflammatory myopathies and mitochondrial diseases) of any gender.

All patients ventilated for at least 48 hours with orotracheal tube or tracheostomy because of acute respiratory failure, and considered by physicians to be ready for weaning according to clinical criteria and weaning parameters. No patients with other respiratory or cardiovascular clinical diagnosis associated were considered, nor patients with mixed NMD diagnosis.

Intervention

The intervention assessed was the process of weaning from mechanical ventilation in people with NMD using a protocol with criteria for deciding if the patient is ready for extubation with 30 min to 2 hours SBT at the end point of the protocol. The following protocols were considered for inclusion:

1. Pressure support ventilation, with gradual reduction of the support pressure.

2. Synchronized intermittent mandatory ventilation, with gradual reduction of respiratory rate and support pressure.

3. CPAP, with gradual reduction of applied pressure.

4. ‘T’ piece, with progressive increase of spontaneous ventilation time.

Comparison

Any comparison between the different protocols was considered. If the studies classified the weaning based on the outcomes: simple (successful after first attempt of spontaneous breathing trial - SBT); difficult (requiring up to three attempts or less than 7 days to reach success; prolonged (requiring more than 7 days to reach success), comparisons would also be considered.

Outcomes

Primary outcome

Weaning success, defined as the ability to maintain spontaneous ventilation without the need for reintubation and invasive mechanical ventilation for 48 hours after extubation.[14]

Secondary outcomes

- Duration of weaning in patients with acute and prolonged mechanical ventilation - defined as the time between the weaning protocol initiation and the moment of extubation.
- Duration of ICU stay in patients with acute and prolonged mechanical ventilation - defined as the time between ICU admission and ICU discharge.
- Duration of hospital stay in patients with acute and prolonged mechanical ventilation - defined as the time between hospital admission and hospital discharge.
- ICU mortality rate in patients with acute and prolonged mechanical ventilation - defined as the mortality rate during ICU stay.
- Incidence of pneumothorax during mechanical ventilation period.
- Incidence of ventilation associated pneumonia.

Study designs

To ensure this evidence synthesis is based upon the highest quality of evidence, we only considered including randomised controlled trials (RCTs) and non-randomised controlled trials (experimental study with participants subjected to some type of intervention or control group, and with the same outcome of interest measured). There were no restrictions to language in the studies selection.

Search method

Electronic databases were searched from 1st January 2009 up to 31st August 2020: Cochrane Neuromuscular Specialised Register (The Cochrane Library, current issues), MEDLINE, EMBASE, Web of Science and Scopus. We also searched the United States National Institutes of Health Clinical Trials Registry, ClinicalTrials. gov (ClinicalTrials. gov) and the WHO International Clinical Trials Registry Portal (apps. who. int/ trialsearch/).

Search terms included were: 'neuromuscular disease' or all other terms compatible with clinical diagnoses of these types of diseases, such as 'muscular dystrophy', 'Duchenne muscular dystrophy', 'amyotrophic lateral sclerosis', 'congenital myasthenia', 'myasthenia gravis', 'congenital myopathy', 'spinal muscular atrophy', 'Guillian Barré Syndrome', 'severe inherited neuropathies', 'metabolic myopathies', 'Pompe disease', 'inflammatory myopathies' and 'mitochondrial diseases' combined with 'mechanical ventilation' or 'artificial respiration' or 'mechanical ventilation weaning' or 'ventilator weaning' or 'respirator weaning' and all the combination between them. The search strategy is available as an online supplementary file.

Study selection

Two review authors (SCBN and IL) performed the search. Two review authors (SCBN and RTC) assessed the titles and the abstracts for inclusion independently and induplicate. When the full text was assessed for eligibility criteria it was performed independently as well, and the authors had an

excellent agreement of 99.5%. The disagreements were resolved through consultation of a third review author (IL).

Patient and Public Involvement

In the present systematic review there was no involvement of patients or public. The paper proposed to use results previously authorised and published by other authors, without there being any need for patient or public involvement. The research question was developed based on the questions raised by other authors, most of the time according to the clinical difficult and necessity of improving the weaning protocols for this population. The results presented are available in the publication for NMD patients and public in general.

RESULTS

After searching scrutinously all the databases proposed from January 2009 to August 2020 no studies fulfilled the inclusion criteria regarding different weaning protocols on neuromuscular disease patients receiving mechanical ventilation for respiratory failure. A flowchart shows the detailed process of selection (Fig1).

Fig1. Flowchart showing publication selection.[18]

Although 24 studies were selected to full-text reading, 3 letters to the editor[20-22] and 2 narrative reviews[23,24] were identified. In addition, 11 studies presented retrospective analysis, 7 of which were of general population[12,16,25-29] and 4 with NMD patients.[4,30-32] All the retrospective evaluated and described weaning outcomes. Prospective analysis as observational study, but without a control group, was found in 6 studies[33-38] and in 2 it was described 2 groups in their observations evaluating prognostic factors related to MV weaning outcomes[35] or the impact of a chest physiotherapy protocol on the prevention of post-extubation atelectasis in NMD population.[38] With this, only 2 studies met the criteria for non-randomised study profile, having a group of group.[39,40] These two articles are presented in the Discussion section below.

DISCUSSION

We found no high quality evidence either for or against any of the weaning protocols proposed (PSV, SIMV, CPAP or 'T' piece) in MND patients under mechanical ventilation.

The decision about the ideal time to extubate these patients and wean them from ventilatory support is much harder for the patients that deal with respiratory muscle weakness and chronic ventilatory failure, increasing repeated extubation fails and tracheotomies rates.[4]

In the retrospective studies group with NMD patients it was described that early extubation (< 6 hours) after a thymectomy in myasthenia gravis crisis was related to a lower reintubation rate, lower postoperative pulmonary infection and shorter duration of ICU stay compared to late extubation (> 6 hours).[30] Another interesting factor associated with prolonged mechanical ventilation and tracheostomy prolonged need in these patients is neurogenic dysphagia.[31] And non-invasive ventilation was highlighted as a feasible intervention to be used after weaning failure with survival improvement and lower reintubation rate[4], as well as instead of invasive mechanical ventilation and future weaning, where no mortality difference was noted.[32]

The observational prospective studies without control group showed that non-invasive ventilation initiated after spontaneous breathing cycles for Guillain-Barré Syndrom patients under MV is a potential therapeutic strategy.[34] And the study that observed the comparison between different 5 weaning predictors described that the Timed Inspiratory Effort index had a better performance than the others (integrative weaning index, non-invasive tension-time index, maximum inspiratory pressure, and breathing frequency/tidal volume – RSBI).[36]

Two prospective studies with different groups, that were not included because did not because they did not evaluate weaning protocols, attempted to compare prognostic factors of weaning in patients with ALS[35] and the ability to prevent atelectasis after extubation with respiratory physiotherapy.[38] In the first, it was observed that tracheostomy and use of MV was associated with longer survival, compared to patients who were not directly submitted to invasive MV. The worst prognosis was related to older patients and to the time of respiratory

symptoms onset.[35] The other study demonstrated, with randomised groups, that a post-extubation chest physiotherapy protocol decreased the incidence of atelectasis in paediatric NMD patients.[38]

Sun et al.[40] investigated patients with myasthenia gravis crisis who were hospitalized and needed invasive mechanical ventilation. All the patients were submitted to ventilatory weaning with a gradual reduction in support pressure as protocol, up to values that allowed the spontaneous breathing trial in this ventilatory mode. In addition to the SBT, the analysis of the Rapid and Shallow Breathing Index (RSBI) and the fraction of diaphragm thickening fraction (DTF) by bedside ultrasound were also performed. The patients were divided into a successful weaning group and a weaning failure group. Of the 37 patients evaluated, with 63 evaluation measures taken, the characteristics of the groups were similar at the beginning of the SBT. Between 50 and 60 minutes from the beginning of the SBT, the authors reported that there was a statistically significant increase in the RSBI compared to the initial 5 minutes (80.41 x 57.29 - p = 0.029), as well as a reduction in the DTF (24.46 x 61.89 - p = 0.000) in the weaning failure group (n = 30). These variables were not observed in the successful weaning group (n = 33).

The findings of this study allow us to deduce that the weaning protocol using pressure support, as well as the analysis of the RSBI and/or the DTF during spontaneous breathing trial, can be a predictive value for the success or failure of weaning.[40]

Vianello et al.[39], on the other hand, studied patients diagnosed with NMD and who were admitted to ICUs requiring ventilatory support. In their inclusion criteria there were patients who remained on MV for > 48 hours and who underwent a weaning protocol with a gradual reduction in support pressure. The authors compare the use of NIV immediately after extubation associated with mechanically assisted cough versus a control group of patients with NMD who received standard medical therapy, without the interventions mentioned, after extubation. All patients underwent an SBT in PSV mode with PS < 8 cmH2O and were considered able to be extubated when they showed no signs of intolerance.

The results described demonstrate, despite the absence of difference in the mortality outcome, that the need for reintubation (30% x 100% - p = 0.002) and tracheostomy (30% x 90% - p = 0.01) was significantly greater in the group that received standard medical therapy, although all patients were considered ready for extubation by the protocol using the ventilatory pressure support mode.[39]

According to the other studies observed during the search, weaning has been studied and applied to this population in the aforementioned types of protocols. But the results are not satisfactory for any of them, with high failure rates in the process anyway.

The search for the best way to promote weaning from mechanical ventilation for the population of patients with NMD has led professionals and researchers to focus on the use of NIV as a way of progressing and continuing weaning from MV.[4,34,39] This type of approach is justified by the absence of studies with an appropriate methodology that identify a better way to conduct weaning in these patients. The combination of NIV with invasive MV has led to a reduction in reintubation rates, despite the increase in the number of patients dependent on this therapy.[4,39,41] This observation was also described even for prolonged MV patients with NMD.[34]

Although NIV has been described as an excellent alternative for weaning in patients who fail in the conventional conditions for evaluating weaning[23] (protocols proposed for analysis) it seems to be more efficient when installed immediately after MV removal and not after the appearance respiratory failure, when it would be, especially for patients with NMD, associated with a greater probability of failure and the need to return to invasive MV.[4]

Xu et al.[37] observed, in a series of cases of infantile and juvenile patients with Pompe disease, that after conducting weaning in CPAP or PSV, the use of NIV immediately after extubation led to an improvement in respiratory muscle strength, with better respiratory conditions after extubation. However, the result reported by the authors reinforces that the conventional assessment on weaning does not seem to be sufficient for patients with NMD.

Another important consideration is that respiratory failure in patients with NMD is not only due to impaired respiratory muscle strength, but also due to bulbar dysfunction. Traditional methods of assessing the progression of weaning and extubation have important limitations in determining these changes. Craig et al. even conditioned the removal of MV and placement in NIV for progression of the weaning to conventional parameters of spontaneous breathing conditions and also to safe bulbar function.[34]

Lack of evidence of effectiveness, like in this case, is not evidence that the interventions are ineffective, simply means that there were no papers that met the criteria of methodological quality to be evaluated.

Implications for practice

We found no relevant evidence, so we cannot make any recommendations about better weaning protocols for neuromuscular disease patients. The guidelines about ventilatory support management for NMD patients should be more explicit and clear about the basis of the recommendations regarding weaning protocols.

Implications for research

Given the high incidence of NMD patients requiring mechanical ventilation for acute or chronic respiratory failure[10,11] there is a lot of space for randomised controlled trials, with high methodological rigor to better define the best weaning protocol in this population to ensure better outcomes, mainly in the weaning success.

CONCLUSION

The absence of studies presenting the proposed inclusion criteria does not allow concluding the superiority of any specific weaning protocol for patients with NMD or determining the impact of different types of protocols on other outcomes such as duration of mechanical ventilation and weaning, duration of ICU or hospital stay, mortality or complications.

The result of this review encourages other authors and researchers to develop specific research and with an adequate methodology in order to seek better answers on weaning protocols in this population.

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CONFLICTS OF INTERESTS

The authors have declared that no competing interests exist.

No additional data available.

AUTHOR STATEMENT

Data curation: SCBN; RTC.

Formal analysis: SCBN; RTC.

Methodology: SCBN; RTC; IL.

Resources: VRR; GAFF.

Writing - original draft: SCBN; RTC; GAFF.

Writing – review & editing: SCBN; RTC; IL; VRR; GAFF.

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No additional data available.

DATA SHARING STATEMENT

No additional data available.

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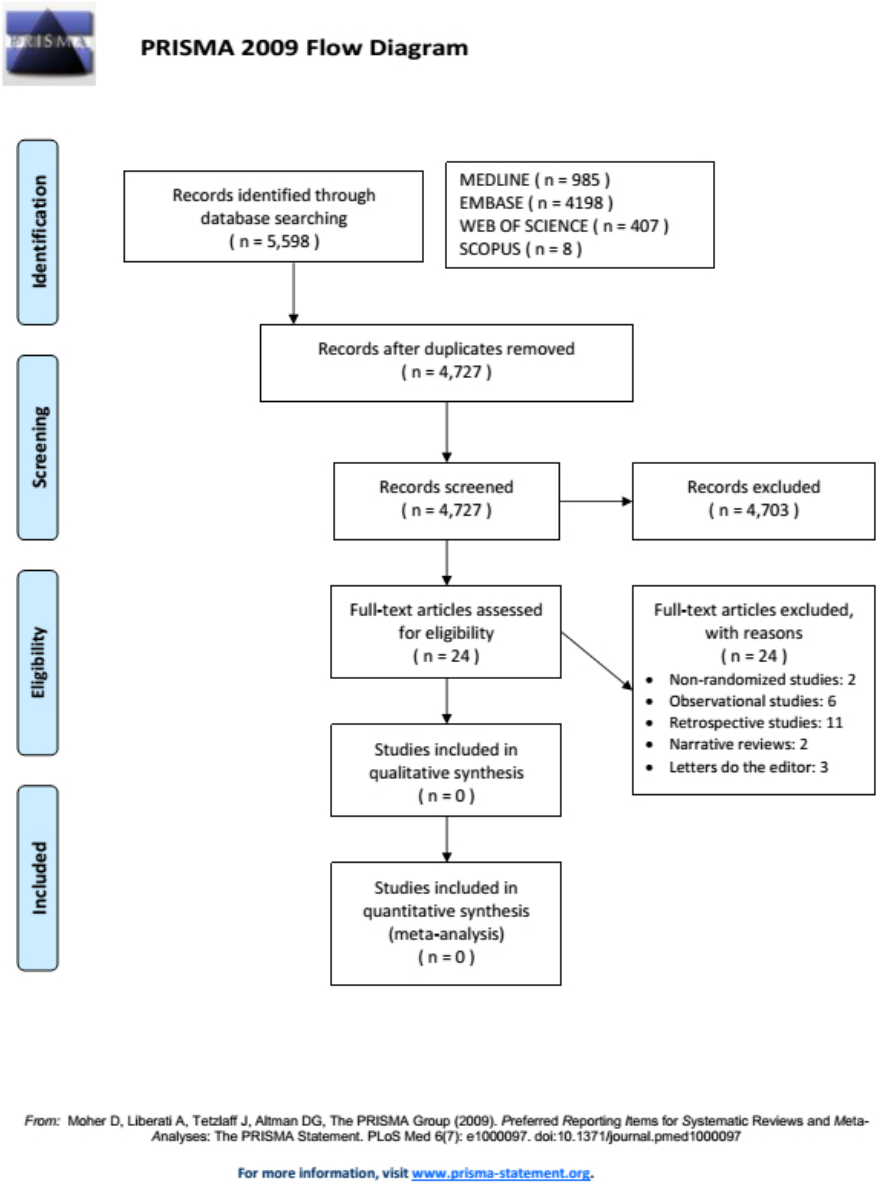

Fig1. Flowchart showing publication selection.

Open access Protocol

BMJ Open

Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review

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ABSTRACT

Introduction Neuromuscular diseases (NMD) are characterised by progressive muscular impairment. The muscle weakness is directly related to respiratory muscles weakness, causing reduction in vital capacity, especially when associated with mechanical ventilation (MV). Conventional MV weaning in NMD is generally difficult. Weaning process can be conducted in protocols such as: 'T' piece or Pressure Support Ventilaton. Weaning failure is frequent because of muscle weakness. Protocol aim is to assess the effects of different weaning protocols in NMD patients receiving invasive MV in weaning success rate, duration of weaning, intensive care unit (ICU) stay, hospital stay and ICU mortality.

Methods and analysis A search will be carried in the Cochrane Neuromuscular Specialised Register, MEDLINE, EMBASE, Web of Science, Scopus, United States National Institutes of Health Clinical Trials Registry, ClinicalTrials.gov and WHO International Clinical Trial Registry Protal, of randomised controlled trials (RCTs) and quasi-RCTs. Inclusion criteria of individuals are adults (above 16 years old) and children (from 5 to 16 years old), with clinical diagnosis of NMD (muscular dystrophy, amyotrophic lateral sclerosis, congenital myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillian Barré Syndrome, severe inherited neuropathies, metabolic myopathies, inflammatory myopathies, mitochondrial diseases) of any gender. All patients ventilated for at least 48 hours due to respiratory failure and clinically considered ready for weaning. Other respiratory or cardiovascular diagnosis associated will not be included. Intervention assessed will be weaning from MV using a protocol with 30 min to 2 hours of spontaneous breathing trial at the end point. All comparisons of different protocols will be considered.

Ethics and dissemination Formal ethical approval is not required as primary data will not be collected, since it will be a systematic review. All studies included should have ethical committee approval. The results will be disseminated through a peer-reviewed publication and in conferences and congresses or symposia.

PROSPERO registration number CRD42019117393.

Strengths and limitations of this study

- This study will help to identify the best way to conduct mechanical ventilation (MV) weaning in patients with neuromuscular diseases (NMD), improving the outcomes of this population when using MV.
- It will be difficult to find articles that meet the inclusion criteria leading to greater difficulty for statistical analysis.
- There are very different approaches in the weaning process of patients with NMD, and that will bring difficult to compare the protocols.
- Too many NMD will need to be included because of NMD heterogeneity.

INTRODUCTION

Neuromuscular disease (NMD) can be defined as a chronic and progressive disease, which may present with different clinical characteristics, in which its pattern is based on the location where the injury occurs in a motor unit.[1 2] NMD are characterised by progressive muscular impairment, with difficulty in ambulation, swallowing and ventilation, with progressive reduction of vital capacity and increased work of breathing.[3] These changes lead to the development of chronic respiratory insufficiency, which is an important cause of prolonged ventilatory dependence.[4]

Muscle weakness is directly related to weakness of respiratory muscles, especially the diaphragm. Diaphragmatic weakness, often found in patients with NMD causes a reduction in the capacity to generate force, especially when associated with the use of controlled mechanical ventilation.[5]

Intensive care unit (ICU) admission, regardless of the presence of NMD, may be a cause of neuromuscular disorders that lead to muscle impairment.[6] It is estimated that such a condition occurs in up to 62% of critically ill patients in the ICU.[7] The NMD patients experience this respiratory impairment, in general, by a large proportion of motor units that innervate the respiratory muscles affected.[2]

Some risk factors such as use of sedatives, malnutrition, systemic inflammation and prolonged mechanical ventilation may further impair the neuromuscular performance of people admitted to ICU.[8]

The majority of critically ill patients admitted to ICU require ventilatory support for acute or chronic respiratory failure,[3] specially the NMD ones. In addition, the pattern of neuromuscular abnormalities associated with critical illness, defined as ICU-acquired weakness (ICUAW),[4] can lead to prolonged mechanical ventilation, a longer hospital stay and increased ventilation.[4]

The emergence of respiratory symptoms, with progressive hypercapnia, can lead to death from respiratory failure.[3] Long-term invasive or non-invasive mechanical ventilation is the main intervention for people who present with acute respiratory acidosis; progressive decline in vital capacity (<10–15 mL/kg); or progressive decline in maximal inspiratory pressure (<20–30 cmH_2O).[3 9]

Weaning from mechanical ventilation is the process of transition to spontaneous ventilation.[10] In people with NMD, conventional weaning is generally not possible.[11]

Weaning difficulty may occur in different populations, such as elderly with prolonged ICU hospitalisation, people with chronic respiratory diseases or NMD.[12] Therefore, the decision to progress to extubation is more challenging in this group of people with advanced respiratory muscle weakness, and this can lead to a need for tracheostomy and prolonged mechanical ventilation.[4]

Difficult weaning can be defined as the requirement of up to three spontaneous breathing trials (SBT) in a period of no longer than 7 days of mechanical ventilation to achieve extubation.[10 13]

The weaning process may be conducted in different protocols such as the following:

- 'T' piece: in which the patient receives only supplemental oxygen through a T-shaped tube connected to an endotracheal tube (orotracheal or tracheostomy).[10]
- Continuous positive airway pressure (CPAP): the weaning protocol involves using a continuous pressure, equal to the previous positive end-expiratory pressure level used before.[10]
- Pressure support: the use of progressive lower levels of inspiratory pressure support until it reaches 5–8 cmH_2O.[10]

Successful weaning is defined as the ability to maintain spontaneous ventilation without the need for reintubation and invasive mechanical ventilation for 48 hours after extubation.[10] For patients with NMD, due to the difficulty of weaning, it may be also defined as the absence of a need for tracheostomy and mechanical ventilation for 5 days after extubation.[4]

Postweaning monitoring should observe whether two of the following findings are present: respiratory acidosis (pH <7.35; $PaCO_2$ >45 mm Hg); SpO_2 <90% or PaO_2 <60 mm Hg with FiO_2 >50%; RR >35 rpm; decreased level of consciousness, restlessness or excessive sweating; or signs suggestive of respiratory muscle fatigue, such as the use of accessory muscles or paradoxical movement of the abdomen, in order to determinate the need to re-establish mechanical ventilation again.[4 10]

Weaning failure from invasive ventilation is frequent in people with NMD due to muscle weakness and gradual hypercapnia.[4] In this way, the non-invasive ventilation, even after weaning failure, is an option. And a future weaning can be conducted when and if clinically possible.[4 12] Although this whole process significantly increases health costs with this patient population.

Objectives

The aim of this systematic review is to assess the effects of different weaning protocols in people with NMD receiving invasive mechanical ventilation. Our secondary aim is to assess how the different protocols affect weaning success, duration of weaning, duration of stay in the ICU, duration of hospital stay, ICU mortality and also to assess adverse effects.

METHODS

Eligibility criteria

Studies will be selected according to the criteria outlined below.

Study designs

We will include randomised controlled trials (RCTs) and quasi-RCTs (experimental study with participants subjected to some type of intervention or control group, and with the same outcome of interest measured. But in this kind of study, also known as non-randomised trial, populations are subjected to any of the groups using other methods of allocating, usually not truly random). Other study types, such as non-randomised trials, crossover studies and case–control studies will be described in the 'Discussion' section of the review, but they will not be included in the Results section. We will include studies reported as full-text, those published as abstract only and unpublished data. There will be no restrictions as to language.

Participants

We will consider for inclusion adults (above 16 years old) and children (from 5 to 16 years old) people with a clinical diagnosis of a NMD (muscular dystrophy of any origin including Duchenne muscular dystrophy, amyotrophic lateral sclerosis, congenital myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillian Barré Syndrome, severe inherited neuropathies, metabolic myopathies (Pompe disease), inflammatory myopathies and mitochondrial diseases) of any gender.

We will consider all patients ventilated for at least 48 hours with orotracheal tube or tracheostomy because of acute respiratory failure, and considered by physicians to be ready for weaning according to clinical

criteria and weaning parameters. No patients with other respiratory or cardiovascular clinical diagnosis associated will be included, nor patients with mixed NMD diagnosis.

If any subset of participants with NMD is analysed, these patients will be included.

Interventions

The intervention assessed will be the process of weaning from mechanical ventilation in people with NMD using a protocol with criteria for deciding if the patient is ready for extubation with 30 min to 2 hours SBT at the end point of the protocol.

We will consider the following protocols for inclusion.

1. Pressure support ventilation, with gradual reduction of the support pressure.
2. Synchronised intermittent mandatory ventilation, with gradual reduction of respiratory rate and support pressure.
3. CPAP, with gradual reduction of applied pressure.
4. 'T' piece, with progressive increase of spontaneous ventilation time.

Comparators

We will consider any comparisons of the different protocols.

The protocols will also be compared in relation to the classification of weaning outcomes, in order to identify which protocols develop better outcomes.

- Simple—successful after first attempt.
- Difficult—require up to three attempts (or less than 7 days to reach success).
- Prolonged—require more than 7 days to reach success.

Outcomes

Primary outcome

Weaning success is defined as the ability to maintain spontaneous ventilation without the need for reintubation and invasive mechanical ventilation for 48 hours after extubation.[10]

Secondary outcomes

- Duration of weaning in patients with acute and prolonged mechanical ventilation—defined as the time between the weaning protocol initiation and the moment of extubation.
- Duration of ICU stay in patients with acute and prolonged mechanical ventilation—defined as the time between ICU admission and ICU discharge.
- Duration of hospital stay in patients with acute and prolonged mechanical ventilation—defined as the time between hospital admission and hospital discharge.
- ICU mortality rate in patients with acute and prolonged mechanical ventilation—defined as the mortality rate during ICU stay.
- Incidence of pneumothorax during mechanical ventilation period.
- Incidence of ventilation associated pneumonia.

Language

We will include articles reported in English and other languages. There will be no restrictions.

Information sources

Electronic searches

We will search the Cochrane Neuromuscular Specialised Register (The Cochrane Library, current issues), MEDLINE, EMBASE, Web of Science and Scopus. We will scan conference abstracts for relevant studies.

We will also search the United States National Institutes of Health Clinical Trials Registry, ClinicalTrials.gov (ClinicalTrials.gov) and the WHO International Clinical Trials Registry Portal (apps.who.int/trialsearch/).

We will search all databases from January 2009 to December 2019, and we will impose no restriction on language of publication.

We will identify non-randomised studies for inclusion in the discussion from the same search results.

We will search reference lists of all relevant and included trials and review articles for additional references. We will search for errata or retractions of included trials. We will also search relevant manufacturers' websites for trial information. And we will search grey literature, in reports of technical research and projects related to government programme, to identify other studies.

We will contact study authors of included trials to identify additional trials whether published or unpublished.

If no RCTs or quasi-RCTs in this area are not found, the authors will review other well-designed observational studies, where the population (NMD), intervention (mechanical ventilation weaning) and outcome (weaning success) are clearly documented, in the 'Discussion' section of the review. We will identify these (non-randomised studies) via a search in MEDLINE (from inception to the present), EMBASE (from inception to the present), Web of Science (from inception to the present) and Scopus (from inception to the present). This will be done in order to give a comprehensive descriptive narrative of any non-randomised data.

Search strategy

Search terms will include: 'neuromuscular disease' or all other terms compatible with clinical diagnoses of these types of diseases, such as 'muscular dystrophy', 'Duchenne muscular dystrophy', 'amyotrophic lateral sclerosis', 'congenital myasthenia', 'myasthenia gravis', 'congenital myopathy', 'spinal muscular atrophy', 'Guillian Barré Syndrome', 'severe inherited neuropathies', 'metabolic myopathies', 'Pompe disease', 'inflammatory myopathies' and 'mitochondrial diseases' combined with 'mechanical ventilation' or 'artificial respiration' or 'mechanical ventilation weaning' or 'ventilator weaning' or 'respirator weaning' and all the combination between them.

An example of the search strategy is available as a online supplementary file.

Study records

Selection of studies

Two review authors (SCBN and RTC) will independently screen titles and abstracts of all the potential studies retrieved by the search for inclusion and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will retrieve full-text study reports/publications, and two review authors (SCBN and RTC) will independently screen the full text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies.

We will resolve any disagreements through discussion or, if required, through consultation with a third review author (GAFF).

We will report the selection process in sufficient detail to complete a Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data extraction form that we will initially pilot on at least one trial included in the review to collect study characteristics and outcome data. One review author (SCBN) will extract study characteristics from included trials. We will collect information on study design and setting, participant characteristics (including disease severity and age), study eligibility criteria, details of the intervention(s) given, the outcomes assessed, the source of study funding and any conflicts of interest stated by the investigators.

Two review authors (SCBN and RTC) will independently extract outcome data from included trials. We will note in the 'Characteristics of included studies' table if the trials did not report outcome data in a usable way. We will resolve any disagreements by consensus or consult a third review author (GAFF). One review author (SCBN) will transfer data into Review Manager (RevMan) V.5.3.[14] A second review author (RTC) will check the outcome data entries.

The same review author (RTC) 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. To minimise bias in the review process, the review authors will not screen studies for inclusion, extract data, or assess the risk of bias in trials they themselves have authored. In such circumstances, we will involve a third review author (GAFF).

Risk of bias individual studies

Two review authors (SCBN and RTC) will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[15] These authors will resolve disagreements by discussion or by involving another review author (GAFF).

We will assess the risk of bias according to the following domains:

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

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (eg, for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, 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.

If we are able to pool a sufficient number of studies, that is, more than 10 trials,[15] we will create and examine a funnel plot to explore possible small study biases.

Data synthesis

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RR) with corresponding 95% CI and continuous data as mean difference (MD) with 95% CI, or as standardised mean difference with 95% CI 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. This will be identified if there are two or more trials with comparable populations and interventions.

Where a single trial reports multiple trial arms, we will include only the arms relevant to the review question.

All data will be pooled according to age group, dividing them into two groups (adults—over 16 years old, and children—between 5 and 16 years old). After this grouping, the analysis will be done, first, comparing the success rate and failure rate in each of the groups. Subsequently, the data will also be evaluated taking into consideration the weaning outcomes in simple, difficult and prolonged (as described in the types of interventions).

Unit of analysis issues

We do not expect to have any crossover or cluster randomised controlled trials, since weaning is a one-off event and also due to the lack of control group, since all

patients are submitted to the same intervention, which is weaning from mechanical ventilation.

If we are able to find cluster randomised controlled trials with different clusters of different NMD, we will conduct this 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 random-effects results and explore possible causes by prespecified subgroup analysis.

We will be following the rough guide to interpretation outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

- 0%–40%: might not be important;
- 30%–60%: may represent moderate heterogeneity;
- 50%–90%: may represent substantial heterogeneity and
- 75%–100%: considerable heterogeneity.

Data synthesis

If the review includes more than one comparison that 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.
- Weaning success.
- Duration of weaning (time difference between weaning protocol initiation and the moment of extubation moment).
- Duration of ICU stay.
- Duration of hospital stay.
- ICU mortality rate in patients with acute and prolonged mechanical ventilation—defined as the mortality rate during ICU stay.
- Incidence of pneumothorax during mechanical ventilation period.
- Incidence of ventilation associated pneumonia.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence (studies that contribute data for the prespecified outcomes). We will use methods and recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions[15] using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade or upgrade the quality of studies using footnotes, and we will make comments to aid readers' understanding of the review where necessary. Two authors will independently grade the quality of the evidence. They will resolve disagreements by discussion and by consultation with a third review author.

Subgroup analysis and investigation of heterogeneity

- We plan to perform the following subgroup analyses.
- Simple weaning: successful after first attempt.
- Difficult weaning: require up to three attempts.
- Prolonged weaning: require more than 7 days to reach success.
- Children: from 5 to 16 years old.
- Adults: above 16 years old.

We will use both primary and secondary outcome measures in all subgroup analyses. We will use the formal test for subgroup interactions in Review Manager V.5.3.[14]

Sensitivity analysis

We plan to undertake the following sensitivity analyses.

3wRepeat the analysis by excluding studies at high risk of bias (sequence generation, allocation concealment, blinding of personnel, outcome assessment and attrition).

If there are one or more very large trials, we will repeat the analysis by excluding them to examine how much they dominate the results.

Reaching conclusions

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

Patient and public involvement

In the present protocol of systematic review and in the subsequent systematic review, there will be no involvement of patients or public.

The paper proposes to use results previously authorised and published by other authors, without there being any need for patient or public involvement. The research question was developed based on the questions raised by other authors, most of the time according to the clinical difficult and necessity of improving the weaning protocols for this population.

The results of the present study will be published in indexed journal so it can be available for NMD patients, in general, and public, specially health professionals.

CONCLUSION

This systematic review will provide evidence in different weaning protocols that can be applied to the NMD patients, analysing the weaning success rate, leading to extubation. The hypothesis is that one specific protocol has higher success weaning rates.

Where sufficient data are available, we will conduct a meta-analysis to confirm the relationship between the different protocols and duration of weaning, duration of stay in the ICU, duration of hospital stay and ICU mortality. It will also be able to assess adverse effects of weaning protocols that fail to lead to extubation.

Moreover, if the hypothesis is confirmed, the review will clarify the reasons any weaning strategy interfere to higher success weaning rates.

Overall, the review will complement the evidence based on mechanical ventilation weaning for NMD patients.

Contributors SCBN: screen titles, abstracts and full text to identify studies for inclusion or exclusion; extract study characteristics; extract outcome data; transfer data into RevMan; assess risk of bias. RTC: screen titles, abstracts and full text to identify studies for inclusion or exclusion; extract outcome data; check outcome data entries; spot-check study characteristics for accuracy; assess risk of bias. IL: development of the text; statistical analysis and revision of the final text. VRR: development of the text; statistical analysis, revision of the final text. GAFF: discussion about the disagreements the two authors have in any issues; screen studies the other two authors have authored.

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Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Search strategy for MEDLINE

1 - exp Neuromuscular Diseases/co, di, mo, nu, pa, ph, pp, pc, rh, th [Complications, Diagnosis, Mortality, Nursing, Pathology, Physiology, Physiopathology, Prevention & Control, Rehabilitation, Therapy]

2 - Myotonic Dystrophy/ or Muscular Dystrophy, Duchenne/ or dystrophy.mp. - 46861

3 - muscular dystrophy.mp. or exp Muscular Dystrophies/ - 32736

4 - Myasthenia Gravis/ or myasthenia.mp. - 17216

5 - congenital myasthenia.mp. or exp Myasthenic Syndromes, Congenital/ - 654

6 - myopathy.mp. or *Muscular Diseases/ - 31947

7 - Myopathies, Structural, Congenital/ or congenital myopathy.mp. - 1225

8 - inflammatory myopathy.mp. or *Myositis/ - 7195

9 - metabolic myopathy.mp. or Mitochondrial Myopathies/ - 1972

10 - pompe disease.mp. - 1063

11 - spinal muscular atrophy.mp. or exp Muscular Atrophy, Spinal/ - 6338

12 - Polyradiculoneuropathy/ or exp Guillain-Barre Syndrome/ or guillian barre.mp. or Polyneuropathies/ - 13731

13 - Peripheral Nervous System Diseases/ or severe inherited neuropathy.mp. - 22861

14 - amyotrophic lateral sclerosis.mp. or exp Amyotrophic Lateral Sclerosis/ - 24339

15 - 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 - 270807

16 - Positive-Pressure Respiration/ or Respiration, Artificial/ or Ventilator Weaning/ - 65155

17 - Weaning/ or weaning.mp. - 33982

18 - Airway Extubation/ or spontaneous breathing trial.mp. - 1798

19 - 16 or 17 or 18 - 95029

20 - 15 and 19

Search strategy for EMBASE

#1 - 'neuromuscular disease' OR 'muscular dystrophy' OR myasthenia OR myopathy OR 'glycogen storage disease type 2' OR 'muscle atrophy' OR polyradiculoneuropathy OR 'peripheral neuropathy' OR 'amyotrophic lateral sclerosis' - 159,527

#2 - 'artificial ventilation' OR 'ventilator weaning' OR extubation OR 'spontaneous breathing trial' - 5,215

#3 - #1 AND #2 AND [2009-2020]/py

Search strategy for WEB OF SCIENCE

#1 - Todos os campos: (neuromuscular disease) OR Todos os campos: (muscular dystrophy) OR Todos os campos: (myasthenia) OR Todos os campos: (myopathy) OR Todos os campos: (glycogen storage disease type 2) OR Todos os campos: (muscle atrophy) OR Todos os campos: (polyradiculoneuropathy) OR Todos os campos: (peripheral neuropathy) OR Todos os campos: (amyotrophic lateral sclerosis) Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=2009-2020 - 100.078

#2 - Todos os campos: (artificial ventilation) OR Todos os campos: (ventilator weaning) OR Todos os campos: (extubation) OR Todosos campos: (spontaneous breathing trial) Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=2009-2020 - 9.840

#3 - #1 AND #2 - Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=2009-2020

Search strategy for SCOPUS

('artificial AND ventilation' OR 'ventilator AND weaning' OR extubation OR 'spontaneous AND breathing AND trial') AND ('neuromuscular AND disease' OR 'muscular AND dystrophy' OR myasthenia OR myopathy OR 'glycogen AND storage AND disease AND type AND 2' OR 'muscle AND atrophy' OR polyradiculoneuropathy OR 'peripheral AND neuropathy' OR 'amyotrophic AND lateral AND sclerosis') AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009))

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Sup.2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	N/A
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	N/A
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13-14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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