

BMJ Open 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 (ICU) and hospital stay and mortality.

Design Systematic review.

Data sources Electronic databases (MEDLINE, EMBASE, Web of Science and Scopus) were searched from January 2009 to August 2020.

Eligibility criteria for selecting studies Randomised controlled trials (RCTs) and non-RCT that evaluated patients with NMD (adults and children from 5 years old) in the weaning process managed with a protocol (pressure support ventilation; synchronised intermittent mandatory ventilation; continuous positive airway pressure; '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 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 patients with NMD 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.

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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} NMDs 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 acute and chronic respiratory failure, which

Strengths and limitations of this study

- The review highlighted the lack of specific protocols for mechanical ventilation weaning in patients with neuromuscular disease.
- Observational and retrospective studies are the most common for patients with neuromuscular disease on ventilator weaning.
- After the search, it was not possible to determine the most interesting and efficient weaning protocol for this population.
- Non-invasive ventilation is described as a promising resource for patients with neuromuscular disease after mechanical ventilation.

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 and (3) upper airway compromise.⁷⁻⁹ The patients with NMD 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 intensive care unit (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, 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);



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or progressive decline in maximal inspiratory pressure (<20–30 cm H₂O).^{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 hospitalisation, 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 cm H₂O.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

Postweaning 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 (respiratory rate) >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

The review authors followed the Cochrane Handbook for Systematic Reviews of Interventions¹⁷ and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 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 an NMD (muscular dystrophy of any origin including Duchenne muscular dystrophy, amyotrophic lateral sclerosis (ALS), congenital myasthenia, myasthenia gravis, congenital myopathy, spinal muscular atrophy, Guillain-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 spontaneous breathing trial (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. 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.

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 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 on the highest quality of evidence, we only considered including randomised controlled trials (RCTs) and non-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 1 January 2009 up to 31 August 2020: Cochrane Neuromuscular Specialised Register (The Cochrane Library, current issues), MEDLINE, EMBASE, Web of Science and Scopus. We also searched the US National Institutes of Health Clinical Trials Registry, ClinicalTrials.gov (ClinicalTrials.gov) and the WHO International Clinical Trials Registry Portal (apps.who.int/trialsearch/). Predating 2009 were deemed to be irrelevant to the current experiences of mechanical ventilation weaning for NMD due to considerable changes in these patients management over recent decades.

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’, ‘Guillain 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 supplemental file 1.

Study selection

Two review authors (SCGBN and IL) performed the search. Two review authors (SCGBN and RT-C) 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 difficulty and necessity of improving the weaning protocols for this population. The results presented are available in the publication for patients with NMD 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 patients with NMD receiving mechanical ventilation for respiratory failure. A flow chart shows the detailed process of selection (figure 1).

Although 24 studies were selected to full-text reading, none met the eligibility criteria. The excluded publications comprised 2 non-randomised studies,^{20 21} 6 observational studies,^{22–27} 11 retrospective studies,^{4 12 16 28–35} 2 narrative reviews^{36 37} and 3 letters to the editor.^{38–40} The non-randomised studies were not included as eligible despite having a control group, because they did not compare different weaning protocols. In both cases, patients with NMD were submitted to pressure support weaning protocol and the outcomes measured were different from those included in the methods. These two articles are presented in the Discussion section below due to relevant information.

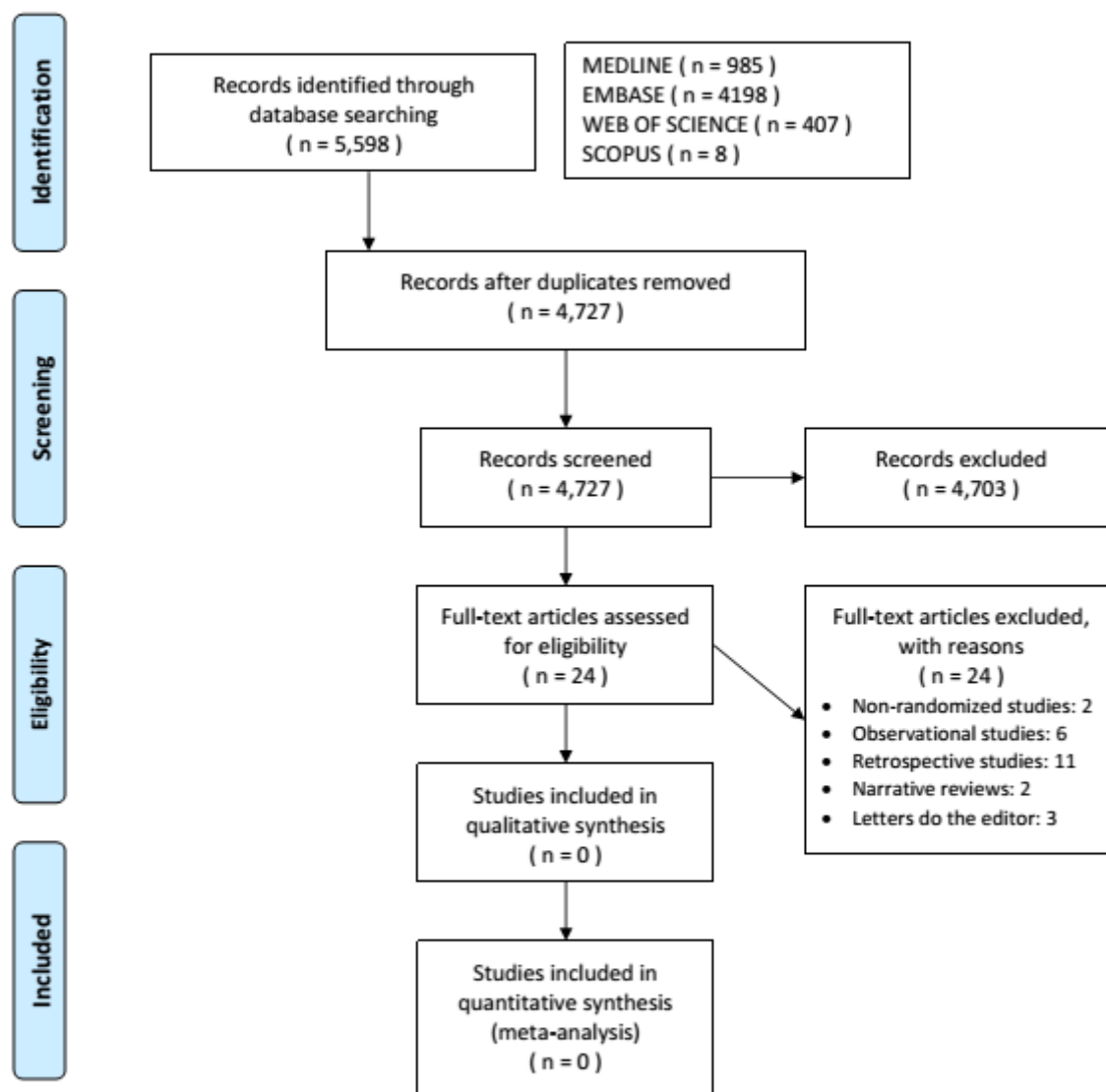
DISCUSSION

We found no high-quality evidence either for or against any of the weaning protocols proposed (pressure support ventilation (PSV), synchronised intermittent mandatory ventilation (SIMV), continuous positive airway pressure (CPAP), or ‘T’ piece) in patients with NMD under mechanical ventilation.

Sun *et al*²⁰ investigated patients with myasthenia gravis crisis who were hospitalised 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 SBT 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



PRISMA 2009 Flow Diagram



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For more information, visit www.prisma-statement.org.

Figure 1 Flow chart showing publication selection.¹⁸ PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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 min from the beginning of the SBT, the authors reported that there was a statistically

significant increase in the RSBI compared with the initial 5 min ($80.41 \times 57.29, p=0.029$), as well as a reduction in the DTF ($24.46 \times 61.89, p=0.000$) 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 SBT, can be a predictive value for the success or failure of weaning.

Vianello *et al.*²¹ 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 mechanical ventilation (MV) for >48 hours and who underwent a weaning protocol with a gradual reduction in support pressure. The authors compare the use of non-invasive ventilation (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 $PS < 8$ cm H₂O 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 ($30\% \times 100\% - p=0.002$) and tracheostomy ($30\% \times 90\% - p=0.01$) 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.²¹

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 patients with NMD, 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 with late extubation (>6 hours).³³ Another interesting factor associated with prolonged mechanical ventilation and tracheostomy prolonged need in these patients is neurogenic dysphagia.³⁴ 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.³⁵

The observational prospective studies without control group showed that non-invasive ventilation initiated after spontaneous breathing cycles for Guillain-Barré Syndrome patients under MV is a potential therapeutic strategy.²³ And the study that observed the comparison between different five 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).²⁵

Two prospective studies with different groups, that were not included because they did not evaluate weaning protocols, attempted to compare prognostic factors of weaning in patients with ALS²⁴ and the ability to prevent atelectasis after extubation with respiratory physiotherapy.²⁷ In the

first, it was observed that tracheostomy and use of MV was associated with longer survival, compared with 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.²⁴ The other study demonstrated, with randomised groups, that a postextubation chest physiotherapy protocol decreased the incidence of atelectasis in paediatric patients with NMD.²⁷

According to the other studies observed during the search, weaning has been studied and applied to this population in the 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 21 23} 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 21 41} This observation was also described even for prolonged MV patients with NMD.²³

Although NIV has been described as an excellent alternative for weaning in patients who fail in the conventional conditions for evaluating weaning³⁶ (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.*²⁶ 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 due to impaired respiratory muscle strength and bulbar dysfunction. Traditional methods of assessing the progression of weaning and extubation have important limitations in determining these changes. Craig *et al.*²³ 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.

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

patients with NMD. The guidelines about ventilatory support management for patients with NMD should be more explicit and clear about the basis of the recommendations regarding weaning protocols.

Implications for research

Given the high incidence of patients with NMD requiring mechanical ventilation for acute or chronic respiratory failure,^{10 11} there is a lot of space for RCTs, with high methodological rigour 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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