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Effect of mechanical insufflation-exsufflation for ineffective cough on weaning duration in diseases of the peripheral or central nervous system (MEDINE): study protocol for a randomised controlled trial in a neurological weaning centre

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ABSTRACT

Introduction Patients with neurological or neurosurgical disease can suffer from impaired cough, which may result in life-threatening retention of tracheobronchial secretions, atelectasis, pneumonia and finally death. Due to a lack of alternatives and pathophysiological plausibility, the application of mechanical insufflation-exsufflation (MI-E) has already become international standard care in neuromuscular disease and spinal cord injury although a lack of evidence for efficacy. High-quality studies to support the use of MI-E in neurological and neurosurgical patients during weaning from mechanical ventilation are missing. The goal of this exploratory study is to display the effect size of MI-E intervention on the duration of mechanical ventilation and additional outcomes.

Methods and analysis One hundred adult patients with a cough deficiency or retention of secretion admitted to a neurological intensive care unit (ICU) are planned to be recruited for this randomised controlled trial. Patients are randomised 1:1 to receive either MI-E or best standard care. Observation will take place until discharge from the hospital, death or end of the study period. The primary endpoint of this trial is the duration of mechanical ventilation from randomisation until successful weaning. The outcome will be analysed with Kaplan-Meier estimation and competing risks analyses. Secondary endpoint is the proportion of patients with successful weaning. Further outcomes will include the incidence of hospital-acquired pneumonia, mortality, decannulation rate, length of stay on the ICU and the total score of the Glasgow Coma Scale.

Ethics and dissemination The study was approved by the Medical Ethics Committee of the University of Oldenburg. The findings of this study will be submitted for publication in a peer-reviewed journal.

Trial registration number DRKS00020981.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Weekly visits by the trial management group on the ward promote earliest possible inclusion and randomisation of the patients after admission to the neurological intensive care unit.
⇒ Due to randomisation and blinding of the data analysts, the risk of confounding is reduced and the internal validity of the study is increased.
⇒ Due to uncertainty regarding the effect size, no formal sample size estimation was conducted for this pilot study.
⇒ Treatment arms are not blinded.

INTRODUCTION

In Germany, there is a capacity of about 1100 beds for weaning patients from mechanical ventilation in a neurological-neurosurgical early rehabilitation setting.[1] Severely affected neurological patients often suffer from cough insufficiency, either due to muscular weakness or impaired cough reflex. Ineffective cough can result in life-threatening retention of secretion, atelectasis and pneumonia.[2] Comorbid dysphagia aggravates the retention of secretions; and even the presence of a cuff-securing endotracheal tube or tracheal cannula does not completely prevent aspiration of saliva.[3]

Due to a lack of alternatives in the management of insufficient cough and retention of secretion, the application of mechanical insufflation-exsufflation (MI-E) in patients with neuromuscular disease or spinal cord injury has become an international standard. Although MI-E has been demonstrated to be

safe in use for ventilated patients with or without tracheotomy,[4] there is only weak evidence for efficacy.[5] Very few studies have been conducted and some of these have been found to have a high risk of bias.[6] In a retrospective cohort study, the use of MI-E reduced the incidence of ventilator-associated pneumonia.[7] However, the focus was on critically ill patients in general and not on long-term ventilated patients with neurological diseases. In a lung-simulation study, it was demonstrated that MI-E can move mucus out of the respiratory system.[8] In a randomised crossover trial, it was shown that the use of MI-E in combination with expiratory rib cage compressions (ERCC) cleared a higher volume of sputum than ERCC alone.[9] However, there seems to be no study focusing on patients with cough insufficiency due to cerebral disease or critical illness polyneuropathy/critical illness myopathie, which are the conditions found in neurological and neurosurgical early rehabilitation.[10] Specifically, there is no study yet that explores the MI-E effect on patient outcomes such as the duration of ventilation or the stay on intensive care units (ICUs).

In our neurological intensive care unit (NICU), we established the application of MI-E for all patients with cough insufficiency with retention of secretion with and without mechanical ventilation via either invasive airway or mask.

Objectives

The primary objective of the trial is to estimate the effect of MI-E on the duration of ventilation for neurological patients with neurological or neurosurgical illnesses in intensive care and early rehabilitation units. The secondary objective is to estimate the effect of MI-E on the chance of successful weaning. Other secondary objectives are comparisons of hospital-acquired pneumonia, mortality, decannulation, length of stay in the ICU and the total score of the Glasgow Coma Scale.

Trial design

The study is designed as a single-centre randomised controlled study. The study has two study arms and is open-label. The primary endpoint is duration of ventilation measured from randomisation until successful weaning. Patients treated at a NICU are eligible for inclusion. Participants are randomised to receive either standard care or standard care with MI-E in addition. Randomisation will be performed as block randomisation with a 1:1 allocation. Patients will be observed from randomisation until death, discharge from the hospital or end of study on 16 April 2025, whatever occurs first. Transfers into other hospitals for specific procedures are expected in about 10% of the patients. MI-E will not be continued in other hospitals. Therefore patients, who are transferred to another hospital, but readmitted to our hospital within 4 days, will continue to take part in the study. If a patient is not readmitted within 4 days, the participant will be treated as if discharged from our hospital.

METHODS AND ANALYSIS

This protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[11]

Study setting

The NICU is part of a certified centre for weaning from mechanical ventilation, certified in neurological and neurosurgical early rehabilitation by the German Society for Neurorehabilitation.

Study participants

Adult patients treated at the NICU will be considered for inclusion. Participants must fulfil the following two inclusion criteria: First, the patient is suffering from a severe neurological or neurosurgical disease, defined by a score of less than 35 points in the Early Rehabilitation Barthel Index.[12] Second, there is a cough insufficiency and/or retention of secretion. Cough insufficiency is identified by peak cough flow of less than 270 L/min, non-cooperative patients, or when the item 'cough to suction' on the airway care score (ACS; see table 1) is less than moderate (score of this item greater than 1).[13] Retention of secretion is diagnosed when the total score of the ACS is greater than 7.[14]

Exclusion criteria are underage patients, bullous emphysema, the presence of pneumothorax during current clinical treatment, or an unstable sternum. Patients with amyotrophic lateral sclerosis as well as other progressive neuromuscular disorders and paraplegia will also be excluded. Patients with continuous intravenous sedation, orally intubated patients, and patients expected to die during intensive care treatment are excluded as well.

To guarantee for earliest possible inclusion and randomisation of the patients after admission to the NICU, the daily clinical patient visits are augmented by visits by the trial management group taking place once per week.

Table 1 Airway care score as shown in Tanwar *et al* (p86),[13] distributed under a CC-BY-NC-SA 4.0 license

Grading	Cough to suction	Sputum quantity	Sputum character	Sputum viscosity	Suctioning frequency
0	Vigorous	None	Clear	Watery	>3 hours
1	Moderate	1 pass	Tan	Frothy	Every 2–3 hours
2	Weak	2 passes	Yellow	Thick	Every 1–2 hours
3	None	≥3 passes	Green	Tenacious	<Every 1 hour

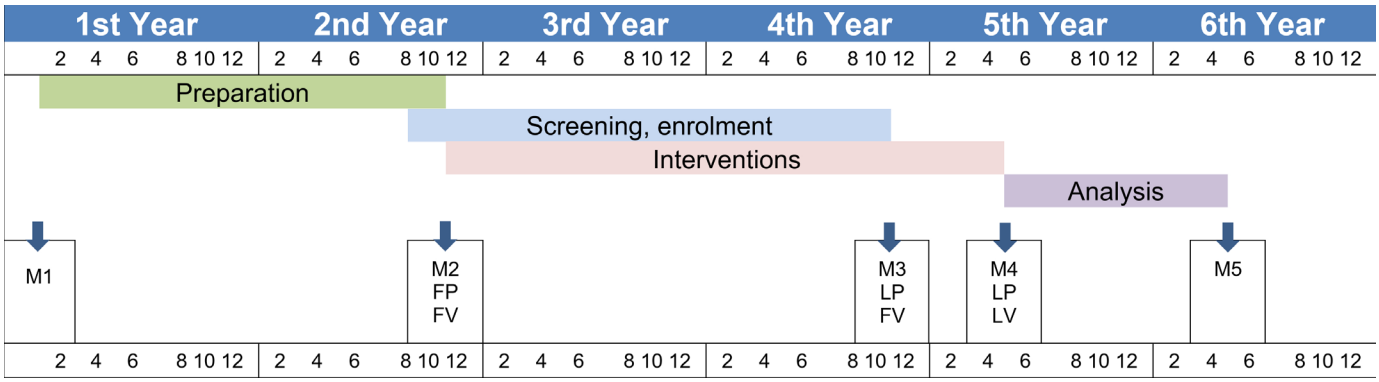

Figure 1 Time flow (months) and milestones (M1–M5) of the study. M1: ethics submitted; M5: end of study. C, completed; FP, first patient; FV, first visit; LP, last patient; LV, last visit.

Intervention and standard care

Application of the MI-E device Cough Assist E70 (Koninklijke Philipps N.V., Amsterdam, Netherlands) will be carried out in the interventional group using the established clinical standards.[2] The MI-E first supplies the patient with positive pressure, via endotracheal tube, tracheal cannula or mask, and consecutively the lungs are inflated. The device then builds up negative pressure, which extracts the air from the lungs, thereby removing secretions from the airways. MI-E will be applied once per shift in a three shifts per day system and additionally by patient needs. The following standard settings are used: insufflation pressure: 40–50 cmH_2O, exsufflation pressure: 50–60 cmH_2O, insufflation time: 1.5–2.0 s, exsufflation time: 1.5–2.0 s and pause: 1.5–2.0 s. Three cough cycles are applied, and the procedure is repeated until tracheobronchial secretions are eliminated. The settings are adapted to the clinical situation comprising tolerance by the patient and achieved tidal volume. The definitive settings will be published along with the results of the study. Adherence to the study protocol was fostered by training of the clinical staff, including senior physicians (anaesthesiologists, neurologists and intensivists) and providing training materials such as an overview of inclusion criteria, a study description and a flowchart of the recruitment procedure. Furthermore, all treatment data were collected from the mechanical insufflator-exsufflators every 2 weeks.

Both the intervention group and the control group will receive standard care that is commonly used in intensive care medicine.[2 15] Standard care consists of different methods to reduce the amount of secretion in the airways or to remove the secretion from the airways:

- Administration of drugs that reduce the amount of saliva.
- Humidification of the inhaled air.
- Physiotherapy and daily mobilisation.
- Secretion management including suction of secretion.
- An additional suction possibility above the cuff of the tracheal cannula (subglottic suctioning).

These treatment options will be applied to the participants depending on their individual needs.

Outcomes

The duration of ventilation in days from randomisation until successful weaning is the primary endpoint and the proportion of successful weanings represents the secondary endpoint. Weaning is defined as successful when the participant has not been ventilated for more than 48 hours.[16] Further outcomes are:

- The proportion of hospital-acquired pneumonia.
- Mortality.
- The duration of intensive care stay in days since randomisation until end of observation.
- The proportion of decannulation.
- A change in the total score of the Glasgow Coma Scale[17] from admission to discharge.

Timeline

An overview of the study timeline is given in figure 1. Recruitment is planned to be carried out for a period of 2 years. As early as possible after admittance to the NICU, it is checked if a patient fits the inclusion criteria. If no exclusion criteria apply either, informed consent will be retrieved and the patient will be included in the study. The first patient has been included in the study on 17 October 2022.

Sample size

Due to uncertainty concerning the expected effect size, we will conduct the study as a pilot trial and elect to forego a formal sample size estimation. A further study with up to 1000 patients is planned if this trial suggests sufficient effect sizes of MI-E on the duration of ventilation. By following a general recommendation for pilot trials of recruiting at least 9% of the number of cases in the following confirmatory trial,[18] a sample size of 100 patients is selected for MEDINE.

Randomisation, allocation concealment and blinding

Assignment to study arms will be carried out with permuted block randomisation. Block sizes will be random (either 4 or 6) and investigators will be blinded to the size of each block. R[19] will be used to create a list with block randomisation for 120 patients. This list will be

imported into the programme Research Electronic Data Capture (REDCap),[20] a data capture tool. The hospital staff is blinded with respect to the list in REDCap.

After enrolment and assignment of the study arms, patients and medical staff will not be blinded. However, researchers conducting the data analysis are not part of the patient's treatment and will be blinded. The data analysts will only receive pseudonymised data through REDCap and will have no direct access to patient data.

Due to the complex nature of the weaning process, stratification according to expected confounders is not possible. Confounders will be identified through collecting a comprehensive set of clinical data on sex, age, diagnosis, comorbidities, disease severity, neurological state, diagnostic findings, mechanical ventilation and complications on inclusion and every 2 weeks until discharge. Potential confounders will be assessed at baseline and will be compared between treatment groups. All potential confounding factors will be included as a covariate factor in the statistical analysis.

Data collection and management

REDCap 11.1.17 will be used for data capture. REDCap is a browser-based electronic data capture tool for clinical research databases. The IT-infrastructure of the participating university includes the following components:

- Two virtual servers with the firmware 'Red HAT' (for the Apache-Webserver—one for the development instance and one for the product instance).
- Two MySQL databases (for saving all project data and user data).
- LDAP protocol (for user authentication).
- Network drive (for saving uploaded data of the user and also backups).

For each new included participant, a new electronic case report will be created in REDCap. The electronic case report forms are equipped with an audit trail. An identification number will be generated for every care report that will be used for pseudonymisation. The name of the patient and the ID will be written on a list that only the clinical principal investigators have access to. Only the ID is used when data are entered in REDCap and researchers responsible for data analysis only have access to the pseudonymised data in REDCap.

This pseudonymisation list will be stored at the hospital in a locked cabinet. The principal investigators are responsible for keeping the pseudonymisation list in compliance with data protection regulations and for destroying the list after the retention period has expired.

Statistical analysis

The main response variable is duration of mechanical ventilation. The variable is right censored with competing risks (death, transfer to other health facilities). For a first description of the response variable, Kaplan-Meier estimators will be calculated, comparing the intervention groups for the whole sample and for further subgroups, regarding illness, sex and other grouping variables. The main analysis will be performed using the Fine-Grey Model in case of proportional subdistribution hazards[21] and by usage of Accelerated Failure Time Models[22] in case of non-proportional hazards. For the estimation of the main effect size, we will use bivariate regression models, parsimonious models after variable selection and fully saturated models. Further exploratory analyses will also be conducted. The analysis of further endpoints will be descriptive.

Protocol violations

In some cases, MI-E may be used on patients in the control group if there is an urgent medical indication. The decision to use MI-E on a patient in the control group will be determined by the local clinical physicians. The change in treatment will be recorded and considered during the analysis. Data will be analysed on an intention-to-treat basis, with all patients included according to their assignment. Per-protocol analyses will be performed as sensitivity analyses. Crossover of patients from the treatment to the control group is not expected.

Premature termination of the study

Because of the severe condition that the study participants are in, death is expected in up to 30% of all patients.[23] After the occurrence of 20 fatal events, a masked statistical safety evaluation will be conducted. Overall survival will be analysed with a Kaplan-Meier estimator, a Cox proportional-hazards model, and a log-rank test with a significance level of 0.2. Here, a higher type I error is tolerated to reduce the type II error, which is assumed to be more important in this context. The resulting power in dependence of the HR between treatment and control group is shown in figure 2. In case of significance, the principal investigators will be informed and further exploratory analyses will be done, including an analysis of efficacy. The principal investigators will decide if the study should be continued based on the safety and efficacy analyses, using unmasked data.

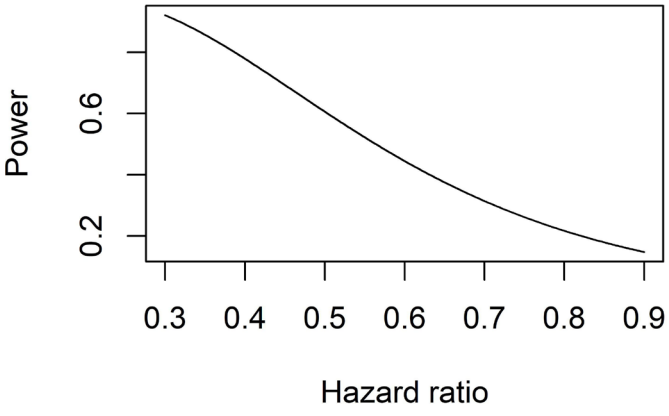

Figure 2 Power of the log rank test, comparing overall survival between treatment and control after 20 events have occurred.

Harms

Since no sufficient scientific data are available to date to prove the benefit of therapy with the MI-E, the risk of not receiving this therapy due to assignment to the control group cannot be quantified. Participants in the control group may have a poorer ability to mobilise secretions from the airways, and thus may require artificial ventilation for a longer period. They also may experience more frequent hospital-acquired cases of pneumonia. Treatment with MI-E is generally safe and well tolerated by patients. In isolated cases, pneumothorax has been reported to occur as a result of treatment.[24] Pneumothorax may require the use of a drain to remove air that has leaked from the lung from the chest.[25] No information on the frequency of this air leak has been provided in literature.

Adverse events will be monitored continuously and categorised by severity. In the case of a suspected unexpected serious adverse reaction, principal investigators will examine the case and notify the ethics committee. Serious adverse events will include events that threaten recovery and prolong treatment in the ICU as well as death.

Clinical trials insurance is not necessary because MI-E is an established clinical method covered by the liability insurance of the Evangelisches Krankenhauses Oldenburg.

Patient and public involvement

Due to the severe medical conditions examined, involvement of the patients was not possible. There was no public involvement in planning the study either.

ETHICS AND DISSEMINATION

Ethical considerations

The study was approved by the Medical Ethics Committee of the University of Oldenburg with the trial identifier 2021-008 and registered with the German registry of clinical trials. All participants will be individually informed about the study and will only participate in the study if they or their legal representatives have given written consent. The participants' protocols and patient consent form were approved by the responsible medical ethics committee. Besides, the study complies with the requirements of the Declaration of Helsinki.[26] The clinical investigators hold certificates in good clinical practice.

Dissemination

The results of this study will be presented at scientific conferences and in peer-reviewed journals, regardless of the trial outcome. No later than 2 years after conducting the main analysis, we will deliver a completely deidentified data set to an appropriate data archive for sharing purposes.

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Contributors MG and OS conceived the overall study idea. AT, MG, OS, FO-S and AS planned the study. AK planned the data management. TG designed the eCRFs. AT, MG, OS, TG, FO-S and AK are the steering committee of the study. The data management committee comprises AT, FO-S, AK and TG. TG, OS and MG form the trial management group. All authors have contributed to the manuscript. AK, AS, TG and MG drafted the initial manuscript. AT, MG, OS, FO-S and TG revised the manuscript. All authors have approved the final version of the manuscript.

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Competing interests None declared.

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

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