A Randomized, Sham Controlled, Double-blinded, Multi-center Trial to Evaluate the Efficacy of the VentFree Respiratory Muscle Stimulator to Assist Ventilator Weaning in Critically Ill Patients

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56776

Source
ToetsingOnline

Brief title
PREVENT

Condition

- Other condition
- Respiratory disorders NEC

Synonym
weaning from mechanical ventilation; reduced ventilation time

Health condition

Invasive mechanical ventilation, critical illness

Research involving
Human

Sponsors and support

Primary sponsor: Liberate Medical
Source(s) of monetary or material Support: Liberate Medical

Intervention

Keyword: abdominal muscle stimulation, mechanical ventilation, respiratory muscle stimulation, ventilator weaning

Outcome measures

Primary outcome

The primary endpoint is the time from first FES treatment administration to

successful liberation. For more details and definitions, see Protocol paragraph

10.2.2.

Secondary outcome

Key secondary endpoints in this study are:

1. Cough peak flow (24 hours post extubation)

2. Maximum expiratory pressure (24 hours post extubation)

Other secondary endpoints in this study are:

1. Incidence of device-related adverse events (hospital discharge)

2. Time from first FES treatment administration to ICU discharge

3. Time from first FES treatment administration to hospital discharge

4. Incidence of patients who were successfully liberated from mechanical

ventilation (day 28 or ICU discharge, whichever comes first)

5. Incidence of reintubations (ICU discharge, 90 days post treatment)

6. Incidence of readmissions to the ICU (90 days post treatment)

7. Incidence of readmissions to the hospital (90 days post treatment)

8. Incidence of acute respiratory infections (hospital discharge)

9. Incidence of hospital acquired infections (hospital discharge)

10. Incidence of tracheostomy (ICU discharge)

11. Mortality (hospital discharge, 90 days post treatment)

12. Maximum inspiratory pressure (24 hours post extubation)

13. Mobility as assessed by the ICU Mobility Scale (ICU discharge)

14. Quality of life as assessed by EQ-5D-5L (90 days post treatment)

Study description

Background summary

Mechanical ventilation is used as a life-saving intervention for conditions such as acute respiratory failure, coma, and acute exacerbation of COPD. Unfortunately, mechanical ventilation can also cause life-threatening complications including barotrauma, ventilator associated pneumonia, muscle atrophy and psychological conditions. The probability of survival decreases in line with number of days of ventilator support. Hospital mortality is almost double in those patients who take more than 7 days to wean from ventilator support when compared to patients who require less. Furthermore, prolonged periods in the ICU result in reduced functional status and increased mortality up to one year after discharge.

In the US, the number of patients requiring mechanical ventilation for more than four days (i.e. prolonged mechanical ventilation) is rising at a rate of 5.5% per year - a rate that is more than four times greater than the overall increase in hospitalizations (1.2%). Patients who require prolonged mechanical ventilation require more than double the resources needed than patients who require short term mechanical ventilation (approximately $55,000 vs $22,000) and are estimated to cost the US health care system $30 billion per year. Accordingly, treatments aimed at reducing the duration of mechanical ventilation have the potential to benefit patients, by reducing morbidity and mortality and improving quality of life, and to benefit society, by reducing ICU, inpatient and community health care costs.

After the pathology responsible for the institution of mechanical ventilation has resolved and when patients are clinically stable, the current standard of care is to conduct a weaning trial, consisting of a period of completely unsupported breathing (e.g. T-tube trial) or a period of minimal ventilator support (e.g. pressure support ventilation, or PSV). If the patient does well during the weaning trial he/she can be considered for extubation; otherwise, the patient is returned to the ventilator. When patients do not pass the first weaning trial then either daily spontaneous breathing trials (SBT) or a gradual reduction in PSV is implemented. The rationale of these strategies is to recondition the respiratory muscles weakened during the preceding pre-weaning period of mechanical ventilation. The duration of mechanical ventilation for patients who do not pass the initial weaning trail can last between days and months. In the most severe of cases, patients are never liberated from mechanical ventilation. Therefore, novel interventions designed to reduce the duration of mechanical ventilation are sorely needed.

Often, the initial clinical assessment to identify readiness to wean is delayed, exposing patients to unnecessary discomfort of mechanical ventilation and increased risk of ventilator-associated complications.

ICU acquired weakness is common among patients who receive mechanical ventilation and primarily affects the respiratory and peripheral muscles. In about 40% of patients, there is a rapid loss of diaphragm mass during the first five days of mechanical ventilation, which results in a large reduction in its force production. Similarly, approximately 30% of patients experience a rapid loss of lateral abdominal muscle mass during the first week of mechanical ventilation. As such, these patients experience considerable expiratory muscle weakness.

Expiratory muscles play an important role in patients who have difficulty weaning from mechanical ventilation. For example, maximum expiratory pressure (MEP), the reference standard measure of expiratory muscle strength, is an independent predictor of weaning success and delayed extubation. In addition, an effective cough, which is dependent on expiratory muscle strength and measured using cough peak flow (CPF), assists in the prediction of weaning success, morbidity and mortality. Though the abdominal muscles are expiratory muscles, their function also affects inspiration as they play an important role in optimizing the neuromuscular coupling of the diaphragm, enhancing the load-capacity balance of the muscle. Therefore, improvements in expiratory muscle strength have the potential to reduce the duration of mechanical ventilation and increase the probability of successful liberation from it.

Inspiratory muscle training using a threshold loading device is currently the only available therapy that targets respiratory muscle atrophy in mechanically ventilated patients. It has been shown to improve inspiratory muscle strength and weaning success in patients who have otherwise failed to wean from mechanical ventilation. Unfortunately, inspiratory muscle training depends on

patient motivation and cooperation. Therefore, this volitional technique is often not suitable for use in the ICU, where patients are commonly sedated, delirious, paralyzed, or cognitively impaired. Transvenous phrenic nerve pacing is currently being studied as potential intervention for improving diaphragm strength in difficult-to-wean patients (NCT03096639) and could be utilized in sedated patients. Unfortunately, there are currently no available therapies that target expiratory muscle atrophy in mechanically ventilated patients.

Neuromuscular electrical stimulation (NMES) applies small electrical pulses to the motor nerves supplying a muscle to elicit a contraction. NMES of the proximal muscles can preserve muscle mass and strength. When NMES is applied to the abdominal wall muscles in synchrony with exhalation (so called abdominal functional electrical stimulation [FES]), the effect on ventilation is like a physiological contraction of the abdominal wall muscles. An important advantage of using FES with critically ill patients is that it can be used to recruit the abdominal wall muscles in the absence of patients* voluntary or automatic recruitment of those muscles.

Previous studies have shown that abdominal FES can acutely improve respiratory function and provide a training effect to the respiratory system. When used over a period of time, the repeated application of abdominal FES results in a lasting improvement in unassisted (i.e., without abdominal FES) forced vital capacity (FVC), forced exhaled volume in one second (FEV1), peak expiratory flow (PEF), and MEP. In a pilot study including 11 mechanically ventilated patients with tetraplegia, a training program of abdominal FES increased tidal volume and reduced weaning duration (compared with historical controls).

We propose to investigate FES of the abdominal wall muscles in synchrony with the expiratory phase of breathing in patients requiring mechanical ventilation. This intervention, also referred to as abdominal functional electrical stimulation (or FES), was recently commercialized into a novel medical device called the VentFree Respiratory Muscle Stimulator (Liberate Medical, LLC).

Study objective

The primary objective of the trial is to determine whether abdominal FES reduces the duration of invasive mechanical ventilation in critically ill adult patients compared to a sham control.

The secondary objectives are to determine whether abdominal FES increases the strength of the respiratory muscles, improves quality of life after discharge and reduces reintubations, hospital acquired infections, hospital and ICU length of stay and 90-day readmissions.

Study design

This is a randomized, sham controlled, double-blind multicenter global clinical trial to evaluate exhalation synchronized abdominal FES in critically ill invasively ventilated patients. Eligible participants will be randomized 1:1 to the VentFree Respiratory Muscle Stimulator or a sham treatment. FES or sham treatment will be applied as an adjunct to standard of care.

Intervention

All participants will receive exhalation synchronized abdominal FES for 30 minutes twice per day, for a minimum of five days per week, for 28 days or Intensive Care Unit (ICU) discharge, whichever comes first. In the VentFree treatment group, FES will be applied with a frequency of 30 Hz and a pulse width of 350 µs. The stimulation amplitude will be set to 90% of the participant*s maximum tolerable level. The sham group will receive FES applied with the same frequency and pulse width as the VentFree treatment group, but with a stimulation amplitude set at 10 mA or less so that no muscle contraction is seen.

Study burden and risks

Potential risks associated with VentFree Respiratory Muscle Stimulator include: skin irritation, muscle soreness, temporary increase in the work of breathing, electrical shock, ventilator asynchrony, respiratory muscle injury or fatigue, and electrode burns. Potential risks to VentFree operators include electrical shock.

Participants in the VentFree pilot studies experienced the following non-serious adverse events that were possibly related to the intervention with VentFree: increased MAP, increased respiratory rate and heart rate, decreased oxygen saturation, and discomfort. Participant discomfort was additionally reported twice in one patient and was considered to be definitely related to VentFree. None of these adverse events resulted in injury to the participant.

As with all investigational medical devices, the long-term results of using the VentFree Respiratory Muscle Stimulator are not known at the present time.

Exhalation synchronized abdominal stimulation could be a safe and effective method of improving respiratory function in mechanically ventilated patients and reducing mechanical ventilation duration and dependency. Previous research has demonstrated the feasibility and safety of this intervention in the critically ill patient. Furthermore, the patient will be monitored continuously in a controlled ICU environment and FES will be performed by a researcher experienced with this technique. Therefore, potential risks can be identified early and anticipated upon early, if necessary. The burden to participation is considered minimal especially since we are studying a potential treatment effect and patients with contra-indications / high risks for FES will be

excluded from participation (see exclusion criteria).

Risks associated with participation in the clinical investigation include loss of confidentiality. All protected health information will be secured to the extent possible according to applicable law.

It is not anticipated that there will be any interactions with concomitant medical treatments.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Participant is >= 22 years of age.
2. Participant has been receiving invasive mechanical ventilation for >= 24

hours prior to enrollment.

Exclusion criteria

1. Participant has been receiving invasive mechanical ventilation for > 96 hours.
2. Participant is scheduled or expected to be disconnected from mechanical ventilation <= 24 hours after enrollment.
3. Participant was intubated for >= 24 hours during a prior episode of invasive mechanical ventilation during current hospitalization.
4. Participant has a BMI =>40 Kg/m2.
5. Participant has no contraction of the abdominal wall muscles in response to abdominal FES as determined by ultrasound.
6. Participant has a pre-existing neuromuscular or muscular disorder that could affect the respiratory muscles (e.g., spinal cord injury or Guillain-Barré syndrome).
7. Participant has had open abdominal surgery <=4 weeks prior to enrollment.
8. Participant has open or damaged skin at area of electrode placements.
9. Participant has a pacemaker and/or implanted electronic device.
10. Participant is known or expected to be pregnant.
NOTE: A negative urine or blood pregnancy test will be documented during screening for women of child-bearing potential.
11. Participant is actively pharmacologically paralyzed at the time of enrollment.
NOTE: Participants receiving neuromuscular blockers may be enrolled after a >= 12 hour washout period.
12. Participant is tracheostomized at the time of enrollment.
13. Participant is on home non-invasive ventilation (except for CPAP or BiPAP for obstructive sleep apnea).
14. Participant is receiving or expected to receive comfort measures (palliative, hospice, comfort care, etc.) at the time of screening or enrollment.
15. Participant is participating in any of the following:
• A study with the same or similar primary endpoint
• A study investigating electrical stimulation or respiratory muscle therapy
• Any study in which the investigator determines may interfere with the results of this study
16. Participant is unable or unwilling to comply with protocol requirements, including assessments, tests, and follow-up visits.
17. Participant has any other medical condition which in the opinion of the Investigator will make participation medically unsafe or interfere with the study results.
18. Participant or legally authorized representative is unwilling to provide written informed consent.
19. Participant or legally authorized representative is unable to provide

written informed consent.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-09-2024
Enrollment:	48
Type:	Actual

Medical products/devices used

Generic name:	VentFree Respiratory Muscle Stimulator
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	30-04-2024
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-06-2024

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-11-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-12-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05759013
CCMO	NL84195.000.23