Partial neuromuscular blockade to facilitate lung and diaphragm protective mechanical ventilation in ICU patients: A randomized controlled pilot study.

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Primary Objective: The primary goal is to investigate the feasibility and safety of prolonged (24 hours) partial neuromuscular blockade in ventilated patients with high respiratory drive in partially supported mode.Secondary Objectives: The...

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

Summary

ID

NL-OMON50261

Source
ToetsingOnline

Brief title
Partial neuromuscular blockade for lung protective mechanical ventilation

Condition

- Other condition

Synonym
Diaphragm dysfunction, lung injury due to mechanical ventilation

Health condition

Middenrif / longfunctie

Research involving

Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: VUmc Amsterdam;Radboudumc Nijmegen

Intervention

Keyword: - Diaphragm, - High respiratory drive, - Lung protective mechanical ventilation, - Neuromuscular blockade

Outcome measures

Primary outcome

Feasibility to establish and maintain lung protective ventilation for 24 hours

with partial neuromuscular blockade in ventilated ICU patients with high

respiratory drive in partially supported mode. *Feasible* is define as: *the

ability to maintain tidal volume <6ml/kg PBW during the whole study protocol,

without developing any directly related serious adverse events.*

Therefore, the following parameters are collected:

Feasibility

• Percentage of breaths with tidal volume < 6ml/kg PBW

• Number of patients completing the study without meeting the stopping criteria

(see section 7.4.2) or serious adverse events.

• Number of patients that have been withdrawn after inclusion, and reason for

withdrawal.

• Number of eligible patients of the total ICU population, and reason why the

patient is not eligible for inclusion.

• Time needed to recruit patients and collect data.

Safety:

• Number of directly related adverse events

• Blood gas analysis: pCO2 and pH

• Hemodynamic parameters: heart rate and blood pressure

• Days on mechanical ventilation after the intervention

• ICU mortality

Secondary outcome

The effect of prolonged partial neuromuscular blocking on diaphragm function

and respiratory, hemodynamic and inflammatory parameters compared to standard

care. Therefore, the following parameters are collected:

• Respiratory and diaphragm function, assessed by measuring:

o respiratory rate, tidal volume and SpO2

o work of breathing (WOB) and pressure-time product (PTP)

o blood gas analysis: PaO2, PaCO2, pH

• Hemodynamic parameters, assessed by measuring clinical parameters such as

blood pressure and heart rate.

• Inflammatory parameters in blood; including TNF-α, IL-6 and IL-1β

7.1.3 Other study parameters

In addition, we recorded the following data:

• Sex, age and body mass index (BMI)

• Reason for admission and co-morbidity

• Amount of days on controlled mechanical ventilation before study period

• RASS, dose of sedatives and analgesics

• Ventilator settings: FiO2, PEEP, pressure support level and PaO2/FiO2 ratio

• If EAdi catheter in situ: EAdi signal and neuromuscular efficiency (NME)

Study description

Background summary

Mechanical ventilation is a life-saving intervention in patients with acute respiratory failure (ARF) as it unloads the respiratory muscles and can maintain adequate alveolar gas exchange. Mechanical ventilation can be delivered in two ventilator modes: controlled mechanical ventilation, where all the work of breathing is performed by the ventilator and partially supported ventilation, where the work of breathing is shared between the patient and the ventilator. The use of controlled mechanical ventilation requires high levels of sedation, which is associated with adverse outcome. In addition, there is increasing evidence that controlled mechanical ventilation itself could have detrimental effects on the respiratory muscles due to prolonged inactivity (disuse atrophy). Partially supported modes, have recognized beneficial effects, including lung recruitment and reduced risk of ventilator-induces diaphragm dysfunction (VIDD). Therefore, it seems reasonable to switch to a partially supported mode as soon as feasible. However, in some patients this transition may lead to an increased respiratory drive with high tidal volumes (Vt) and transpulmonary pressures (Pl). In daily practice, these patients are often re-sedated and ventilated in controlled mode, resulting in a vicious circle in which they become difficult to wean from mechanical ventilation.

Recently, we have published a study in which a low-dose neuromuscular blocking agent (NMBA) was administered to patients with lung injury and increased Vt (> 8ml/kg predicted body weight(PBW)) in partially supported modes. We demonstrated that partial neuromuscular blockade facilitates lung-protective ventilation (Vt <6ml/kg PBW and Pl reduced from 27cmH2O to 11cmH2O), reduces work of breathing (WOB), while maintaining diaphragm activity. This proof-of-concept study was well received by experts in the field and the study was published in the highest ranked medical journal for intensive care medicine. An important limitation of the study was that it was conducted in a small, selected group of patients and during short period of time (2 hours). In addition, in our proof of concept study no control group was evaluated.

Clearly, there is a need for a pilot study to demonstrate the feasibility and safety of this strategy for prolonged period of time, before we can conduct a large RCT with clinical relevant outcome parameters. Data obtained from this pilot RCT are an important step towards innovative pharmacological intervention

in patients with high respiratory drives in partially assisted modes.

Study objective

Primary Objective:
The primary goal is to investigate the feasibility and safety of prolonged (24 hours) partial neuromuscular blockade in ventilated patients with high respiratory drive in partially supported mode.

Secondary Objectives:
The secondary goal is to evaluate the effect of this strategy on diaphragm function, lung injury, hemodynamics and systemic inflammation compared to standard care.

Study design

The study is a single centre, clinical pilot RCT and will be performed during one year period in an academic medical-surgical intensive care unit (ICU).

Intervention

Intervention group: titration until tidal volume of 6ml/kg predicted body weight is reached, followed by continuous administration of partial neuromuscular blockade with rocuronium bromide for 24 hrs.

Control group: receive standard of care

Study burden and risks

Based on results of our previous proof-of-concept study, patients may benefit in participating in this study. There is a strong physiological rationale for protecting patients against high tidal volumes and concomitant high transpulmonary pressures [13, 14]. Ultimately, we want to perform a randomized controlled trial to test if partial neuromuscular blockade will improve outcome. However, first we need to investigate the feasibility of prolonged administration of partial neuromuscular blocking agents on lung protective ventilation and the effect of this strategy on diaphragm function, respiratory, hemodynamic and inflammatory parameters compared to standard care. Data obtained from this second proof-of-concept study are an important step towards innovative pharmacological intervention in patients with high respiratory drives in partially assisted modes.

Administration of rocuronium bromide
Risks of the use of rocuronium are the development of distress when the patient is not adequately sedated. Therefore, partial neuromuscular blocking agents will only be started when the patient is adequately sedated, indicated by a

RASS <= -3 used to assess sedation depth during the different phases of the study. In our earlier performed study on partial neuromuscular blockade was found that some patients developed a mild hypercapnic acidosis and mild hemodynamic effects like tachycardia and hypertension. Therefore, we will not include patients with a pH < 7.30 and/or hemodynamic instability.
*
Blood withdrawal
We will aim to combine blood gas analysis for the study with blood gas analysis for clinical purpose. Only for analysis of the inflammatory parameters we will require three samples of blood of maximum 5.0ml of blood per sample. All blood samples will be withdrawn from the indwelling arterial catheter that is already in situ for clinical purpose. No adverse events are anticipated from blood withdrawal.

Risk - benefit analysis
A sound risk - benefit analysis is of great importance when studies are performed in mechanically ventilated patients. As outlined in this section risks for patients in the current study are minimized for administration of rocuronium bromide (exclusion of patients with pH < 7.30 and / or hemodynamic instability). These risks are negligible.
Studying the effect of prolonged administration of partially neuromuscular blockade (with rocuronium bromide) in mechanically ventilated patients with high respiratory drive in partially supported modes is highly needed. Respiratory muscle atrophy and lung injury is common in this group of patients and is associated with higher mortality rates and prolonged mechanical ventilation. We reason that decreasing Vt to 6ml/kg PBW may reduce negative effects of high drive and improve outcomes. As such, there is a potential benefit for the participants, but this is not sure. The impact on outcome has to be investigated with a randomized controlled trial. However, first we have to investigate the feasibility of prolonged administration of partial neuromuscular blocking agents on lung protective ventilation and the effect of this strategy on diaphragm function and respiratory, hemodynamic and inflammatory parameters compared to standard care. In conclusion, risks of the intervention are negligible, and there is a potential benefit for participating. As such, the risk-benefit ratio is acceptable.

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

- high respiratory drive, defined as tidal volume > 8ml/kg PBW on inspiratory support of 12cmH2O.
- sedation level: RASS <= -3
- ventilated in pressure support mode

Exclusion criteria

- recent use of NMBA (<2 hrs)
- arterial pH <7.25
- hemodynamic instability, i.e. high dose vasopressors (>0.5 µg/kg/min) or inotropes (dobutamine >15 µg/kg/min or enoximone >25 µg/kg/min)
- intracranial pressure >20 cmH2O
- past medical history of neuromuscular disorders
- pregnancy
- known previous anaphylactic reaction to NMBA*s.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-09-2018
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Esmeron
Generic name:	Rocuroniumbromide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-06-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	11-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2018-000748-24-NL
CCMO	NL65192.029.18