

Effects of different early rehabilitation techniques on haemodynamic and metabolic parameters in sedated patients: protocol for a randomised, single-blind, cross-over trial

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ABSTRACT

Introduction: Early rehabilitation has become widespread practice for patients in intensive care; however, the prevalence of intensive care unit-acquired weakness remains high and the majority of physiotherapy is carried out in bed. Several inbed rehabilitation methods exist, but we hypothesise that techniques that provoke muscle contractions are more effective than passive techniques.

Methods: A randomised, controlled cross-over study will be carried out to evaluate and compare the effectiveness of early rehabilitation techniques on cardiac output (CO) in sedated patients in intensive care. 20 intubated and sedated patients will undergo 4 10 min rehabilitation sessions. 2 sessions will involve 'passive' techniques based on mobilisations and inbed cycle ergometry and 2 involving electrostimulation of the quadriceps muscle and Functional Electrical Stimulation-cycling (FES-cycling). The primary outcome is CO measured by Doppler ultrasound. The secondary outcomes are right ventricular function, pulmonary systolic arterial pressure, muscle oxygenation and minute ventilation during exercise.

Results and conclusion: Approval has been granted by our Institutional Review Board (Comité de Protection des Personnes Nord-Ouest 3). The results of the trial will be presented at national and international meetings and published in peer-reviewed journals.

Trial registration number: NCT02920684.

KEY MESSAGES

- ▶ Which physiotherapy intervention produces the greatest physiological effect in sedated patients confined to bed?
- ▶ To evaluate the effectiveness of different rehabilitation techniques for sedated patients confined to bed by evaluating the effects on haemodynamics and muscle parameters.
- ▶ This study is the first to evaluate the physiological effects of early rehabilitation in sedated patients and to provide more information on the effectiveness of physiotherapy interventions.

Kayambu *et al*² published a meta-analysis in 2013 on the effects of physical exercise in intensive care units (ICU). They found that it improved physical capacity, respiratory muscle strength and quality of life, and reduced the length of hospital stay and ventilation time. However, there was no effect on limb muscle strength (measured using the MRC scale) or on mortality.² A meta-analysis published in 2015 by Castro-Avida did not find any effect on function, muscle strength or quality of life. Moreover, early rehabilitation does not appear to prevent ICU-acquired weakness (risk ratio: 0.75 (95% CI 0.51 to 1.09)).³ These results were confirmed by a recent study of 192 patients that showed that despite early rehabilitation, 1 in 2 survivors (52%) develop ICU-acquired weakness.⁴ These disappointing results could be attributed to the low intensity of exercises carried out since the majority of exercise consisted of mobilisation in bed. Only 2.9% of patients were taken out of bed.⁴

Low-intensity bed-exercises are common practice in ICU.^{4 5} Few patients are taken out

INTRODUCTION

Early rehabilitation in intensive care has been largely developed over the last 10 years.¹ Despite several studies with positive results, the benefits of early rehabilitation on recovery and improvement of motor performance still remain to be demonstrated.^{2 3}



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of bed, mostly because of care team fears, medical instability, a technical environment that is difficult to manage etc. It is therefore very difficult to reach a high enough training intensity for benefits to occur. It is thus essential to determine optimal inbed rehabilitation techniques and intensities to prevent, or limit, ICU-acquired weakness.¹ Quantifying the optimal exercise intensity in patients under mechanical ventilation is not simple. In exercise physiology, the cardiovascular response to training is directly proportional to the skeletal muscle oxygen demands. As the rate of work increases, the cardiac output (CO) increases in a nearly linear manner to meet the increasing oxygen demand, and blood flow is directed to the active skeletal muscles.

We hypothesise that techniques that involve muscle contractions will produce greater physiological effects than techniques that do not.

The aim of this study was to evaluate and compare the effect of four different rehabilitation techniques on cardiovascular and metabolic function in sedated patients confined to bed.

Objective

Primary objective

To evaluate and compare the effect of different rehabilitation techniques on patients confined to bed on CO.

Secondary objectives

To evaluate and compare the effect of different rehabilitation techniques for patients confined to bed on right ventricular function, pulmonary systolic arterial pressure as well as muscle oxygenation and minute ventilation during exercise.

METHOD

Study design

A single-centre, randomised, blind, cross-over trial comparing CO during four rehabilitation techniques in patients confined to bed and sedated under mechanical ventilation. The study will be carried out in the Intensive Care Unit department of Le Havre Hospital Group. The patients will participate in four consecutive 10 min rehabilitation sessions in bed involving 10 min of passive lower limb mobilisation, 10 min of electrostimulation of the quadriceps muscle, 10 min of passive peddling on an inbed cyclo-ergometer and 10 min of functional electrical stimulation coupled with passive peddling (FES-cycling). The order of the sessions will be randomised.

Participants

Patients will be included if they fulfil the following inclusion criteria: age over 18 years, intubated and ventilated at least at 24 hours on the 'Pressure Support' mode and Ramsay score >4.

Patients will be excluded if they have any of the following: are haemodynamically unstable (increased

catecholamine over the last 24 hours), have a pacemaker or other contraindications to electrostimulation, have other conditions which may affect their participation in rehabilitation (osteo-articular or neuromuscular disorders or severe psychiatric disorders), patients with severe anaemia (<8 g/dL), central neurological pathology, sedentary prior to admission to ICU, under 'Assist Controlled' ventilation, FiO₂ above 80%, on neuromuscular blockers, conscious, non-echogenic if they fight against the mobilisation.

Recruitment

After 24 hours of mechanical ventilation, if the patient fulfils the inclusion criteria, the information letter will be given to his/her family. Cardiac Doppler ultrasound will then be carried out by an experienced doctor. The purpose of the ultrasound is to objectively evaluate the possibility of interpreting the measurements carried out and to collect baseline data for the patient. If the patient is echogenic, he/she will be included. The cross-sectional surface area (CSA) of the left ventricular outflow tract and right atrial pressure will be measured at this time.

Randomisation

The order of the rehabilitation techniques will be randomised using a Latin square design. Randomisation will be carried out by the Clinical Research Unit via computer software. The investigator will receive the randomly generated treatment allocation in a sealed envelope just before the session.

Recordings

The cardiac Doppler ultrasound and the muscle oxygenation recording by near infrared spectroscopy will begin at rest, 2 min before beginning the exercise. Ultrasound recordings will be carried out before each exercise, every 3 min during each exercise and during the first 5 min of rest following each exercise.

Ventilation settings (pressure support level and positive end-expiratory pressure), oxygenation (FiO₂), catecholamine level and sedation will not be changed for the entire duration of the protocol.

Intervention

Passive lower limb mobilisations

A senior physiotherapist will carry out movements of global leg flexion and leg extension as well as hip abduction and adduction for 10 min.

Inbed cycle ergometry

A senior physiotherapist will position the patient's lower limbs on the inbed cycle ergometer. The peddling frequency will be set to 20 rev/min,⁶ for 10 min.

Quadriceps neuromuscular electrical stimulation

Two electrodes (5×9 cm) will be positioned at each extremity of both quadriceps muscles to stimulate the

whole of both muscles. A rectangular, intermittent, bidirectional current with no ramp will be used and the intensity will be modulated to obtain a palpable muscle contraction. The other electrical stimulation parameters will be identical for all patients (length: 300 μ s, frequency: 35 Hz). These settings are based on usual electrostimulation protocols.⁷

FES-cycling

Two electrodes (5×9 cm) will be positioned at each extremity of both quadriceps muscles to stimulate the whole of both muscles. The peddling frequency will be set to 20 rev/min for 10 min. A rectangular, intermittent, bidirectional current with no ramp will be used and the intensity will be modulated to obtain a palpable muscle contraction. The other electrical stimulation parameters will be identical for all patients (length: 300 μ s, frequency: 35 Hz).⁸ During the ergometric cycling, the stimulator will be controlled by a personal computer. The software will ensure that muscle contractions are induced at the appropriate pedal angles during knee extension.

Rest and recovery

There will be a 30 min rest period between each technique in order to allow the cardiorespiratory system to return to its baseline state.

Blinding

Patients will be sedated during the interventions and evaluations. The therapist who sets up the equipment will not be blind to the treatment technique.

Data collection

Cardiac output

The primary outcome will be CO. It will be continuously measured using cardiac Doppler ultrasound (CX-50).⁹ The velocity time integral (VTI) will be recorded by pulsed Doppler, using an apical five-chamber view. The VTI will be measured on an image with at least three QRS complexes on the electrocardiogram. A mean of three VTIs will be calculated every 3 min. CO will be calculated using the formula: $VTI \times CSA \times \text{cardiac frequency}$.¹⁰

Tricuspid annular plane systolic excursion

The longitudinal displacement of the lateral part of the tricuspid valve will be measured in the TM mode with a four-chamber view.¹¹ The tricuspid annular plane systolic excursion will be measured every 3 min.

Pulmonary arterial systolic pressure

The pulmonary arterial systolic pressure (PASP) is the sum of the pressure gradient between the right ventricle and the pulmonary artery (ΔP), and right atrial pressure (RAP): $PASP = \Delta P + RAP$.¹²

ΔP will be evaluated by measuring the tricuspid regurgitation (TR). TR jet was visualised with colour

flow mapping, and the TR gradient was measured with continuous wave Doppler with a four-chamber view. We used the modified Bernoulli equation ($\Delta P = 4v^2$) to calculate gradients from velocities.¹² PASP will be measured every 3 min.

Vastus lateralis near infrared spectroscopy

A wireless portable, continuous-wave, spatially resolved spectroscopy NIRS device (Portamon, Artinis, The Netherlands) will be used to measure relative change in total haemoglobin (THb), oxyhaemoglobin and oxymyoglobin (HbO₂) and deoxyhaemoglobin and deoxymyoglobin (HHb). The NIRS optode will be positioned longitudinally 10 cm above the patella on the right vastus lateralis and will continuously record at a sampling frequency of 1 Hz.¹³ To avoid the influence of room light, the optode will be fixed to the skin with a black band.

Expiratory tidal volume and respiratory rate

Respiratory rate and tidal expiratory volume will be monitored by the ICU ventilator. Values will be recorded every 30 s and the mean will be calculated every 3 min.

Power calculation and sample size

CO will be measured using cardiac ultrasonography. There are few data on changes in CO during early rehabilitation in ICU. We chose to use existing data evaluated by cardiac ultrasound during a passive leg raise test. Based on the results of previous studies,¹⁴ 19 participants should be included to detect a difference in the mean CO of 1.1 L between groups, and to reject the null hypothesis with a power of 90%.¹⁴ The associated type I probability error is 0.05. We plan to include 20 patients in total.

Statistical analysis

Normally distributed data will be expressed as means (\pm SDs) and non-normally distributed data will be expressed as medians (and IQRs). A mean of three VTIs will be calculated every 3 min. Each image must contain at least three QRS complexes. The values of THb, HbO₂ and HHb will be collected continuously and means will be calculated every 3 min. Within-group data will be analysed using paired t-tests or Wilcoxon signed-rank tests. Two-way analysis of variance will be used to compare changes during the sessions between groups. A Bonferroni t-test will be used post hoc. The level of significance will be set at ≤ 0.05 .

Ethics and dissemination

The study has been approved by our Institutional Review Board (Comité de Protection des Personnes Nord-Ouest 3). In conformity with the Declaration of Helsinki, all participants will be recruited voluntarily and they will sign an informed consent form. The results of the trial will be presented at national and international meetings and published in peer-reviewed journals. Results will be

registered ClinicalTrials.gov. We will also disseminate the main results to all participants in a letter. The study has been registered with ClinicalTrials.gov (NCT02920684).

Strengths and limitations

This study is the first to evaluate the physiological effects of early rehabilitation in sedated patients.

Sedated patients will reduce the risk of interpretation bias.

The study has three main limitations. First, it is single centre. Second, the evaluation of a single session does not provide information regarding long-term clinical effectiveness; however, the results will provide a basis for such a study. Finally, the results cannot be extrapolated to conscious patients.

An important strength is that four different physiotherapy interventions will be investigated.

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Competing interests FEG and TB are employees by ADIR Association. Other authors declare that they have no conflict of interest.

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