STUDY PROTOCOL

PROTOCOL TITLE:
Feeding with Indirect calorimetry and Cycling in the Elderly (FICE)

PROTOCOL VERSION: 3
PROTOCOL DATE: 27/02/2018

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STUDY SITE:
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1. BACKGROUND AND RATIONALE

Critically ill patients in the intensive care unit (ICU) experience a high degree of physiological stress and catabolism. This results in rapid muscle breakdown and deconditioning, resulting in prolonged functional disability which persists even after the critical illness. To minimize this, it is important that patients are given adequate nutrition and physical therapy during the period of critical illness.

Currently, our surgical ICU (SICU) patients receive feeding based on a weight-based empiric formula (25 kcal/kg/day). This method of estimating caloric requirement is inaccurate in underweight, overweight and oedematous patients. In our study, we will be examining the use of indirect calorimetry, which is the gold standard for assessing energy requirements. Studies done on indirect calorimetry directed feeding have not shown a significant impact on functional outcome. We hypothesize that the patients included in these studies may not have received adequate physical therapy.

With regards to physical therapy, our SICU patients receive regular standard physiotherapy sessions. Studies have shown that physical therapy in the critically ill improves functional outcome only marginally. We hypothesize that the marginal result could be due to inadequate feeding of the patients studied. In our study, we will be examining the use of cycle ergometry. Cycle ergometry has been shown to be safe and feasible in critical care patients, however there have been no studies examining its effect on functional outcome.

We hypothesize that indirect calorimetry directed nutritional support in combination with enhanced physical therapy using cycle ergometry synergistically improves functional outcome of critically ill patients.

1.1. General Introduction

Indirect calorimetry is the gold standard for assessing energy requirements. It involves measuring the amount of oxygen consumed by the patient and the amount of carbon dioxide produced by the patient. Using the Weir formula, the energy expenditure of the patient can be calculated. Although indirect calorimetry is considered the gold standard, it is not routinely used in the SICU.

Cycle ergometry enables active and passive cycling in bed bound patients. It has been mainly used in the outpatient rehabilitation setting. It has been shown to be feasible and safe to be used in the ICU setting. However, there are no studies examining its effectiveness in improving functional outcome in critical care patients.

1.2. Rationale and justification for the Study

We hypothesize that indirect calorimetry directed feeding in combination with enhanced physical therapy using cycle ergometry synergistically improves functional outcome of critically ill patients.

We are conducting this study in the hope to eventually improve functional outcomes in critically ill patients, particularly the elderly population as they have low reserves to start with. The burden of disability among the patients discharged from the ICU is increasing due to our aging population.

a. Rationale for the Study Purpose

Critically ill patients in the intensive care unit (ICU) experience a high degree of physiological stress and catabolism. This results in rapid muscle breakdown and deconditioning, resulting in prolonged functional disability which persists even after the critical illness. To minimize this, it is important that patients are given adequate nutrition and physical therapy during the period of critical illness.

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b. Rationale for Study Population

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critically ill patients, particularly the elderly population as they have low reserves to start with. The burden of disability among the patients discharged from the ICU is increasing due to our aging population.

c. Rationale for Study Design

We will be conducting a randomized controlled trial as it is most suitable to answer our clinical question.

2. HYPOTHESIS AND OBJECTIVES

2.1. Hypothesis

Feeding by indirect calorimetry and early exercise with cycle ergometry will reduce muscle mass loss in the older critical ill patient and improve functional outcomes.

2.2. Primary Objectives

Adequate feeding and early exercise by cycle ergometry will reduce muscle mass loss as estimated by quadriceps muscle ultrasound

2.3. Secondary Objectives

The secondary outcomes are 1) ICU mortality 2) ICU and hospital length of stay 3) functional assessments of mobility such as Chelsea Critical Care Physical Assessment Tool (CPAx) and Functional Status Score for the ICU (FSS-ICU). 4) Assessment of strength i.e Handgrip Strength using dynamometer and Medical Research Council Sum Score (MRC-SS).

2.4. Potential Risks and benefits:

a. End Points - Efficacy

We would expect patients who undergo early exercise and feeding have improved functional outcomes, mobilise earlier and avoid problems of prolonged hospital stay. This would avoid the severe problems of deconditioning and muscle loss in the older patient.

b. End Points - Safety

Patients might have some mild cardiovascular instability as with any exercise regimen and hence the strict temporary exclusion criteria before the commencement of the exercise. Patients are closely monitored on ICU and any deviation from baseline parameters will lead to the termination of the exercise cycle ergometry. Other ICU studies have showed the

safety of the cycle ergometry in this group of ICU patients.

3. STUDY POPULATION

3.1. List the number of subjects to be enrolled.

50 patients - 25 study subjects in Group A - Intervention arm, 25 study subjects in Group B - Control arm

3.2. Criteria for Recruitment

All patients admitted to SICU (ward 21 and ward 23) will be screened for inclusion and exclusion criteria. Patients will then be recruited if the criteria are fulfilled.

3.3. Inclusion Criteria

1) At least 60 years old
2) Mechanically ventilated within 3 days of ICU admission
3) expected to be mechanically ventilated for more than 3 days at time of recruitment
4) Able to ambulate with or without a gait aid before hospitalization
5) Able to be enterally fed within 48 hours of ICU admission

3.4. Exclusion Criteria

1) Unable to follow commands at baseline before hospital admission (e.g. Severe dementia)
2) Acute condition where cycling is a contraindication (e.g. leg fracture)
3) not expected to survive the subsequent 48 hours
4) Body habitus unable to fit the cycle ergometry
5) Patients at high risk of refeeding (i.e. NUTRIC score >= 5): malnourished patients with anorexia nervosa, chronic malabsorption syndromes, chronic alcoholism, or patients with massive weight loss.
6) Extremes of BMI: i.e. BMI < 16 or > 30
7) Liver failure
8) Cycling exemptions precluding cycling within the first 4 days of mechanical ventilation
9) Requirement for inspired oxygen content (FiO2) greater than 0.8
10) Expected to be on renal replacement therapy for longer than 12 hours per session
11) PEEP > 15mmHg
12) Air leaks through chest drains
13) Palliative goals of care or limitation of treatment established by the CARE form
14) Readmissions to ICU

3.4.1 Temporary cycling exemptions (to be reviewed before daily cycle ergometry sessions)

1. Respiratory
    a. Persistent O2 saturation <88%

2. Cardiovascular
    a. Active myocardial ischemia (MI)
    b. Unstable or uncontrolled arrhythmia
    c. Any increase in vasoactive infusions within the last 2 hours
    d. Mean arterial pressure (MAP) <60 or >110 mmHg within the last 2 hours
    e. Heart rate (HR) <40 or >140 beats per minute (BPM) within the last 2 hours

3. Receipt of neuromuscular blocking agents within the last 4 hours
4. Uncontrolled pain
5. Severe agitation (Richmond Agitation and Sedation Scale, RASS [48]) >2) within the last 2 hours
6. Change in goals to palliative care
7. Team perception that cycling was not appropriate, despite absence of above exemption criteria

3.4.2 Indication for the premature termination of cycle ergometry

1. unplanned extubation
2. suspected new unstable or uncontrolled arrhythmia, or suspected myocardial ischaemia
3. ICU physician request to terminate session
4. PT terminated session due to physiologic concerns.
5. Study subject request to terminate session.

3.5. Withdrawal Criteria

1) Patient subsequent refusal or withdrawal of consent
2) Upon DSRB review

3.6. Subject Replacement

Subjects who drop out will not be replaced and will be evaluated based on intention to treat

4. STUDY SCHEDULE

Patients recruited and randomised to Group A (intervention), will undergo daily indirect calorimetry to obtain their resting energy expenditure (REE), have their enteral feeds titrated to the REE, and commenced on the cycle ergometry for up to 14 days. In Group B

(control), patients will have standard care and nutrition prescribed by the treating physician and standard physiotherapy as determined by the treating physician.

5. STUDY DESIGN

5.1. Summary of Study Design

This is a single centre randomised single blinded controlled study examining the effects of targeted feeding based on indirect calorimetry and early exercise based on the cycle ergometry.

6. METHODS AND ASSESSMENTS

6.1. Randomisation and Blinding

Randomisation will be done by simple randomisation service via sealedenvelope.com. Group A will be the intervention group; Group B will be the control group. Unmasking can occur at the request of the treating physician or upon approval from the principal investigator. The study participant will not be blinded as it will be not be possible to blind the use of the cycle ergometry machine to the study participant. Assessors of the outcome measures e.g. muscle ultrasound operator and functional outcomes will be blinded to the interventions.

6.2. Study Visits and Procedures

a. Screening and Procedures

Patients admitted to SICU NUH will be screened based on inclusion and exclusion criteria within 24 hours of admission. If the patient is sedated, the PIF leaflet will be given to the listed next of kin or the study subject if there are not cognitively impaired. The patient or NOK will be given 24 hours to consider the PIF and to ask any questions before recruitment. Once recruited, randomisation will occur and the patient will be allocated into each treatment arm.

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b. Study Visits and Procedures

After recruitment, the patients allocated to group A will undergo baseline quadriceps muscle ultrasound and daily indirect calorimetry measurements while intubated. The measured REE and energy expenditure from CE will be recorded on the patient's notes. The dose of enteral feed will then be prescribed and administered to the patient. If the patient gets extubated during the study period of 14 days, the patient will be fed based on the last

recorded REE measured by the IC with the addition of estimated energy expenditure from the cycle ergometry.

The study subjects will undergo quadriceps ultrasound measurements up to 4x during the study period (twice a week for 14 days). CE will commence daily for 60mins for up to 14 days if there are no temporary cycling exemptions (see 3.4.1) and can be terminated by 3.4.2.

c. Final Study Visit:

Bedside functional outcome measurements will be obtained at ICU discharge and at day 14 of the study.

d. Post Study Follow up.

Bedside functional outcome measurements will be performed on patients at hospital discharge.

e. Discontinuation Visit and Procedures

Subjects may withdraw voluntarily from participation in the study at any time. Subjects may also withdraw voluntarily from receiving the study intervention for any reason. If voluntary withdrawal occurs, the subject will be asked to continue scheduled evaluations, complete an end of study evaluation, and be given appropriate care.

7. SAFETY MEASUREMENTS

7.1. Collecting, Recording and Reporting of "Unanticipated Problems Involving Risk to Subjects or Others" – UPIRTSO events to the NHG Domain Specific Review Boards (DSRB)

UPIRTSO events refers to problems, in general, to include any incident, experience, or outcome (including adverse events) that meets ALL of the following criteria:

1. **Unexpected**
   In terms of nature, severity or frequency of the problem as described in the study documentation (eg: Protocol, Consent documents etc).

2. **Related or possibly related to participation in the research**
   Possibly related means there is a reasonable possibility that the problem may have been caused by the procedures involved in the research; and

3. **Risk of harm**
   Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Reporting Timeline for UPIRTSO Events to the NHG DSRB.

1. Urgent Reporting: All problems involving local deaths, whether related or not, should be reported immediately – within 24 hours after first knowledge by the investigator.

2. Expedited Reporting: All other problems must be reported as soon as possible but not later than 7 calendar days after first knowledge by the NHG investigator.

7.2. Collecting, Recording and Reporting of Serious Adverse Events (SAEs)

1. **For Principal Investigator initiated Trials**

Previous studies have showed the safety of the cycle ergometry. All ICU and High dependency patients are closely monitored. In the event of any adverse cardiovascular or respiratory events, the cycling can be terminated and the study subject allowed to rest. All SAEs that are unexpected and related to the cycling will be reported. The PI will be responsible for informing DSRB no later than 15 calendar days after first knowledge that the case qualifies for expedited reporting. Follow-information will be actively sought and submitted as it becomes available.

7.3. Complaint Handling –

all complaints will be directed to the PI of the study Dr Will Loh.

8. DATA ANALYSIS

8.1. Data Quality Assurance

Discuss the measures undertaken to ensure that the data obtained from this research is accurate, complete and reliable.

8.2. Data Entry and Storage

Data will be entered electronically and all paper forms will be kept in a locked and sequired cupboard with 2 electronically accessed physical doors. All data in this study will be managed by the investigators and study coordinator only.

9. SAMPLE SIZE

9.1. Determination of Sample Size

This is a pilot study as the combination of these 2 novel therapies have not been previously studied. However, based on previous femoral muscle ultrasound studies performed on other population study groups, we estimate that to detect a 25% reduction in quadriceps femoris muscle thickness, we would require 21 patients in each arm for a power of 0.8. We plan to recruit 25 subjects in each arm to cover for drop outs.

10. ETHICAL CONSIDERATIONS

10.1. Informed Consent

Patients or if incapacitated, the legal representative, will be approached to obtain informed consent. In obtaining and documenting informed consent, the investigator will comply with the SGGCP guidelines and to the ethical principles that have their origin in the Declaration of Helsinki. The PIF will be given and the patient or legal representative will be given up to 24 hours to consent for this study. Consent will be taken by the investigators in this study. If the legal representative consents to the study, once the study participant regains the ability to consent, they will be reconsented again for the study.

10.2. Confidentiality of Data and Patient Records

All investigators will maintain confidentiality and study records will be stored on institutional password protected computers and physical records will be stored in locked cupboards with double doored electronic access doors.

11. PUBLICATIONS

The study outcomes will be published in abstract, poster and journals.

12. RETENTION OF TRIAL DOCUMENTS

Records for all participants, all source documentation as well as IRB records and other regulatory documentation will be retained by the PI in a secure storage facility in the

department of anaesthesia. The records will be accessible for inspection and copying by authorized authorities. All documents will be retained for the duration stipulated by the relevant statutory and NUHS research policies.