ProMICstudy

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON28381

Source
NTR

Brief title
TBA

Health condition

Conditions required ventilator support in the Intensive Care Unit

Sponsors and support

Primary sponsor: Ziekenhuis Gelderse Vallei, Wageningen University, Karolinska Institute
Source(s) of monetary or material Support: Hospital Gelderse Vallei, Ede

Intervention

Outcome measures

Primary outcome

• To investigate the effect of high vs standard enteral protein provision on the regulation of intramuscular autophagy flux in ICU patients

• To investigate the effect of high vs standard enteral protein provision on the evolution of mitochondrial dysfunction and hypermetabolic inflammatory status in ICU patients

• To uncover a possible association between PGE2, protein intake and the course of disease in ICU patients

Secondary outcome

• To investigate the localization of the autophagy block and relation of autophagy changes to nutrient levels in the serum

• To investigate if and how parameters of the hypermetabolic inflammatory state are related to the progression of mitochondrial function in ICU patients

• To investigate if and how the progression of mitochondrial function is related to physical performance and clinical outcomes in ICU patients

• To investigate how mitochondrial dynamics progress over time and how this is associated with mitochondrial function in ICU patients

• To investigate the oxylipins profile measured by LCMSMS and lipopolysaccharide (LPS) levels

• To investigate how the prostaglandin levels are related to the inflammatory levels of cytokines.

• To investigate how oxylipin levels associate with changes in autophagy and mitochondrial function and vise versa.

Study description

Background summary

Rationale: The close connections of the Gelderse Vallei hospital to Wageningen University and the Karolinska Institute provides the opportunity to investigate the proposed association between protein provision and functional disease outcome at a basal level by measuring autophagy flux, mitochondrial function and prostaglandin levels. This sub-study will explore explanations behind the associations.

Objective: To investigate the effect of increased protein provision (compared to standard protein provision) during intensive care unit (ICU) admission on ex vivo muscular cell autophagy flux, leucocyte mitochondrial function and oxylipins, specifically prostaglandin E2 (PGE2) in critically ill patients.

Study design: This study consists of a combination of 3 single-centre prospective cohort sub-studies within the PRECISe-trial.
Study population: ICU patients who consented to the PRECISe-trial who meet the additional in- and exclusion criteria for this set of combined sub-studies will be included. A maximum of 60 patients will be included in consecutive order.

Methodology: Within 48 hours after ICU admission, first blood collection will take place. After

that, blood will be collected on day 3 and day 6. During each blood collection, a maximum of 75 mL of blood will be obtained.
Primary study parameters/endpoints: Autophagy flux measured in primary human myotubes incubated for 24h with serum from ICU patients, mitochondrial function in peripheral blood mononuclear cells (PBMCs) measured via functional respirometry (oroboros) and prostaglandin E2 (PGE2) levels as measured by LCMSMS.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Included patients will usually already have an arterial catheter in situ; therefore, blood sampling, in this case, contains minimal risk and is entirely painless. No direct benefits are present for the included patients. However, with this study, important information can be obtained, which will be of added value to the results of the PRECISe-trial. In this way, mechanisms that have not been studied before in such a randomized controlled trial (RCT) can be revealed and may contribute to a better understanding of the PRECISe-trial results.

Study objective

Analyses of the in vitro regulation of the intramuscular autophagy flux with plasma from patients with regular and high enteral protein feeding might elucidate the possible role of this hypothesis.

This study aims to assess the effect of high vs standard protein provision on peripheral blood mononuclear cell (PBMC) mitochondrial function of ICU patients because of these controversies.

Protein plays a vital role in gut-integrity, and therefore, in this clinical observational study, patients' oxylipin profiles and the gut permeability marker lipopolysaccharide (LPS) will be measured and related to clinical outcome measures by principal component analysis.

Study design

Within 24 hours after inclusion (which is within 48 hours after ICU admission) first blood collection will take place. Thereafter, blood will be collected on day 3 and day 6. During each blood collection, a maximum of 62 mL blood will be obtained.

Immediately after blood sampling, PBMCs will be isolated. Mitochondrial function will be analysed in PBMCs by means of a validated functional profiling test (Oroboros; Human and Animal physiology, WUR, Wageningen). Moreover, validated genomic and proteomic analysis of factors involved in mitochondrial dynamics and autophagy will be performed (e.g.Western blot & quantitative polymerase chain reaction).

Metabolic and inflammatory factors, such as cytokines (e.g., TNF), hormones (e.g. cortisol), proteins associated with catabolism (e.g. uric acid), nutrients and cytokines (e.g. TNF) will be analysed by means of validated blood analysis (e.g. Bio-Plex® Multiplex Immunoassays).

For Oxylipin measurements 8ml EDTA-containing tubes will be put on ice until centrifugation (10′, 10,000 rpm at 4 °C). After centrifugation, plasma will be aliquoted. For analysis, 200 µL

plasma will be stored in 1 mL methanol containing paraoxon, BHT, AUDA, indomethacin, and PMSF to prevent oxidation and breakdown.

Intervention

Blood sampling

Contacts

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Eligibility criteria

Inclusion criteria

In order to be eligible to participate in the PRECISe study, a potential subject must meet all of the following criteria:

1. Adult ≥ 18 years-old admitted to the ICU
2. Unplanned ICU admission
3. Invasive mechanical ventilation initiated <24 hours of ICU admission
4. Expected ICU stay on ventilator support of ≥ 3 days

There are no additional inclusion criteria for this substudy.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in the PRECISe study:

1. Contraindication for enteral nutrition

2. Moribund or expected withholding of treatment
3. Kidney failure with “no dialysis”-code on admission
4. Hepatic encephalopathy
5. Body-mass index <18 kg/m²

Additional exclusion criteria for this set of sub-studies:

1. Current NSAID use
2. Use of chronic corticosteroid or other immunosuppressive medication prior to current hospital admission.
3. Current use of fish oil supplements
4. Haemoglobin level lower than 5,5 mmol/lL
5. Patients referred from another ICU
6. Active autoimmune disease involving the lung, heart, liver, small or large intestine, or neuromuscular system (e.g., myasthenia gravis, multiple sclerosis) AND currently requiring systemic immunosuppressive therapy
7. Patients who experienced a significant medical or surgical event prior to current hospital admission leading to hospitalization within the previous 6 months
8. A disease process (e.g., end-stage cancer) with a projected survival of less than 6 months (pre-ICU admission)
9. Received treatment with chemotherapy, immunotherapy or radiotherapy within the past 12 months
10. Family history of mitochondrial disease(s) or genetic autophagy diseases.
11. COPD Gold-Stadium III or IV or other severe respiratory disorders (FEV1 <30% and FEV1/FVC < 0.7) (pre-ICU admission) (15)
12. Any stage of chronic or acute renal failure (pre-ICU admission, pre-existent SOFA 0 for this SOFA element)
13. Any stage of chronic or acute liver failure (pre-ICU admission, pre-existent SOFA 0 for this SOFA element)
14. Patients supported with haemodialysis or continuous hemofiltration
15. Diabetes Mellitus type I and II (pre ICU-admission)
16. Patients not able to understand the Dutch language
17. Treated with any investigational agent within 12 months prior to study treatment administration.
18. Patients who are ≤ 6 months postpartum pregnancy testing to the discretion of the attending physician
19. (History of) drug abuse

Study design

Design

Study type:	Interventional

Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2021
Enrollment:	60
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Not applicable

Application type:	Not applicable

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
NTR-new	NL9576
Other	METC azM/UM : To be issued

Study results