ISRCTN17621057 https://doi.org/10.1186/ISRCTN17621057

Time course of epigenetic, metabolic and endocrine alterations during critical illness

Submission date
08/12/2015

Recruitment status
No longer recruiting

Registration date
09/12/2015

Overall study status
Ongoing

Last Edited
04/08/2025

Condition category
Other

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Critically ill patients suffer from vital organ failure, undergo remarkable endocrine (hormonal) and metabolic changes, and frequently develop muscle weakness. Patients who survive a critical illness often face continuing debilitating physical and psychological problems after their stay in an intensive care unit (ICU). The exact mechanisms leading to the changes that occur during a critical illness and the long-term consequences that follow remain largely unknown. Recent data has shown that disturbances in stress responses (how the body responds to a stressful situation) may play a crucial role. Furthermore, there is evidence to suggest that changes in what genes are switched on or off (epigenetics) may also be involved in causing the long-term consequences of critical illness. For a long time, it has been known that critical illness has a remarkable time course. In that regard, hormonal changes during a prolonged critical illness differ from those present in the acute (short term) phase of critical illness. So far, however, the dynamics of the metabolic, hormonal and epigenetic changes during a stay in ICU have not been thoroughly studied. In view of finding the right timing for starting certain treatments (interventions) in critically ill patients, this is nevertheless crucial. Indeed, insight in when epigenetic, metabolic and endocrine changes develop may identify a “time window of opportunity” for future interventions and may to an important extent contribute to the planning of future intervention studies. The aim of this study is to map the time course of the epigenetic, metabolic and endocrine changes during critical illness (i.e. find out when these changes happen). In the intensive care units of the University Hospitals of Leuven we will collect blood, mouth mucosa (inside of the mouth), hair and urine samples as well as a muscle and fat biopsy from adult patients. In this way, human samples will be obtained at different stages of a critical illness, from the acute phase of illness until recovery. The results will be compared with demographically matched controls (people who are not critically ill). The levels of stress hormones and how they are being used by the body and any epigenetic changes will be studied and there will be tests looking at muscle function.

Who can participate?
Adults in ICU and matched controls. The matched control group is made up of volunteers who have not been critically ill but have similar health issues.

What does the study involve?
Biological samples are collected from both patients and controls in order to look at epigenetic, metabolic and endocrine changes that occur during a critical illness. This includes the sampling of blood, mouth mucosa, hair, urine, and/or muscle and fat biopsies. These analyses will be complemented with muscle force measurement (checking the strength of the muscles) and electrophysiological tests.

What are the possible benefits and risks of participating?
There is no direct personal benefit for the participating patients, but they can contribute to obtaining new information on the impact of critical illness. This can be important in the future for the treatment of critically ill patients during and after ICU stay and can provide new medical insight. There is no risk to participating.

Where is the study run from?
Five intensive care units (ICUs) at the University Hospital of Leuven (Belgium)

When is the study starting and how long is it expected to run for?
September 2015 to August 2027

Who is funding the study?
1. Methusalem program funded by the Flemish Government through the University of Leuven
2. European Research Council Advanced Grant from the Ideas Programme of the European Union's Seventh Framework Programme
3. Research Foundation-Flanders (FWO) Belgium

Who is the main contact?
Professor Greet Van den Berghe

Contact information

Type(s)
Public

Contact name
Prof Greet Van den Berghe

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
S58533

Study information

Scientific Title
The dynamics of epigenetic, metabolic and endocrine alterations during critical illness: a prospective cross-sectional study

Acronym
CROSS

Study objectives
Critically ill patients suffer from vital organ failure, are characterized by remarkable endocrine and metabolic alterations, and frequently develop muscle weakness. Patients who survive critical illness are often confronted with sustained debilitating physical and psychological problems after ICU stay, including persistent muscle weakness and long-term neurocognitive impairment. This condition is referred to as “the legacy of critical illness”. The exact pathophysiology of these alterations during critical illness and the legacy of critical illness remain largely unknown. The aim of this study is to gain insight in the pathophysiology of critical illness and its long-term consequences. As primary objective, we will study in detail in preset time windows of ICU stay the time course of the epigenetic, metabolic and endocrine alterations that develop in response to critical illness and to unravel potential underlying processes involved in these changes. Secondary objectives include a reanalysis of the time course of the alterations described in the primary objective as well as a longitudinal analysis of within-subjects changes in time for those patients who participate multiple times.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Medical Ethics Committee (Institutional Review Board) of the University Hospitals Leuven, 16/10 /2015, ref: S58533

Study design
Single-center prospective observational cross-sectional study

Primary study design
Observational

Secondary study design
Cross sectional study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
Not available in web format, please use contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Critical illness

Interventions
Biological samples will be collected from patients and controls after informed consent in order to perform the detailed studies as described. This includes the sampling of blood, mouth mucosa, hair, urine, and/or muscle and fat biopsies. These analyses will be complemented with muscle force measurement and electrophysiological tests. The data obtained from these analyses will be correlated with available demographic and clinical data.

Intervention Type
Other

Primary outcome measure
To study in detail, in preset time windows of ICU stay, the time course of the epigenetic, metabolic and endocrine alterations that develop in response to critical illness and to unravel potential underlying processes involved in these changes

Secondary outcome measures
1. Reanalysis of the time course of the alterations described in the primary objective
2. Within-subjects longitudinal analysis of changes for those patients who participate multiple times

Overall study start date
01/09/2015

Completion date
31/08/2027

Eligibility

Key inclusion criteria
1. Patients:
All adult/senior patients at the surgical and medical intensive care units are eligible

2. Controls:
A control group of volunteers who have not been critically ill, but have similar comorbidities as the critically ill patients will be recruited to match demographically with the patient group

Participant type(s)
Mixed

Age group
Mixed

Sex
Both

Target number of participants
Patient recruitment will continue until preset sample numbers (120 per group for blood analyses and 60 per group for biopsy analyses) will have been obtained in four groups based on time in ICU within the first 28 days time window with a comparable distribution of ICU admission categories. At that time, recruitment of patients in a fifth group (> day 28) will also stop. In addition, we will recruit controls who never stayed in the ICU until 120 matched controls have been included for blood analyses and 60 for biopsy analyses

Total final enrolment
374

Key exclusion criteria
1. Patients:
1.1. General:
1.1.1. Age younger than 18 years
1.1.2. Readmission to ICU (unless within 48 hrs)
1.1.3. Declined participation
1.1.4. DNR code
1.1.5. Patients with HIV
1.1.6. Chronic systemic treatment with glucocorticoids prior to ICU admission (added 12/09 /2018: patients who did receive chronic systemic treatment with glucocorticoids prior to ICU admission will be recruited separately to allow investigation of the impact of prior chronic systemic glucocorticoid treatment)
1.2. Blood sampling: absence of arterial line
1.3. Mouth mucosa sampling: normal mouth mucosa not accessible (e.g. post-tumor resection)
1.4. Neuromuscular evaluation:
1.4.1. General:
1.4.1.1. Patients with neuromuscular disorders identified prior to ICU admission / unable to walk without assistance (wheelchair, walking stick, arm support) prior to ICU admission
1.4.1.2. Patients with a neuromuscular disorder as reason for ICU admission
1.4.2. Muscle biopsy: increased bleeding risk
1.4.2.1. Platelet count below 50000/mm3 and/or PT below 40%
1.4.2.2. Known coagulation disorders
1.4.2.3. Use of anti-coagulation or thrombolytic agents
1.4.3. Muscle force by MRC sum score:
1.4.3.1. No muscle biopsy
1.4.3.2. Patient not awake/cooperative (*)
1.4.4. Hand grip strength
1.4.4.1. No muscle biopsy
1.4.4.2. Patients not awake/cooperative (*)
1.4.4.4. Medical Research Council (MRC) score for forearm flexion or wrist extension below 3
1.4.5. Electromyography / nerve conduction studies / direct muscle stimulation
1.4.5.1. No muscle biopsy
(*) patients who give a biopsy but are not awake/cooperative at the time of sampling will be screened for awakening/cooperation up until two days later for MRC sum scoring and hand grip strength
1.5. Fat biopsy: increased bleeding risk:
1.5.1. Platelet count below 50000/mm3 and/or PT below 40%
1.5.2. Known coagulation disorders
1.5.3. Use of anti-coagulation or thrombolytic agents

2. Controls:
2.1. General
2.1.1. Age younger than 18 years
2.1.2. Previous ICU stay (except coronary care unit stay)
2.2. Blood sampling: known severe coagulation disorders (e.g. hemophilia)
2.3. Mouth mucosa sampling: normal mouth mucosa not accessible (e.g. post-tumor resection)
2.4. Muscle and fat biopsy:
2.4.1. Controls with acute or chronic neuromuscular disorders or unable to walk without assistance (wheelchair, walking stick, arm support) will be excluded for muscle biopsy
2.4.2. Increased risk of bleeding:
2.4.2.1. Known coagulation disorders
2.4.2.2. Use of anti-coagulation
2.5. Muscle force / electrophysiology / direct muscle stimulation: no muscle biopsy

Date of first enrolment
11/01/2017

Date of final enrolment
03/09/2020

Locations

Countries of recruitment
Belgium

Study participating centre
KU Leuven University Hospital
Leuven
Belgium
3000

Sponsor information

Organisation
KU Leuven

Sponsor details
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Sponsor type

University/education

ROR
https://ror.org/05f950310

Funder(s)

Funder type
Government

Funder Name
Methusalem program funded by the Flemish Government through the University of Leuven (METH08/07 and METH14/06)

Funder Name
European Research Council Advanced Grant from the Ideas Programme of the European Union's Seventh Framework Programme (AdvG-2012-321670)

Funder Name
Fonds Wetenschappelijk Onderzoek

Alternative Name(s)
Research Foundation Flanders, Flemish Research Foundation, FWO

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Belgium

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal, date to be confirmed later.

Intention to publish date
31/08/2028

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to preserving patient confidentiality. Prof. Greet Van den Berghe will on request detail the restrictions and any conditions under which access to some data may be provided.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Interim results article		15/05/2022	17/08/2023	Yes	No