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Dynamics of the stress response in acute and prolonged critical illness

Submission date
04/07/2016

Recruitment status
No longer recruiting

Registration date
07/07/2016

Overall study status
Completed

Last Edited
23/08/2022

Condition category
Other

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
When we are stressed, the concentration of a hormone called ACTH in the blood rises. This, in turn, increases the amount of stress-hormone cortisol released from the adrenal gland. However, in intensive care unit (ICU) patients this stress response seems to be different. Our research group recently showed that during critical illness high blood levels of cortisol are, to a large extent, due to a decrease in the amount of cortisol broken down in the body, rather than an increase in the amount of the hormone made. These high cortisol levels could in their turn stop the release of ACTH by what is called 'negative feedback inhibition'. However, it remains unknown whether and to what extent the high cortisol levels in ICU patients evoke feedback-inhibition at certain regions in the brain, and whether and how this effect evolves with the duration of critical illness. As such, documenting a change in ACTH and/or cortisol response to the injection of CRH (another hormone of the brain) over time could be highly informative to understand illness evolution and might open perspectives for new treatment strategies.

Who can participate?
Adult patients (age 18 or over) at the medical and surgical ICU. Healthy individuals are recruited to match with the patient group.

What does the study involve?
Participants are randomly allocated to receive an injection of either CRH or salt water, and blood samples are taken. The next day, each participant receives the other injection, and blood samples are taken again.

What are the possible benefits and risks of participating?
There will be no immediate benefits or risks for participants in the study

Where is the study run from?
Five ICUs of the University Hospitals of Leuven (Belgium)

When is the study starting and how long is it expected to run for?
July 2016 to April 2018

Who is funding the study?
1. Methusalem (long term structural funding by the Flemish Government, Belgium)
2. Research Foundation - Flanders (FWO) (Belgium) to the KU Leuven

Who is the main contact?
Prof. Dr Greet Van den Berghe
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
S58941

Study information

Scientific Title
The dynamics of the ACTH and cortisol response to CRH stimulation during critical illness: a randomized, double-blind, placebo-controlled crossover study

Acronym
DACAR

Study objectives
We hypothesize that the sustained increased plasma cortisol concentrations during critical illness could exert negative feedback inhibition on the central components of the HPA axis, causing decreased CRH and/or ACTH synthesis and/or release. Such central inhibition might contribute to the observed low plasma ACTH concentrations and the increased incidence of absolute adrenal insufficiency in the prolonged phase of critical illness.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Ethics Committee (Institutional Review Board) of the University Hospitals Leuven, 23/03/2016, ref: S58941

Primary study design
Interventional

Study design
Randomized double-blind placebo-controlled crossover study

Study type(s)
Other

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

Interventions
The trialists will study unique patients from different time cohorts, with an increasing duration of critical illness, in order to have three sets of patients who represent three different time points in the course of critical illness. After informed consent, each patient from each cohort will be randomized into two crossover study groups for the order of receiving CRH (test) or placebo injection. Consecutive patients will be randomly assigned to ‘first placebo’ or ‘first CRH’ using blinded envelopes, stratified according to the three ‘time in ICU’ cohorts.

Intervention Type
Drug

Phase
Not Applicable

Primary outcome(s)
ACTH and cortisol responses to exogenous CRH/placebo in relation with available baseline demographic and clinical outcome data, collected during ICU stay. Quantification of plasma ACTH and cortisol will be done during 2 consecutive mornings from 10.45-13.00h, after receiving an alternate injection of CRH or placebo each morning, in the acute phase (ICU day 3-6), the intermediate phase (ICU day 7-16) and prolonged phase (ICU day 17-28) of critical illness.

Key secondary outcome(s)
Secondary endpoints (clinical parameters and treatment information) will be collected during their stay in ICU

Completion date
10/05/2018

Eligibility

Key inclusion criteria
For patients:
1. Critically ill patients at the surgical or medical intensive care units, with ongoing intensive care dependency, a stable condition for at least 48h, and an expected stay in ICU for at least 48h
2. Age ≥18 years

For healthy volunteers:
1. Age-, gender- and BMI-matched to the included patients

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
For patients:
1. Predisposing factors of adrenal insufficiency
1.1. Cerebral disease with intracranial hypertension threatening the neuroendocrine system
1.2. Pituitary disorders including (pan)hypopituitarism
1.3. Known adrenal disease (Cushing's syndrome or Addison's disease)
1.4. Chronic treatment with glucocorticoids, other steroids or anti-steroid chemotherapy within the last 3 months
1.5. IV administration of glucocorticoids within the last 72 hours
1.6. Use of etomidate within the last 72 hours
1.7. Use of azoles within the last 7 days
1.8. Other drugs predisposing to adrenal insufficiency: phenytoin, rifampicin, glitazones, imipramin, phenothiazine, phenobarbital
2. Patients known to be pregnant or nursing
3. No arterial line or central venous catheter in place
4. Ethical restrictions
4.1. Moribund
4.2. Declined participation

For healthy volunteers:
1. Recent history of treatment with HPA-axis interfering drugs

Date of first enrolment
30/08/2016

Date of final enrolment
08/05/2018

Locations

Countries of recruitment
Belgium

Study participating centre

University Hospitals Leuven (UZ Leuven)
Herestraat 49
Leuven
Belgium
3000

Sponsor information

Organisation
Katholieke Universiteit Leuven (Belgium)

ROR
https://ror.org/05f950310

Funder(s)

Funder type
Government

Funder Name
Methusalem (long term structural funding by the Flemish Government, Belgium)

Funder Name
Fonds Wetenschappelijk Onderzoek

Alternative Name(s)
Research Foundation Flanders, Flemish Research Foundation, Research Foundation – Flanders, Fonds voor Wetenschappelijk Onderzoek - Vlaanderen, The FWO, Het FWO, FWO

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Belgium

Results and Publications

Individual participant data (IPD) sharing plan

The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/12/2018		Yes	No
Protocol file	version 1.3	05/07/2016	23/08/2022	No	No