Neurotoxic changes in cerebral glucose metabolism during anaesthesia and major surgery; is the polyol pathway activated?

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We will study the cerebral glucose metabolism before, during and after surgery by sampling the cerebrospinal fluid (CSF) via the spinal catheter in patients undergoing thoracic surgery. Changes in cerebral glucose metabolism and activation of the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON48939

Source
ToetsingOnline

Brief title
Changes in cerebral glucose metabolism during anaesthesia

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Glucose metabolism disorders (incl diabetes mellitus)
- Cognitive and attention disorders and disturbances

Synonym
glucose metabolism; sugar level metabolism

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: The European Society of Anaesthesiology (ESA)

Intervention

Keyword: Anaesthesia, Glucose, Metabolism, Polyol

Outcome measures

Primary outcome

The change in cerebral glucose metabolism in the perioperative period as

measured by the difference in CSF/plasma ratio of glucose at different points

in time.

Secondary outcome

- Correlation of perioperative change (increase) of plasma glucose with change

in CSF glucose

- Difference in sorbitol and fructose concentration after induction of

anaesthesia as compared to the awake state

- Difference in sorbitol and fructose concentration during surgery as compared

to the awake state

- Cortisol plasmalevels for the given points in time?

- C-reactive protein (CRP) plasmalevels for the given points in time?

Study description

Background summary

Anaesthesia is very effective in facilitating surgery, which is illustrated by over 1.4 millions of procedures performed each year in The Netherlands alone.

However, postoperative cognitive dysfunction (POCD) is present in up to 8 out of 10 patients, depending on patient age, comorbidities and type of surgery. This has a major impact on quality of life and capability of returning to work after a procedure and the underlying pathophysiology needs to be interrogated to be able to develop proper treatment. POCD has been reported in relation to hypoglycemia. It is also suggested to be associated with hyperglycemia, although this is less constantly reported.

Along with the intended depression of the state of consciousness, anaesthetic drugs also decrease the cerebral glucose metabolism by 25-63%. Paradoxically, plasma glucose increases during surgery, due to the surgical stress response. This so called *stress hyperglycaemia* results from activation of the hypothalamic-pituitary-adrenal axis during surgery. We have shown that even with minor surgery, plasma glucose will increase depending on the length of the procedure. According to the Michaelis-Menten equation, the glucose content of the brain depends on glucose supply (from blood stream) and facilitated transport by the GLUT-1 transporter. An increase in blood plasma glucose will thus cause and increase of glucose in the brain. The combination of decreased glucose metabolism and increased plasma glucose will lead to an excess cerebral glucose supply and demand mismatch during general anaesthesia and surgery.

From studies in patients with diabetes mellitus we know that during chronic hyperglycaemia the normal phosphorylation of glucose via the hexokinase pathway will become saturated and the excess of glucose is processed via the polyol pathway. In this pathway, glucose is metabolized by aldose reductase to sorbitol and fructose. Sorbitol is a hydrophilic alcohol that does not diffuse easily across cell membranes and therefor has osmotic potential. In addition, the formation of sorbitol reduces the capability of the cells to protect against influences of reactive oxygen species. Finally, fructose is capable of irreversibly glycating and damaging proteins, forming advanced glycation end products (AGEs). All cited effects are by itself cytotoxic and thus neurotoxic mechanisms. Evidence on activation of the polyol pathway in the brain is scarce, most likely because it is only possible to measure the metabolites in the cerebrospinal fluid, which is not readily accessible for frequent sampling.

It has been proven to be challenging to study the metabolism of the brain; this includes the anaesthetized patient. As a consequence, there are no data on changes in cerebral metabolism in the perioperative period and anaesthesia and its effect on the brain*s metabolism are still considered a *mystery*.

Study objective

We will study the cerebral glucose metabolism before, during and after surgery by sampling the cerebrospinal fluid (CSF) via the spinal catheter in patients undergoing thoracic surgery. Changes in cerebral glucose metabolism and activation of the polyol pathway (sorbitol and fructose) will be determined to

test the hypothesis.

Study design

We will perform an observational single center cohort study in the Netherlands with an expected duration of 2 years. The study will be conducted at the Amsterdam UMC, location Amsterdam.

Study burden and risks

The burden to the patient is considered to be low. The collection of general data from (electronic) medical records does not affect the patients. Blood sampling will be combined with routine sampling for standard care of thoracic aorta surgery patients where possible. The artery line that*s already present shall be used. The liquor sampling will be done from the reservoir which is placed as part of standard care. The liquor in this reservoir can be viewed as residual material.

CSF sampling: a lumbar drain is placed routinely according to standard work protocol the day before surgery under local anaesthesia and aseptic conditions. A fasting plasma glucose is determined. We will collect the first CSF sample from the reservoir 15 minutes before induction of anaesthesia (t=-15 min), when the patient has had an overnight fast. The second samples are collected before the start of cardiopulmonary bypass and the third samples will be collected after stopping cardiopulmonary bypass. After discharge from the operating theatre, samples will be taken every morning before breakfast (i.e. fasting) until removal of the catheter, at latest 48 hours after surgery. We will collect 2 ml of CSF from the reservoir at every measurement point in polypropylene tubes. An estimated 4-5 repeated paired measurements per patient would be collected.

Blood sampling: when a CSF sample is obtained, a paired plasma sample will be collected from the arterial line that all patients receive before surgery as part of routine clinical care. In this sample, cortisol and CRP will also be measured.

Cerebral perfusion measurement: we will assess the change of cerebral perfusion using transcranial Doppler monitoring. This measurement device will be placed when the patient is under anesthesia and shall be removed before the patient awakes.

Neurocognitive function test: in all participating subjects, we will administer a questionnaire to assess pre- and postoperative cognitive dysfunction, as measured by the Montreal Cognitive Assessment (MoCA). The questionnaire is administered the day before surgery and 2 weeks after surgery.

This study could aid our understanding in the interaction of blood and liquor glucose levels during major surgery and how their metabolism could play a part in the development of postoperative cognitive dysfunction.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- informed consent
- age >18 years
- undergoing elective thoracic aortic surgery

Exclusion criteria

- pre-existing brain disease
- diabetes mellitus
- unable to understand or fill-in questionnaires in Dutch

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	22-05-2019
Enrollment:	19
Type:	Actual

Ethics review

Approved WMO Date:	25-10-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 20502
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL65815.018.18

Study results

Date completed:	26-03-2021
Results posted:	10-08-2022
Actual enrolment:	18

First publication
01-08-2022