Predicting Delayed cerebral ischemia using Micro- and Macrovascular parameters in Subarachnoid hemorrhage patients (PDMMS-study)

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Primary Objective (PHASE 1: feasibility study): - Determine whether measurements of glycocalyx and other microvascular parameters using SDF imaging (on the conjunctiva and sublingually) are feasible in aSAH patients during a period of 2 weeks post-...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Central nervous system vascular disorders
Study type	Observational invasive

Summary

ID

NL-OMON54212

Source
ToetsingOnline

Brief title
MICRO- AND MACROVASCULAR PARAMETERS IN DELAYED CEREBRAL ISCHEMIA

Condition

- Central nervous system vascular disorders
- Vascular haemorrhagic disorders

Synonym
Delayed ischemic neurologic deficit (DIND), Secondary cerebral ischemia

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: delayed cerebral ischemia, glyocalyx, neuroinflammation, subarachnoid hemorrhage

Outcome measures

Primary outcome

- Feasibility of:

1. Sublingual and conjunctival glycocalyx measurements using SDF imaging,

measured using the following parameters:

o Success rate of measurements (number successful measurements/ number of

required measurements, %)

o Complications of measurements

o Communication speed (between treating physician and investigator(s), measured

as time from inclusion and from first signs of DCI to measurement)

o Patient-specific obstacles (e.g. frontal syndrome, intubation,

complications/adverse events) will be carefully reported

o Software (technical issues) and human resources related obstacles

(unavailability of investigator during DCI) measured as frequency of events or

unavailability.

o Global perceived experience of the patient with the SDF measurements, if the

patients if fully aware/conscious (using a 5-point likert scale: I could

tolerate the measurement well: completely disagree, disagree, neutral, agree,

completely agree)

2. Determining patterns of Doppler signal morphology in aSAH and DCI patients

o Doppler signal waveforms (normalized with respect to time (ms) and velocity (cm/s)

Secondary outcome

- Observed glycocalyx variability using:

o SDF imaging measuring glycocalyx thickness derived from red blood cell column width (RBCC, in µm) and total perfused diameter (Dperf, in µm), expressed in Perfused Boundary Region (PBR, in µm)

o Plasma markers of glycocalyx breakdown (ng/L)

- Neuroinflammation

o. Levels of plasma, tear fluid and CSF inflammatory cytokines

- Macrovascular parameters

o Using blood flow velocity expressed in cm/s.

o Doppler signal waveform characteristics (normalized with respect to time (s) and velocity (cm/s)).

- Microvascular parameters obtained from SDF imaging including vessel density (number of microvessels per mm2), vessel volume (mm3), vessel flow (cm/s), and capillary recruitment rate in aSAH patients (%)

- Results of microvascular (from SDF imaging and plasma markers) and macrovascular parameters (TCD measurements) will be related to

o mNHISS, WFNS, GCS

o Surgical treatment (coiling, clipping, no treatment)

o Aneurysm type, location, and size (from CTA/DSA)

o SAH classification: WFNS (clinical) and Fisher classification (radiological)

o Hbac1 on admission and glucose with each measurement

o Functional outcome at six weeks and six months after ictus using the mRs score

o Quality of life at six weeks and six months after ictus using the EQ-5D-5L questionnaire

o Mortality at six weeks and six months after ictus

Other study parameters:

General demographic data will be reported: age, sex, weight and length (BMI), smoking, blood pressure, medication, and complications during admission (occurrence of infections like meningitis, pneumonia, hydrocephalus, endocrinological disorders). This data is routinely obtained from the electronic patient file and will not require additional measurements/actions. These parameters are possible confounders influencing glycocalyx measurements and will be included in logistic regressions.

Study description

Background summary

An aneurysmal subarachnoid hemorrhage (aSAH) is a severe type of stroke affecting approximately 7.2-10.5 per 100.000 persons per year in Western countries, with a mortality ranging from 10 to 50%. Following ictus, aSAH patients are prone to severe complications like hydrocephalus, cardiopulmonary

dysfunction, rebleeds and delayed cerebral ischemia (DCI). DCI is the leading cause of morbidity, mortality, prolonged hospitalization and neuropsychological disturbances in aSAH patients and affects 30% of all aSAH-patients. DCI is defined as the occurrence of new focal deficits (like hemiparesis, apraxia, aphasia or neglect) and/or a decrease in GCS score of two or more points lasting for at least one hour and is suggested after exclusion of other causes like electrolyte disturbances, infection or hydrocephalus. Immediate damage to the brain following ictus defined as early brain injury is suggested to set the stage for DCI. However, the exact underlying mechanisms causing DCI are not fully understood and are thought to be multifactorial. It has become clear that vasospasms eg. narrowing of the cerebral arteries, are the not the sole cause of DCI. Recent studies on DCI following aSAH also suggest a multifactorial etiology of DCI involving many microvascular abnormalities including microthrombosis, neuroinflammation and neurovascular uncoupling. The glycocalyx, a gel-like carbohydrate-rich layer lining the luminal side of the endothelium could be involved in the pathophysiology of DCI. It is involved in regulation of inflammation, in regulation of thrombogenesis and in vasomotor responses through nitric oxide release. This makes the glycocalyx a likely actor contributing to DCI.

Study objective

Primary Objective (PHASE 1: feasibility study):
- Determine whether measurements of glycocalyx and other microvascular parameters using SDF imaging (on the conjunctiva and sublingually) are feasible in aSAH patients during a period of 2 weeks post-ictus
- Determine whether there are specific patterns in the Doppler signal waveform in cerebral arteries of aSAH patients during a period of 2 weeks post-ictus

Secondary Objective (PHASE 2: correlation study):
- Determine microvascular parameters including glycocalyx variability, vessel density, flow velocity, capillary recruitment following aSAH during a two-week follow-up period and assess possible association with DCI.
- Determine the relationship between inflammatory cytokines measured in plasma and tear fluid and glycocalyx damage
- Determine the relationship between changes of the sublingual glycocalyx and changes of the conjunctival glycocalyx using SDF imaging.
- Determine whether changes of the Doppler waveform as obtained with TCD are related to glycocalyx changes.
- Determine whether changes of Doppler waveform as obtained with TCD are associated with DCI
- Determine whether glycocalyx variability as seen on SDF imaging coincides with measured plasma markers of glycocalyx damage

- Determine whether microvascular/macrovascular parameters are related to:
o Findings on initial CT-cerebrum classified using the modified Fisher score
o Treatment modality (endovascular or microsurgical clipping)

o Type, size and location of the aneurysm

- Determine possible relationships between microvascular/macrovascular parameters and clinical outcomes:
o assess a potential relation between microvascular/macrovascular parameters and functional outcome expressed with the modified Rankin skore (mRs) score at six weeks and six months after ictus?
o assess a potential relation between microvascular/macrovascular parameters and quality of life expressed with the EuroQuol-5D-5 Level (EQ-5D-5L) at six weeks and six months after ictus?
o assess a potential relation between microvascular/macrovascular parameters and mortality at six weeks and six months after ictus?

Study design

This study is a single-center prospective observational feasibility (PHASE 1) and correlation (PHASE 2) study, expected to last 24 months.

Setting:
Adult patients admitted to the MUMC+ hospital with a CTA or DSA confirmed aneurysmal SAH will be assessed for eligibility for participation in this study. All aSAH patients in the Limburg region are referred to the MUMC+ hospital, as it is the only regional tertiary health care center providing specialized treatment for intracranial aneurysms. Therefore, no additional promotion of the research is needed to recruit patients.

Clinical phase:
Following informed consent and assessment of eligibility within 72 hours following ictus, a patient can be included in this study. Immediately following inclusion, baseline TCD measurements of the large intracerebral arteries will be performed. Moreover baseline measurement of the sublingual and conjunctival microvasculature including its glycocalyx will be performed using SDF imaging. Tear fluid will be collected and blood samples will be taken to measure markers of glycocalyx disruption and inflammatory cytokines/enzymes. Moreover, in patient with an external ventricular drain (EVD), cerebrospinal fluid (CSF) will be sampled from the reservoir. All these measurements will take place at the patient*s bedside. In the same week of inclusion, two additional TCD measurements, conjunctival and sublingual measurements, tear fluid collection, CSF samples and plasma marker/cytokine samples will take place with one or two days in between. Likewise, in the second week, TCD measurement and SDF imaging will be performed, CSF, tear fluid and blood will be taken for inflammatory markers three times per week. DCI usually presents around three to four days after ictus, with a peak at seven to ten days; therefore a fourteen day follow-up allow us to capture most of DCI events. During a DCI period (new focal deficits, decrease in GCS score > 2 after exclusion of other causes), SDF imaging, TCD measurements, tear fluid collection, CSF samples and blood samples for plasma markers/cytokines will be performed daily until DCI resolves. The

measurements are performed as soon as possible and within 24 hours of the first symptoms, while symptoms are still present. Thereafter, all measurements will be performed three times per week.
Measurement of the glycocalyx using SDF imaging will take around five minutes per location maximum. In our experience, these measurements are easily tolerated by patients; this has also been confirmed by several studies using this technique for both the sublingual and conjunctival microcirculation.
Patient experience with the measurements using SDF imaging sublingually and conjunctivally will be reported using a five-point Likert scale (if the patient is conscious) at the end of each week. Measurements will be performed in the early morning before breakfast after a period of at least six hours of fasting to reduce the effects of glucose on the glycocalyx.
Tear fluid collection is performed via Schirmer's paper strips, inserted at the junction of the middle and lateral thirds of the lower eyelid.
TCD measurements last up to 15 minutes per measurements and do not have any side effects. Measurements are painless and performed at the patient*s bedside.
Finally, blood samples are routine procedures in aSAH patients and take about 1-3 minutes.

Outpatient follow-up phase:
In order to assess the relationship between microvascular parameters and clinical outcome, we will include two assessment tools at the usual outpatient follow-up moments, i.e. at six weeks and six months post-ictus. Firstly, the functional outcome will be measured using mRS based on a structured interview. The mRS explores patient mobility, autonomy, activities and symptoms resulting from the aSAH. It is expressed using an ordinal seven-point scale, with 0 representing no residual symptoms, 5 severe disability and 6 death. The mRS is part of the national quality registry of aSAH patients (QRNS), and is therefore part of standard patient care. Secondly, quality of life will be measured using the EQ-5D-5L questionnaire, which explores mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Completion of the interview and questionnaire will take around 10 - 15 minutes. In case a patient cannot complete this interview and questionnaire him/herself, a proxy will be asked for help. In this case, the intent is that the answers given represent the opinion or experience of the patient.

Study burden and risks

Participation in this study means patients will be subject to a few different kinds of measurements to better understand the nature of the micro- and macrovascular changes following an aSAH.

The glycocalyx measurements using SDF-camera are safe, quick, bed-side and minimally invasive measurements lasting no more than 5 minutes per measurement. The LED light emitted by the camera is not harmful for the tissues that are being investigated (sublingual and conjunctival tissues). Patients might experience slight discomfort with conjunctival measurements due to the

placement of the probe on the conjunctiva, however this should not cause damage to the cornea if performed well. Patients will have a minimum of 6 measurements per area of interest, more if they develop DCI.

Tear fluid collection is a safe, minimally invasive and painless procedure that is well tolerated by patients. The procedure lasts no longer than 5 minutes.

TCD's are routine bedside diagnostic measurements in aSAH patients and therefore do not represent an additional burden for the patient. These measurements are safe, painless, and last up to 25 minutes per measurement. Likewise these measurements will be done at least 6 times, more in the presence of DCI.

Blood samples are easy to obtain in aSAH patients considering the treatment they already get (all patients with an aSAH are hospitalized for three weeks and get intravenous therapy). We consider 5mL blood per sample to be marginal. Patients will not need to be punctured for each blood sample, rather blood will be withdrawn from their venous line, limiting harm and discomfort.

CSF sampling is safe, easy and quick. The patient does not feel the sampling as it happens distally in the reservoir of the external ventricular drain.

Finally, filling in a form on quality of life at six weeks and six months after ictus (EQ-5D-5L questionnaire) will be done at the routine outpatient clinic visits. This questionnaire is easy to fill in and takes no longer than 10 minutes. Questions are clear and to the point, therefore do not require a particular level of acuity/intellect.

These measurements will provide us with valuable information on a disease that is until today not well understood and that causes increased mortality in middle-aged people. We believe that the benefit of the obtained data outweighs the burden for the patient, as the results of these measurements could provide us with new tools to better predict DCI and therefore limit the DCI-induced damage to the patient.

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

- Age >= 18 years
- Diagnosis of an aSAH according to the treating neurologist/neurosurgeon based on CTA/DSA.
- Inclusion within 72h following ictus (to best capture glycocalyx integrity before DCI occurs)

Exclusion criteria

- <18 years
- imminent death within 24 hours
- other causes of SAH like arteriovenous malformations or trauma
- language barrier (non-dutch, english or french-speaking patients)
- oral or ophthalmic trauma or infections
- patient does not have an adequate bone window for trancranial Doppler (TCD) measurements

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-01-2023
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	22-11-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-07-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-12-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-06-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
CCMO	NL76189.068.21