The Role Of The Glycocalyx And Magnesium In Delayed Cerebral Ischemia After Subarachnoid Hemorrhage

Published: 26-10-2011
Last updated: 29-04-2024

Primary objective: The general aim of this study is to elucidate the role of the glycocalyx in the pathogenesis of DCI in SAH and to study the effects of magnesium on glycocalyx volume.Main objectives of this proposal are:- To assess whether the...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Central nervous system vascular disorders
Study type	Observational invasive

Summary

ID

NL-OMON35997

Source
ToetsingOnline

Brief title
Glycocalyx In Subarachnoid Hemorrage - GLISH

Condition

- Central nervous system vascular disorders

Synonym
Subarachnoid hemorrhage ; stroke

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: AMC flexible OIO grant

Intervention

Keyword: Delayed cerebral ischaemia, Glycocalyx, Magnesium, Subarachnoid hemorrhage

Outcome measures

Primary outcome

To evaluate whether the endothelial glycocalyx is affected after SAH and in DCI and is related to severity of SAH.

Differences in glycocalyx volume will be assessed by Sideview Darkfield (SDF) imaging as estimate of glycocalyx volume in patients with SAH and by measurement of glycocalyx constituents in plasma. DCI is diagnosed clinically, excluding other causes of neurologic deterioration. Severity of SAH is defined by the WFNS score.

Secondary outcome

- Association between gylocalyx volume and administration MgSO4 in SAH

- Association between glycocalyx perturbation in SAH and vasomotion changes as non-invasively assessed by finger arterial waveform registration.

- Association between glycocalyx perturbation and blood pressure

- Association between glycocalyx perturbation and clinical outcome, defined by the Rankin scale 3 months after the SAH. The Rankin scale is a 6-point handicap scale that focuses on restrictions in lifestyle.

- Association between glycocalyx perturbation and endothelial damage, platelet activation, thrombin generation and fibrinolytic activity

Study description

Background summary

Subarachnoid hemorrhage (SAH) caused by a ruptured aneurysm accounts for only 5% of strokes, but occurs at a fairly young age and carries a worse prognosis than other types of stroke. Because of this, the loss of productive life years from SAH is as large as that from ischemic stroke, the most frequent subtype of stroke.
Delayed cerebral ischemia (DCI) is consistently the leading cause of death and disability, adversely affecting more than one in five of all patients who have suffered SAH and survived. The characteristics of DCI show resemblance with eclampsia, a common, potentially life-threatening, complication of pregnancy.
At present, the pathophysiology of DCI is incompletely understood. In a meta-analysis of all randomized clinical trials, magnesium shows a tendency to reduce the occurrence of DCI and poor outcome after SAH. A large phase III trial, the MASH-II (Magnesium in Aneurysmal Subarachnoid Hemorrhage) is currently being conducted investigating the potential beneficial effects of magnesium in SAH.
The endothelial glycocalyx is a layer of complex sugars lining the endothelium thereby providing a first line defence mechanism between flowing blood and the vessel wall. The glycocalyx regulates vascular permeability for macromolecules and is involved in vessel tone regulation by mediating shear-dependent NO release. In addition, the glycocalyx has potent anti-thrombotic effects.
Because of recent experiments and previous observations we believe that damage to the endothelial glycocalyx may play a pivotal role in pre-eclampsia. Perturbation of the glycocalyx in experimental models leads to increased vascular leakage, proteinuria and a prothrombotic state. Moreover plasma hyaluronan levels appear to be significantly increased in pre-eclamptic women compared to healthy pregnant controls. Finally, it has been demonstrated that magnesium is required for inhibition of hyaluronidase, an important glycocalyx degrading enzyme, thereby preserving glycocalyx volume. The as yet unexplained beneficial effects of magnesium sulfate in pre-eclampsia could therefore rely on magnesium-related preservation of glycocalyx volume, but this may also play a role in DCI after SAH. There are, however, no reports on the role of the glycocalyx in the development of DCI in SAH patients.
As sulfate may add to the biosynthesis (*sulfation*) of heparan sulfate, their may be a dual role of magnesium sulfate (MgSO4) in preserving and stimulating glycosaminoglycan synthesis.
Based on findings of recently performed experiments we hypothesize that perturbation of the endothelial glycocalyx contributes to impaired flow mediated dilatation and increased permeability of the endothelial surface layer in SAH patients. Additionally magnesium administration results in preservation of glycocalyx volume and diminishes glycocalyx shedding.

Study objective

Primary objective: The general aim of this study is to elucidate the role of

the glycocalyx in the pathogenesis of DCI in SAH and to study the effects of magnesium on glycocalyx volume.
Main objectives of this proposal are:
- To assess whether the glycocalyx is affected in SAH patients and is related to its severity and the development of DCI.
- To evaluate whether glycocalyx perturbation is associated with vasomotion changes as non-invasively assessed by finger arterial waveform registration, in SAH patients.
- To determine whether the proposed beneficial effects of magnesium may be explained by its ability to preserve glycocalyx volume and prevent further glycocalyx shedding.

Study design

A total of 40 SAH patients will be enrolled of which at least twenty patients are included in the MASH II study (MEC 07.241) to allow comparison of MgSO4 treatment and placebo on glycocalyx shedding and -volume. In addition 20 control subjects matched for age and gender will be included to assess differences in glycocalyx perturbation in SAH patients. The subgroup from the MASH-II trial is randomized for 20 day treatment with magnesium sulphate or placebo. MASH-II randomization is performed in block-sizes of 4 patients. Patients or their legally-appropriate substitute decision maker will be approached to participate in the study. They will be informed about the rationale of this study, possible risks and study burden. Eligible candidates or their legally-appropriate substitute decision maker who are willing to participate will be asked to provide informed consent. The following non-invasive measurements will be performed on admission, i.e. prior to initiation of treatment with MgSO4 and at 3, 7 and 20 days following admission: 1. glycocalyx dimensions will be visualized using SDF imaging, 2. noninvasive finger arterial pressure waveform registration by Nexfin (BMeye, Amsterdam, The Netherlands) will be used for continuous monitoring of heart rate, blood pressure, cardiac stroke volume, cardiac output, and peripheral vascular resistance. 24-hour urine samples will be collected. Finally, blood samples will be drawn with routine laboratory assessments on admission. Additionally, laboratory assessments for measurement of coagulation, glycocalyx constituents and enzymes will be performed on admission, i.e. prior to initiation of treatment with MgSO4, and at 3, 7 and 20 days following admission. When patients are discharged before the final measurements on day 20, but have completed all prior measurements, their participation will be concluded as such, i.e. the day 20 measurements will not be performed.
Approximately three months after the initial SAH included subjects will be contacted for a short telephonic questionnaire to asses for clinical outcome defined by the RANKIN scale.
Hypertension is a major risk factor for subarachnoid hemorrhage.(16) Treated and untreated, age and gender matched control subjects will be recruited from the hypertension out-patient clinic of the AMC, Amsterdam and from the patients next of kin. By choosing this control group we should be able to correct for

possible hypertension related, shear-stress induced, changes in glycocalyx perturbation. Additionally, relatives to SAB patients will be asked to participate as control subjecs. Control subjects will undergo one session of non-invasive measurements, additionally a single set of venous blood samples will be taken, totaling 40 ml of blood.

Study burden and risks

Virtually all measurements, with the exemption of bloodsampling, performed in this study are non-invasive. We will attempt to combine blood drawing for research purposes with blood drawings for regular patient care, thus minimizing additional discomfort. If possible, blood will we aspirated from intra-venous lines inserted for regular patient care. Control subjects will undergo a single venapuncture, with risk of a hematoma at the puncture site. The techniques used in this study consist of normal light (SDF-imaging) or localized pressure (finger arterial waveform registration) and are considered safe. The discomfort and risks associated with these measurements are comparable to an abdominal ultrasound examination.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
1105 AZ Amsterdam
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
1105 AZ Amsterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subarachnoid hemorrhage with aneurysmal pattern on CT
or
xanthochromia of the cerebrospinal fluid and aneurysm demonstrated on angiography

Exclusion criteria

Any chronic inflammatory condition
Perimesencephalic hemorrhage
Pattern of hemorrhage on CT not compatible with ruptured aneurysm
Body weight < 50 kg
Death is imminent
Hypermagnesemia on admittance (due to iatrogenic magnesium administration)
No informed consent

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	60

Type:	Actual

Ethics review

Approved WMO	
Application type:	First submission
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

No registrations found.

In other registers

Register	ID
CCMO	NL36494.018.11