The role of tissue factor pathway inhibitor in the development and progression of ischemic cerebral lesions due to cerebral micro-angiopathy

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Primary Objective: 1)Is the release of TFPI by endothelium after admission of heparin different between lacunar stroke patient and healthy controls?2) Is the release of TFPI by endothelium after admission of heparin different between lacunar stroke...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON31866

Source
ToetsingOnline

Brief title
TFPI in lacunar stroke

Condition

- Central nervous system vascular disorders
- Embolism and thrombosis

Synonym
Lacunar stroke. Stroke.

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Ziekenhuis Maastricht
Source(s) of monetary or material Support: Trombosestichting Nederland

Intervention

Keyword: Cerebral small vessel disease, Endothelial dysfunction, Lacunar stroke, TFPI (tissue factor pathway inhibitor)

Outcome measures

Primary outcome

Plasma concentration of TFPI before and after administration of heparin in

controls and lacunar stroke patients.

Secondary outcome

Not applicable

Study description

Background summary

In the Netherlands annually 30.000 individuals suffer from a stroke. A fifth of these are lacunar type 3. Lacunar infarcts are small infarcts (2-20mm in diameter) in de deep cerebral white matter, basal ganglia, or pons, and result from the occlusion of a single small perforating artery supplying the subcortical areas of the brain4. At autopsy, Fisher5 distinguished two types of underlying vascular pathology in patients with lacunar infarcts; lipohyalinosis/arteriolosclerosis and micro-atheromatosis. Even during life, these two types can be distinguished. Patients with a single lacunar infarct, more often have atheromatosis, and patients with concomitant white matter lesions and asymptomatic lacunar infarcts more often have lipohyalinosis or arteriolosclerosis6. More recently, we found that patients with the second subtype have a more unfavorable prognosis7. On the basis of these findings we hypothesized that different entities with different underlying pathofysiological mechanisms exist.
In 2003 we started a prospective follow-up study of patients with a first ever lacunar stroke syndrome with compatible lesion on MR-scanning of the brain (MEC 04-001). By the modified Fazekas scale2, the concomitant white matter lesions (WMH) and asymptomatic lacunar infarcts were scored. After at least 3 months, a

single fasted blood withdrawal was performed , and plasma was stored. D-dimer, Von Willebrand factor (vWF)-antigen, soluble Thrombomodulin (sTM) and tissue factor pathway inhibitor (TFPI) were measured using ELISA or immuno-turbidimetric assay. Chi square analysis was used to relate concentration of plasma markers (divided into tertiles) to severity of white matter lesions (divided into a dichotome variable). In this pilot study we found, high levels of TFPI to be associated with extended WMH (p=0.026). The distribution of sTM and vWF was equal between the two groups. There was no indication of influence of activated coagulation, since D-dimer levels were not associated with severity of disease. We concluded that higher levels of TFPI in lacunar stroke patients with extensive WML could suggest endothelial dysfunction, the lack of difference in plasma levels of vWF and sTM makes this hypothesis unlikely. In the absence of activated clotting as a significant risk factor, the specific contribution of TFPI in the pathogenesis of lacunar stroke is unclear.
TFPI is the main inhibitor of the factor VIIa (FVIIa)/Tissue Factor (TF) pathway of coagulation (extrinsic pathway). TFPI first binds and inhibits factor Xa, followed by binding of TF and FVIIa, leading to an inactive quaternary complex. About 75% of all TFPI is bound, by a positively charged carboxy-terminus, to negatively charged glycosaminoglycans on the luminal surface of the endothelium. By injection of heparin this pool can be released into the circulation8.In most studies only lipoprotein-bound and free TFPI is evaluated, but this only constitutes about 22,5% of the total amount of TFPI. Ariens et al. found normal levels of TFPI before administration of heparin, but abnormal low levels of TFPI after injection of heparin in young patients with venous and arterial thrombosis 9. On the other hand, Leurs et al. found in patients with diabetes mellitus with albuminuria- as a manifestation of generalized angiopathy - high levels of TFPI, compared to patient with DM without albuminuria. After administration of heparin, the increase of TFPI -release was also higher in the group of patients with albuminuria. The authors suggest that this could be the result of altered endothelial glycoaminoglycans. So, in this study, as in our data, high levels of TFPI are an expression of the activated endothelium and not of changes in coagulation, as levels of D-dimer were normal.

Study objective

Primary Objective:
1)Is the release of TFPI by endothelium after admission of heparin different between lacunar stroke patient and healthy controls?
2) Is the release of TFPI by endothelium after admission of heparin different between lacunar stroke patients with or without concomitant ischemic white matter lesions?
Secondary Objective(s): Not applicable

Study design

The study is an non-randomized open intervention study, consisting of an single IV dose of heparin. The infusion of heparin is preceded and followed by blood withdrawal from an antecubital vein.

Intervention

Single dose of heparin 7500 IU (intravenous)

Study burden and risks

Two blood withdrawals, before and after IV administration of a single dose Heparin (7500 IE). Risks associated with the intervention: hematoma puncture site and haemorrhage elsewhere. We want to investigate if endothelial dysfunction in plausible in lacunar stroke.

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

Adult patients with symptomatic lacunar stroke in the past 5 years.
and healthy controls (>18 years old)

Exclusion criteria

History of intracranial or major extracranial bleeding
Use of oral anticoagulants
Hemorrhagic diathesis
Allergy for heparin
For healthy controls:
History of cardiovascular events (stroke, myocardial infarction or periphery artery disease)
Known cardiovascular risk factors (hypertension, diabetes mellitus).

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-10-2008
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Heparin
Generic name:	Heparin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-08-2008
Application type:	First submission
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

ID: 28742
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2008-004280-19-NL
CCMO	NL23829.068.08
OMON	NL-OMON28742