Plasmin generation in tPA-mediated fibrinolysis in patients with stroke

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The primary objective of this pilot study is to test logistics and gather information on possible (technical) problems that may arise during a study investigating the role of plasmin generation during ischemic stroke. Specifically, the following...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular therapeutic procedures
Study type	Observational invasive

Summary

ID

NL-OMON46577

Source
ToetsingOnline

Brief title
Plasmin generation in fibrinolysis for stroke

Condition

- Vascular therapeutic procedures
- Embolism and thrombosis

Synonym
CVA, stroke

Research involving
Human

Sponsors and support

Primary sponsor: Gelre Ziekenhuizen
Source(s) of monetary or material Support: Ministerie van OC&W,Synapse Research Institute;Maastricht

Intervention

Keyword: Fibrinolysis, Plasmin, Stroke, tPA

Outcome measures

Primary outcome

An inventory of possible problems occurring for each of the study aspects a-d specified under **Objectives** will be made and evaluated during and at the end of the study, leading to a **go** or **no go** decision for a larger follow up study. A **no go** decision will be made if problems that potentially jeopardize the entire study could not be solved/are recurring during the pilot study. This will be objectified by the following items that we will include in our inventory:

a) - Patients fulfil inclusion criteria but are **missed** for inclusion in the study (not asked by investigator, this does not include patients who do not want to participate).

- Patients are included that should not have been included as they fulfil (one of the) exclusion criteria.

- Complaints/questions about unclarity of inclusion/exclusion criteria received by investigator(s).

- Transportation to/arrival at the laboratory >2 hours after blood drawal

- Mistakes in informed consent procedure, such as wrong forms were given to patient or representative, signed forms missing/not stored properly, no notification of investigator at the lab of inclusion patient

- Mistakes in blood drawal, for example in type and number of extra tubes drawn.

- Clinical scores are not obtained/reported by investigators.

b) Complaints from patients/representatives about e.g. lengthiness, language used (not layman enough).

c) Partially overlapping with a (e.g. mistakes in blood drawing, logistics, inclusion of patients), but also including: mistakes in technical handling and processing of blood samples at the laboratory, performing tests, aliquoting and freezing plasma for later use, administration of included patients, test results, sample storage. Inventory will be made.

d) Equipment refers to all materials and apparatus used for the laboratory tests, including the fluorometer for plasmin generation and thrombin generation, the flow cytometer for platelet function testing, the STA-R Evolution for coagulation factor measurements, the Cell Dyn Sapphire for differential cell counts, analyzer for blood group determination, absorbance reader for immunosorbent assays (e.g. vWF propeptide and active vWF). Samples will be measured in triplicate for all assays except platelet function and coagulation factor measurements, cell counts and blood group. For these assays there is are internal controls that will aid in identifying erroneous results as a consequence of wrong operation of the equipment. For triplicate measurements (e.g. ELISA assays, thrombin and plasmin generation) the CV (calculated as SD/mean *100%) will indicate whether the variation is too large (>10%) and hence operation is inadequate.

The main laboratory outcome parameter is plasmin generation, which is described by the following parameters (depicted in the figure below):

- Plasmin potential (PP) - total amount of plasmin generated during fibrinolysis (this is considered the main parameter of plasmin generation in this study)

- Lag-time - time until start of plasmin formation

- Time to first peak (TtFpeak) * time to maximum concentration of plasmin formed in the first phase of plasmin generation.

- Time to second peak (TtSpeak) - time to maximum concentration of plasmin is formed on fibrin degradation products.

- Maximum concentration of plasmin * height of the first peak (peak1).

- Velocity of first peak formation - initial rate of plasmin formation.

Secondary outcome

Secondary laboratory parameters are:

- Directly related to plasmin:

o Clot lysis turbidity assay

o Plasminogen

o tPA

o PAI-1

o von Willebrand factor and activated von Willebrand factor

o Fibrinogen

o Plasmin-anti-plasmin (PAP)

- Not directly related to plasmin

o Platelet function test * Platelet Activation Test (PACT)

o D-dimer

o Thrombin generation (0, 1, 5 pM, 5pM+TM; before tPA and 48 hours after tPA treatment)

Also, several clinical data will be collected in this study:

Patient related

- Date of birth (age)

- Ethnicity

- Gender

- Body weight (kg) 1

- Length (cm)

- BMI (obesity)

Therapy related

- Time to tPA treatment from arrival at the hospital

- Comedication (a.o. thrombocyte aggregation inhibitors, DOACs, other anticoagulants) and duration of these medications.

- Dose of tPA (weight based)

- Surgery

- Occurrence of an allergic reaction to tPA (very rare)

Disease related

- Stroke severity score NIHSS 2

- modified Rankin Scale (mRS)

- Prior history of thrombosis

- Prolonged immobility

- Comorbidities

- Type of bleeding if it occurs (e.g. epistaxis, intracerebral)

- Type of recurrent thrombosis if it occurs

- Mortality at 90 days

Study description

Background summary

Acute ischemic stroke (AIS) is one of the leading causes of death and disability across the globe [1-3]. Re-establishing perfusion through the blocked blood vessels is most commonly achieved by pharmacologic thrombolysis with tissue-type plasminogen activator (tPA) [4], a protease that generates the fibrinolytic serine-protease plasmin from its inactive precursor plasminogen [5]. Recombinant (r-)tPA, also called alteplase® or actylase®, is still the only regulatory-approved form of fibrinolytic therapy [6]. Controversy exists on what the optimal dose of IV r-tPA should be, as each individual is likely to have a different level of endogenous fibrinolysis, requiring lower or higher doses to achieve effective and safe thrombolysis. Individualized dosing of r-tPA based on an individuals* endogenous plasmin generation is a promising way to improve r-tPA-mediated thrombolysis in patients with stroke. We have recently developed a plasmin generation assay. In addition, recent studies show that plasmin can cleave von Willebrand Factor (VWF), the multimeric protein crucial for platelet adhesion and aggregation to form the obstructive clot. We have also developed an assay to measure this **plasmin-sensitive** VWF. The current study serves as a pilot study to test the logistics and techniques for a bigger study investigating the role of plasmin in clot lysis during stroke.

Study objective

The primary objective of this pilot study is to test logistics and gather

information on possible (technical) problems that may arise during a study investigating the role of plasmin generation during ischemic stroke. Specifically, the following aspects will be checked:
a) instructions given to investigators and technicians/nurses (i.e. inclusion/exclusion criteria, informed consent procedure, blood draws and transportation to the laboratory, reporting of clinical scores) are comprehensible.
b) informed consent letter(s) is/are comprehensible and not too burdensome for patients and their representatives
c) investigators and technicians are sufficiently skilled in the procedures.
d) correct operation of equipment

An inventory of possible problems occurring for each of these study aspects a-d will be made and evaluated during and at the end of the study, leading to a **go** or **no go** decision for a larger follow up study. A **no go** decision will be made if problems that potentially jeopardize the entire study could not be solved/are recurring during the pilot study.

Study design

Brief description of the study design:
* Prospective observational pilot study.
* Patients will be enrolled at the Gelre Hospitals Apeldoorn.
* We aim to include 29 patients of the department of neurology of the Gelre Hospitals Apeldoorn. Patient inclusion is based on newly diagnosed stroke patients who will be treated with tPA for thrombolysis.
* Blood (4 tubes of 3 mL) will be collected before and after tPA administration (1 and 24 hours after)
* Clinical scores for severity of stroke (NIHSS) and degree of disability (mRS) will be obtained before tPA treatment, at 24 hours, 1 week after tPA treatment (NIHSS) and at 1 week and 90 days (3 months) after tPA treatment, as well as estimated before the stroke occurred (mRS). Although this study is not quantitative and no conclusions on relations between laboratory results and clinical outcome can be drawn (due to small sample size), we will collect these clinical scores to test instructions to investigators/compliance with collecting these scores, as this may not be part of the regular routine.
* We expect the study to last for 2 years.

Study burden and risks

Potential risks: Blood samples will be obtained by venapuncture, which is a standard procedure with minimal risks. After obtaining venous blood, application of pressure on the site of blood drawing for several minutes minimizes the risk of bruising. The patient might feel minor pain or be light-headed from this or may experience some temporary discomfort and short-term swelling at the site of a needle stick. For the first blood draw

(before thrombolysis) the patient would also experience this minor burden from the blood draw without this study; blood will be drawn for routine patient care, for this study only extra tubes will be drawn. The other blood draws are extra and not part of routine care. Of note, at 1 hr after thrombolysis prolonged pressure should be applied to the puncture site, because there is an increased risk of developing a bruise/hematoma due to the tPA treatment.

Potential Benefits: the participating patients may benefit from the measurement of hemoglobin at each of the time points after thrombolysis, as this can be indicative of gastrointestinal bleeding as an adverse event of thrombolysis. Hence, by monitoring Hb for this study this side effect may be detected earlier. Patients do not benefit directly from results of other laboratory measurements. However, the obtained results form the basis for a future, larger study which may lead to safer, personalized tPA treatment based on an individual*s plasmin generation for patients with stroke.

Group relatedness: This study cannot be performed without the voluntary participation of the specified group of CVA patients, as we aim (in the larger, follow up study after this pilot study) to specifically study plasmin generation during and directly after stroke in humans in vivo. We realize these patients may be unable to understand the nature and risks of the current study given their medical condition; hence we will use a two-step informed consent procedure (see paragraph 8.2) We believe that including all patients who are able as well as those who are unable to provide informed consent themselves at the time of hospitalization (in these cases they will only be included if a legal representative provides informed consent for blood drawing and the patient or legal representative provides informed consent for the use of the data and results at a later stage after more comprehensive information) is the only way to obtain a population that is representative for the group of CVA patients, in terms of a.o. severity of stroke. Representativeness of the population is important to draw conclusions that are applicable to CVA patients and in the case of this feasibility study also to support in detecting possible problems in logistiscs (e.g. inclusion/exclusion criteria, informed consent procedure) for a larger follow up study. As mentioned under **potential benefits** the group of CVA patients as a whole may eventually benefit from the results of this explorative and the future larger study as they will lead to improved care for CVA patients, i.e. by personalised tPA dosage that is safer and more effective.

Contacts

Public
Gelre Ziekenhuizen

Albert Schweitzerlaan 31
Apeldoorn 7334 DZ
NL
Scientific
Gelre Ziekenhuizen

Albert Schweitzerlaan 31
Apeldoorn 7334 DZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Suffering from ischemic stroke
- Indicated treatment with tPA for thrombolysis
- Age > 18 years

Exclusion criteria

- Subject presents at the Gelre Hospital Apeldoorn with stroke but send to another hospital for mechanic thrombectomy (endovascular recanalization therapy)
- Stroke onset was more than 4.5 hours ago at the time of presentation at the Gelre Hospital. This precludes treatment with tPA, according to clinical practice guidelines, independent of the study protocol.
- Previously documented coagulation defects
- Age < 18 years

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-12-2018
Enrollment:	29
Type:	Actual

Ethics review

Approved WMO

Date:	23-08-2018
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

No registrations found.

In other registers

Register	ID
CCMO	NL63483.068.17

Study results

Date completed: 04-02-2020

Actual enrolment: 8

Summary results
Trial ended prematurely