Thrombolysis Or Anticoagulation for Cerebral venous Thrombosis

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

Summary

ID

NL-OMON34537

Source
ToetsingOnline

Brief title
TOACT

Condition

- Central nervous system vascular disorders
- Embolism and thrombosis

Synonym
cerebral venous and sinus thrombosis, Cerebral venous thrombosis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Nederlandse Hartstichting

Intervention

Keyword: cerebral venous thrombosis, endovascular thrombolysis, heparin, stroke

Outcome measures

Primary outcome

Outcome on the modified Rankin Scale (mortality included) at 12 months after randomization is considered as the primary study outcome to determine the efficacy of thrombolytic treatment. For the primary endpoint the mRS will be dichotomized between 1 and 2 (i.e. poor outcome is defined as a score of 2 or higher, including death).

Secondary outcome

Secondary Endpoints

- mRS at 6 months

- Recanalization at 6 months using MR-venography or CT venography

- Mortality at 6 months

- Need for surgical intervention in relation to CVT (e.g. craniotomy)

Safety endpoints

- Safety of endovascular thrombolysis as defined by major extracranial hemorrhagic com-plications and symptomatic intracranial hemorrhagic complications within one week fol-lowing the intervention.

- All other serious adverse events

Study description

Background summary

Cerebral venous thrombosis (CVT) is a distinct subtype of stroke that mainly affects young and middle aged patients. While it is a relatively rare disease with an overall adult incidence of approximately 5 cases per million, it does account for 5% of all strokes in adults younger than 45. The most important complications of CVT are venous infarcts (50% of patients) and seizures (40%). Despite heparin treatment, which is now generally accepted as first-line treatment for CVT, 22% of patients remain handicapped or die. Large prospective cohort studies have resulted in the identification of a number of risk factors that predict a high probability of poor outcome. In approximately 30% of all CVT patients one or more of these risk factors is present and 40% of these patients remain handicapped or die. More aggressive treatment strategies, such as endovascular thrombolysis, might be warranted in this subset of patients. Endovascular thrombolysis aims to dissolve the existing thrombus by application of a thrombolytic substance within the occluded sinuses, which may result in a more rapid venous recanalization. Published experience with endovascular thrombolysis for treatment of CVT is promising, but is only based on case reports and small case series. Most experts therefore believe that a randomized clinical trial is urgently needed.

Study objective

The objective of this study is to determine the clinical efficacy of endovascular thrombolytic treatment (ET) as compared to standard treatment (any therapeutic heparin regimen) in patients with proven cerebral venous sinus thrombosis and a high chance of poor outcome.

Study design

The study will be an international, multicenter prospective, randomized, open-label, blinded endpoint (PROBE) trial. A blinded, placebo controlled trial is unethical due to the invasive nature of an endovascular procedure. To minimize the risk of bias associated with an open-label study, the primary and secondary endpoints will be assessed by a trained nurse or neurologist who is blinded to the treatment allocation. The PROBE design has the additional advantage that the effect of treatment will be tested as it will be provided in clinical practice.

Intervention

Eligible patients who give their informed consent are randomized (1:1) to receive either
- Investigational treatment: endovascular thrombolytic treatment
- Standard care: (continuation of) any therapeutic heparin regimen.

Investigational treatment: Thrombolytic procedure
Various methods for endovascular thrombolysis for CVT exits. The TOACT trial does not prescribe an explicit protocol for ET that must be used. The exact thrombolytic procedure is a decision of the local investigators, and should comply with local procedures and experience. The minimum requirement is that a catheter is introduced into one or more thrombosed sinuses under angiographic control. The interventionalist may use either alteplase or urokinase as a thrombolytic drug. The combined use of rt-PA and urokinase in a single patient is not allowed. The thrombolytic drug must be infused directly into the thrombosed sinus. The use of bolus infusions, as well as the duration and dosage of the thrombolytic treatment is the decision of the local investigators and may vary according to the degree of recanalization achieved. Continuous local infusion in the cerebral sinus by leaving a catheter in situ is allowed and at the discretion of the interventionalist, as is the use of standard endovascular mechanical methods of clot disruption and removal. Anticoagulation during thrombolytic procedure with heparin (LMWH or unfractionated heparin) is preferable, but not mandatory, and is up to the local investigator. All local investigators should submit a local thrombolysis protocol from their own department for central review and approval before they can join the study. The interventionalist performing the procedure must be experienced in neuro-endovascular techniques. In addition, experience with either ET for CVT or ischemic stroke is required.

Standard care: Heparin
The patients randomized to standard care will receive (or continue) either intravenous adjusted dose unfractionated heparin (aPTT value kept within 1.5 to 2.5 times the normal value), or any type of body-weight adjusted low molecular weight heparin in therapeutic dose, according to local custom and international guidelines. All investigators must submit a local heparinisation protocol for central approval before they can join the study.

Study burden and risks

Based on published results regarding the use of endovascular thrombolysis in CVT patients, there are some indications that this therapy is beneficial for the treatment of CVT. Patients included in the trial have a 50% of receiving endovascular thrombolysis. These patients therefore may directly benefit from the study. The potential complications that may occur during endovascular thrombolysis are the most important risk of the study. These potential complications are described in paragraph E9.

After discharge, patients will be examined at the outpatient clinical twice, once after 6 months and once after 12 months. During these follow-up moments patients will be interviewed and will receive a standard physical examination.

Before the 6 month follow-up visit, all patients will undergo cerebral imaging one time to determine recanalization rate. MRI will used for this purpose, but

if MRI is unavailable, or not possible, CT-scanning with venography will be used.

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

1. CVT, confirmed by cerebral angiography (with intra-arte¬rial contrast injection), magnetic resonance venography or computed tomographic venography.
2. Severe form of CVT with a high chance of poor outcome, as defined by the presence of one or more of the following risk factors
a. Intracerebral hemorrhagic lesion due to CVT
b. Mental status disorder
c. Coma (Glasgow coma scale < 9)
d. Thrombosis of the deep cerebral venous system

3. Uncertainty by the treating physician if ET or standard heparin therapy is the optimal therapy for the patient.

Exclusion criteria

• Age less than 18 years
• Duration from diagnosis to randomization of more than 10 days
• Recurrent CVT
• Any thrombolytic therapy within last 7 days
• Pregnancy (women in the puerperium may be included)
• Isolated cavernous sinus thrombosis
• Isolated intracranial hypertension (without focal neurological signs, with the exception of papilloedema and 6th cranial nerve palsy)
• Contraindication for anti-coagulant or thrombolytic treatment
* documented generalized bleeding disorder
* concurrent thrombocytopenia (<100 x 10E9/L)
* documented severe hepatic or renal dysfunction, that inter¬fe¬res with nor¬mal coa¬gula¬tion
* uncontrolled severe hypertension (diastolic > 120 mm Hg)
* known recent (< 3 months) gastrointestinal tract hemorrhage (not including he¬morrhage from rectal hemorrhoids)
• Any known associated condition (such as terminal cancer) with a poor short term (1 year) prognosis inde¬pendent of CVT
• Clinical and radiological signs of impending transtentorial herniation due to large space-occupying lesions (e.g. large cerebral venous infarcts or hemorrhages)*
• Recent (< 2 weeks) major surgical proce¬dure (does not include lumbar puncture) or severe cranial trauma
• Known allergy against contrast fluid used during endovascular procedures or the thrombolytic drug used in that particular centre
• Previously legally incompetent prior to CVT
• No informed consent

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-09-2011
Enrollment:	38
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alteplase
Generic name:	alteplase
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Urokinase
Generic name:	Urokinase
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	06-07-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	27-02-2014
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-020302-15-NL
CCMO	NL32468.018.10