Thrombolysis Or Anticoagulation for Cerebral venous Thrombosis: rationale and design of the TO-ACT trial

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Abstract

Rationale
Endovascular thrombolysis, with or without mechanical clot removal (ET), may be beneficial for a subgroup of patients with cerebral venous sinus thrombosis (CVT), who have a poor prognosis despite treatment with heparin. Published experience with ET is promising, but only based on case series and not on controlled trials.

Aim
The objective of the TO-ACT trial is to determine if ET improves the functional outcome of patients with a severe form of CVT.

Design
The TO-ACT trial is a multi-centre, prospective, randomized, open-label, blinded endpoint (PROBE) trial. Patients are eligible if they have a radiologically proven CVT, a high probability of poor outcome (defined by presence of one or more of the following risk factors: mental status disorder, coma, intracranial hemorrhagic lesion or thrombosis of the deep cerebral venous system) and if the responsible physician is uncertain if ET or standard anti-coagulant treatment is better. 164 patients (82 in each treatment arm) will be included to detect a 50% relative reduction (from 40 to 20%) of poor outcomes (two-sided alpha 0.05, 80% power).

Study
Patients will be randomized to receive either ET or standard therapy (therapeutic doses of heparin). ET consists of local application of rt-PA or urokinase within the thrombosed sinuses. Mechanical clot removal, such as thrombosisuction, is allowed, but not mandatory. Patients randomized to ET will be treated with heparin before and after the interventional procedure, according to international guidelines. Glasgow coma score, NIH stroke scale and relevant laboratory parameters are assessed at baseline.

Outcomes
The primary endpoint is the modified Rankin score (mRS) at 12 months, with a score ≥2 defined as poor outcome. Secondary outcomes are 6 months mRS, mortality and recanalization rate. Major intra- and extracranial hemorrhagic
complications within one week after the intervention are the principal safety outcomes. Results will be analyzed according to the “intention-to-treat” principle. Blinded assessors (physicians or research nurses) not involved in the treatment of the patient will assess endpoints with standardized questionnaires.
Introduction

Cerebral venous and sinus thrombosis (CVT) has an estimated incidence of 3-4 per million/year. It occurs in similar clinical circumstances as the more common conditions of leg-vein thrombosis and pulmonary embolism, such as pregnancy and post partum, in patients with hematological diseases or cancer, but also in local conditions, such as head trauma, infections, and meningitis. The main consequences of CVT are localized cerebral edema due to impaired venous drainage, cerebral venous infarcts (often hemorrhagic), and intracerebral or localized subarachnoid hemorrhages. Venous obstruction and impaired drainage of the cerebrospinal fluid cause acute or chronic intracranial hypertension, often with papilledema and sometimes threatened vision. Venous cerebral infarcts and hemorrhages may cause epilepsy, severe neurological morbidity or death. On the other hand, thrombosed cerebral veins and sinuses may recanalize without leaving any permanent damage, and the majority of patients recover without sequelae.

Heparin is considered the standard therapy for patients with CVT. The efficacy of heparin therapy has been examined in three small randomized trials, two in Europe and one in India. These studies showed a beneficial, but statistically non-significant effect of heparin. Meta-analysis of the two studies that met predefined methodological standards showed a pooled relative risk reduction of 46% (95% CI 0.16 to 1.31) for death or dependency after anticoagulant therapy as compared to placebo.

Despite the effect of anti-coagulant treatment, approximately 20% of the patients has an incomplete recovery, defined as a Rankin score of 2 or worse. In the “International Study on Cerebral Vein and dural sinus Thrombosis” (ISCVT), the largest prospective cohort study of 624 patients, 21% had a poor outcome (death 8%, Rankin 2 or worse: 13%) after an average follow-up of 16 months. Most patients (80%) had been treated with heparin. In a logistic regression analysis the following factors were associated with a poor outcome: age, male gender, mental status disorder, coma, thrombosis of the deep cerebral venous system, intracranial hemorrhage, infection of the central nervous system and malignancy. The three disease-related factors most strongly associated with incomplete recovery were mental status disorder, coma, and thrombosis.
of the deep venous system, all with odds ratios of 2 or higher. In 30% of all patients (186/624) one or more of these three risk factors were present. Of these patients, 40% was handicapped or had died at 6 months. Thus, based on these variables, it is possible to identify about 1/3 of all patients with CVT with a high risk of incomplete recovery, despite treatment with heparin. For those patients, endovascular treatment may give better results than treatment with heparin.

While heparin mainly prevents extension of thrombosis, endovascular thrombolysis (ET) can dissolve the thrombus by application of a thrombolytic substance within the occluded sinuses, which may result in rapid recanalization. The theoretical advantage of ET over systemic thrombolysis is that the drug is only delivered where needed and downstream from areas of vascular congestion which are at risk to hemorrhage. ET can be combined with mechanical endovascular techniques, such as thrombus disruption with a guiding catheter, thrombosuction with a rheolytic catheter, and thrombus removal with a balloon catheter.10-12 To apply the thrombolytic drugs into the sinus, a catheter has to be advanced into the thrombus, usually via the femoral or jugular vein, and gradually moved to a more distal position while the thrombus is dissolved. Often, the catheter is left in situ, and the thrombolytic drug is infused locally for variable periods of time, often for 24 to 72 hours.12,13

The published experience with ET for CVT consists of case reports and case series.13,14 Interpretation of the results is difficult because of the variability of patient selection and procedures. Some studies do not give data on the clinical condition of the patient before endovascular treatment or the clinical outcome after the procedure. A systematic review of all published cases up to July 2001 identified 72 publications describing a total of 169 patients, all single case reports or uncontrolled case series.13 Urokinase and rt-PA were the most frequently used thrombolytic drugs, respectively in 75% and 22% of the patients. Infusion of the thrombolytic drug was performed locally in the cerebral venous system in 88% of the patients and systemically in 10% (in 2% a combination was applied). There was much variability in dosage and duration of ET. Duration of thrombolytic treatment ranged from less than one hour to more than 10 days, but without an apparent association with outcome. One third of the patients had an intracranial hemorrhage on their pre-treatment (CT or MR) scan, and 32% were comatose. New symptomatic intracranial hemorrhages
were reported in 5% of the cases. Mortality at the end of follow-up was 9%, and 4% of the patients were dependent (Rankin 3-5). Since these studies are uncontrolled, they do not allow reliable conclusions about the efficacy of ET for CVT. However, the large number of patients in coma (32%, as opposed to 5% in the ISCVT study) suggests that the clinical spectrum in these publications included many severe cases. Yet, the pooled outcome is similar to that in heparin treated patients in the ISCVT. This suggests that ET may be a more effective treatment for CVT than heparin. However, the apparently good results may also be explained by publication bias. In the ISCVT, only 13 (of 624) patients were treated with ET, 5 of whom (38%) were dead or dependent at 6 months follow-up. Furthermore, in a single-centre prospective case series, 6 of 20 patients treated with ET died. A Cochrane review did not identify controlled clinical trials regarding endovascular treatment for CVT, and the authors concluded that a trial is urgently needed.

From all available data we conclude that a randomized trial to compare heparin and ET for the treatment of patients with severe CVT is justified and needed.

Methods

Design
The ‘Thrombolysis Or Anticoagulation for Cerebral venous Thrombosis (TO-ACT) study’ is an international, multicenter prospective, randomized, open-label, blinded endpoint (PROBE) trial. A blinded, placebo controlled trial is unethical due to the invasive nature of the endovascular procedure. To minimize the risk of bias associated with an open-label study the primary and secondary endpoints will be assessed by trained nurse or neurologists, blinded to the treatment allocation.

Patient population
All adult patients with severe CVT who are admitted to one of the participating hospitals are eligible for randomization if they meet the inclusion and exclusion criteria described below.
Inclusion Criteria

- CVT, confirmed by cerebral angiography (with intra-arterial contrast injection), magnetic resonance imaging (preferably with MR-venography) or computed tomographic venography.
- Severe form of CVT, as defined by the presence of one or more of the following risk factors
  - Intracerebral hemorrhagic lesion due to CVT
  - Mental status disorder
  - Coma (Glasgow coma scale < 9)
  - Thrombosis of the deep cerebral venous system
- 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 papilledema and 6th cranial nerve palsy)
- Cerebellar venous thrombosis with 4th ventricle compression and hydrocephalus, which requires surgery
- Isolated thrombosis of the cerebral veins, without thrombosis of any of the sinuses, such as cortical venous thrombosis
- Contraindication for anti-coagulant or thrombolytic treatment
  - documented generalized bleeding disorder
  - thrombocytopenia (<100 x 10E9/L)
  - documented severe hepatic or renal dysfunction, that interferes with normal coagulation
  - uncontrolled severe hypertension (diastolic > 120 mm Hg)
  - known recent (< 3 months) gastrointestinal tract hemorrhage (not including hemorrhage from rectal hemorrhoids)
- Any known associated condition (such as terminal cancer) with a poor short term (1 year) prognosis independent 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 procedure (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
• Legally incompetent prior to CVT

Additional notes on the exclusion criteria:
1. Intracerebral hemorrhage, hemorrhagic infarction, or subarachnoid hemorrhage as a result of CVT are not exclusion criteria.
2. Initial treatment with heparin is not an exclusion criterion. Patients who deteriorate while on heparin treatment may be included and randomized if they fulfill the criteria.

Randomization
After eligibility has been confirmed and written informed consent obtained, a 1:1 randomized allocation will be made to endovascular thrombolytic treatment or (continuation of) any therapeutic heparin regimen. The randomization procedure is computer- and web-based, within permuted blocks and stratified by:
- Pre-treatment intracranial hemorrhage
- Coma

Randomization software is made available by the Clinical Research Unit of the Academic Medical Centre.

Treatment
The investigational or standard care treatment should begin as soon as possible after the diagnosis, and not later than 24 hours after randomization.

Investigational treatment: endovascular thrombolysis
Various methods exist for endovascular treatment of CVT. The TO-ACT trial does not prescribe a mandatory protocol for ET. The exact thrombolytic procedure is a decision of the local investigators, and should comply with local procedures and experience, but within boundaries, as described below.
The minimum requirement is that a catheter is introduced into one or more thrombosed sinuses under angiographic control. Access to the cerebral venous system must be via the jugular or femoral vein. The use of a multi-side hole catheter (instead of an end-hole) is advisable. The interventionalist may use either alteplase (rt-PA) or urokinase. 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. The aim of the procedure is to restore venous flow – to the extent possible - in the thrombosed veins and/or sinuses. Complete recanalization of the cerebral venous system is commendable, but not mandatory, and often not attainable. Maximum dosages for both urokinase and rt-PA are as follows.

Dosage limits for rt-PA:
- Intrasinus injection during interventional procedure: maximum 30 mg
- Continuous local infusion: maximum 1.5 mg/hr

Dosage limits for urokinase:
- Intrasinus injection during interventional procedure: maximum 600,000 IU
- Continuous local infusion: maximum 100,000 IU/hr

Note: These are maximum dosages, not the advised dosages. Interventionalists should attempt to achieve recanalization with the lowest possible dose.

Continuous infusion into the cerebral sinus by leaving a catheter in situ is allowed and depends upon the initially achieved degree of recanalization. The decision whether or not to use continuous infusion is left to the interventionalist. Placement of the catheter should be as distally in the thrombosed sinus as possible. Radiological control of venous flow should be performed at least every 24 hours, but preferably every 12 hours, as long as the catheter is in situ. The duration of continuous infusion may not exceed 72 hours, and should be discontinued earlier if sufficient recanalization has occurred. If there is no apparent progression of recanalization after 24 hours of infusion, the continuous infusion should also be terminated.
The use of mechanical clot disruption and removal, such as microcatheters, balloon angioplasty and rheolytic catheters, is allowed and at the discretion of the responsible physicians, in accordance with local policy and experience.\textsuperscript{10-12} The use of mechanical clot removal will be documented in all cases.

Anticoagulation during thrombolytic procedures with heparin (low-molecular weight heparin or unfractionated heparin) is allowed, but not mandatory, and is up to the local investigator. Heparin therapy must be started (or continued) after thrombolytic procedure in all patients, as standard treatment for CVT, according to international guidelines.\textsuperscript{4,5} Heparin must be started at the latest 24 hours after termination of the thrombolysis. If continuous infusion with urokinase or alteplase is used after the primary endovascular procedure, termination of this infusion is considered the end of the thrombolytic procedure.

All investigators must submit a local ET 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 ET either for CVT or ischemic stroke is required.

Thrombolytic treatment will be stopped immediately if one of the following complications arises:
- Major extracranial hemorrhage
- Clinical deterioration due to new intracranial hemorrhage or due to hemorrhagic transformation of a cerebral infarct
- Need for (neuro-)surgical intervention

\textit{Standard care: Heparin}

The patients randomized to standard care will receive (or continue) either intravenous adjusted dose unfractionated heparin (aPTT value 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.\textsuperscript{4,5} Investigators are free to choose the type of heparin, although the steering committee advocates the use of low-molecular heparins because of a better safety profile in leg-vein thrombosis and possibly also in CVT (18). All investigators must submit a local heparinisation protocol for central approval before they can join the study. Any change in type of heparin will be documented.
Long term anticoagulation
After the acute phase, patients in both treatment arms should receive oral anticoagulation (vitamin K antagonists), as standard treatment after CVT, for a minimum of 3 months if a transient risk factor was present and 6-12 months in other cases, in agreement with international guidelines. The exact duration of long term anticoagulation is left to the local investigator. Oral anticoagulation should not be started within 48 hours after the thrombolytic procedure.

Primary outcome
Outcome on the modified Rankin Scale (mRS) at 12 months after randomization is the primary 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 outcomes
1. Incomplete recovery (mRS ≥ 2) at 6 months
2. Rate of death or dependency at 6 and 12 months (mRS 3-6)
3. mRS (non-dichotomized) at 6 and 12 months
4. Recanalization at 6 months assessed with MR-venography or CT venography
5. All cause mortality at 6 and 12 months
6. Surgical intervention in relation to CVT (ventricular shunting procedures and craniotomy or craniectomy)

Safety outcomes
1. Safety of ET as defined by major extracranial hemorrhagic complications and symptomatic intracranial hemorrhagic complications within one week following the intervention
2. All other serious adverse events

Data Safety Monitoring Board
The Data Safety Monitoring Board (DSMB) is an independent committee of trial experts who will monitor safety and effectiveness data. The DSMB consists of three members: 2 clinicians and 1 epidemiologist. The DSMB performs ongoing safety surveillance, with emphasis upon serious adverse events, notably hemorrhagic, thrombo-embolic and other complications. The DSMB can recommend the Steering Committee of the study to terminate the study
when there is clear and substantial evidence of harm or benefit. The DSMB will additionally perform two interim analyses after 55 and 110 patients (1/3rd and 2/3rd of all patients) have been randomized and completed the 12-month follow-up evaluation.

**Reporting of serious adverse events**

The study utilizes a web-based Serious Adverse Event (SAE) Reporting system. The digital SAE form contains all information required by the regulatory authorities. In the case of a serious event or a suspected unexpected serious adverse reaction (SUSAR), the site investigator must report details of the SAE/SUSAR to the AMC trial centre within 24 hours by filling in this web-based form. The AMC trial centre in turn will notify the appropriate national coordinator of the presence and nature of the SAE/SUSAR within 24 hours. The national coordinators are responsible for submitting unblinded reports of SAE/SUSARs to the appropriate regulatory authorities and ethics committees of their country in accordance with their local laws and within the required time windows. If for whatever reason, a site investigator cannot submit an SAE/SUSAR form through the web-based system, the AMC trials centre should be informed by any other means of communication (fax, phone or email) within 24 hours.

**Sample size**

Calculation of the sample size is based on an expected incidence of incomplete recovery of 40%, defined as a score of 2 or worse on the modified Rankin Scale or death, among patients receiving standard treatment (heparin group). Reduction of this number to 20% or less would represent a clinically important improvement. Using a two group Chi-square test with a 0.05 two-sided significance level we will have 80% power to detect this difference when the sample size in each group is 82 patients (164 patients in total).

**Statistical Analyses**

*Univariate and multivariate analyses*

The results will be analyzed according to the “intention-to-treat” principle. The primary analysis will focus on the number of patients in poor clinical condition at 12 months after randomization (mRS ≥ 2, including death). The effect size will be expressed in relative risk estimates and absolute risk reduction. With regard to the Rankin scale scores (mRS ≥ 2) at 6 months, and rate of death or dependency
at 6 and 12 months (mRS 3-6), we will follow the same approach. Additionally we shall analyze the 6 and 12-months Rankin scores with multivariate logistic regression, with adjustment (if necessary) for relevant baseline imbalances. The remaining secondary outcome parameters (survival, recanalization, full mRS score and surgical interventions) will be analyzed with Kaplan-Meier survival curves and the log-rank test, $X^2$ test, Mann-Whitney test and ordinal logistic regression, when appropriate. In all analyses, statistical uncertainty will be expressed as 95% confidence intervals.

**Interim analyses**

The DSMB will perform two unblinded interim analyses on the safety endpoints and the primary outcome to assess the strength of the efficacy data when one-third (55) and two-thirds (110) of the patients have been randomized and followed-up. As a stopping rule we use the Haybittle-Peto method:
- Interim analysis 1: $p = 0.001$
- Interim analysis 2: $p = 0.001$
- Final analysis: $p = 0.05$

The DSMB will also check the assumptions for the sample size calculation. The analysis will be performed by an independent statistician of the AMC Clinical Research Unit, who has no responsibility for the management of the trial. The DSMB can recommend the Steering Committee of the trial to:
- Terminate the study when there is clear and substantial evidence of benefit of either of the two treatment arms. The Steering Committee and the DSMB will agree on stopping rules and the statistical methods for analysis of efficacy beforehand.
- Terminate the study if accrual rate is too low or the calculated sample size turns out to be too small to detect a treatment benefit of ET.

**Predefined subgroup-analyses**

Because only a limited number of patients are included in this trial, the results of subgroup analyses can only be used for hypothesis generation, not to determine treatment efficacy within subgroups. Subgroup analyses will also be performed in case of a negative primary outcome. Predefined subgroups are:
- Patients with an intracranial hemorrhage before randomization
- Patients who were comatose before randomization
Patients with a thrombosis of the deep cerebral venous system
- Patients treated with rt-PA vs. urokinase
- Patients treated with mechanical thrombectomy in addition to thrombolysis

**Study organization**

**Steering committee**
Jan Stam, neurologist, Amsterdam, The Netherlands (chair)
José Ferro, neurologist, Lisbon, Portugal
Marie-Germaine Bousser, neurologist, Paris, France
Patricia Canhão, neurologist, Lisbon, Portugal
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**Data safety and monitoring board**
Jaap Kappelle, neurologist, University Medical Center Utrecht, The Netherlands (chair)
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**Trial registration**
This study is registered at www.clinicaltrials.gov (NCT01204333).
References


