

Should the stroke patient be reperfused, and if so, how?

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Most strokes (85%) are ischemic. The central core of densely ischemic tissue is surrounded by a potentially salvageable “penumbral” zone amenable to thrombolytic therapy. Four major studies with recombinant tissue plasminogen activator (rt-PA) have shown that intravenous rt-PA is beneficial if used within a 3-hour timeframe by experienced centers in selected patients: 43% of patients are functionally independent at 30 days, early mortality is 13%, and the intracerebral hemorrhage rate is 3.3%. In a less evaluated procedure, intra-arterial thrombolysis, a thrombolytic drug is released directly into the occluded artery. The two methods can be combined. Backed by the hugely informative input of multimodal magnetic resonance imaging, thrombolysis now represents the most exciting challenge in vascular neurology, despite the formidable logistic constraints of the 3-hour treatment window.

Keywords: stroke; cerebrovascular disease; clinical study; treatment; thrombolytic; streptokinase; rt-PA; prourokinase; multimodal magnetic resonance imaging

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Stroke is the leading cause of disability in the Western world and is responsible for more deaths than any other disease with the exceptions of heart disease and cancer. The burden of cerebrovascular disease is immense; care and rehabilitation of stroke patients consume approximately 6% of all health care resources in developed countries.¹ A wide variety of strategies to treat this common and devastating condition have been investigated in recent years; undoubtedly the most successful to date has been the provision of thrombolytic therapy. In North America and a number of European countries, thrombolysis is now an established

intervention for selected patients with acute ischemic stroke presenting within 3 hours of onset of symptoms. A variety of thrombolytic agents and modes of delivery have been evaluated. This article reviews the evidence that addresses the question “Should the stroke patient be reperfused, and, if so, how?”

BACKGROUND

Thrombolysis has been used for a number of years in the management for patients with myocardial infarction and its efficacy has been demonstrated by a series of large randomized, placebo-controlled trials.^{2,3} Thrombolysis leads to reper-

SELECTED ABBREVIATIONS AND ACRONYMS

ASK	Australian StreptoKinase trial in stroke
ATLANTIS	Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke
dwMRI	diffusion-weighted magnetic resonance imaging
ECASS	European Cooperative Acute Stroke Study
MAST-E	Multicenter Acute STroke study–Europe
MAST-I	Multicenter Acute STroke study–Italy
MCA	middle cerebral artery
mmMRI	multimodal magnetic resonance imaging
NINDS-TPAST	National Institute of Neurological Diseases and Stroke—Tissue Plasminogen Activator Stroke Trial
PROACT	PROlyse in Acute Cerebral Thromboembolism
pwMRI	perfusion-weighted magnetic resonance imaging
rt-PA	recombinant tissue plasminogen activator
STARS	Standard Treatment with Alteplase to Reverse Stroke



fusion of vessels occluded by coronary atherothrombosis, which in turn reduces mortality and preserves left ventricular function.

Most strokes are atherothrombotic or embolic (85%), while the remainder are hemorrhagic. It was hoped that the same "open artery hypothesis" would hold true for patients with ischemic or nonhemorrhagic stroke, and that intervention to accelerate reperfusion would improve both mortality and functional outcome. In patients with stroke, it appears that a central core of densely ischemic tissue is surrounded by a "penumbral" zone of potentially salvageable tissue that is amenable to either neuroprotective or reperfusion therapy (*Figure 1*). The po-

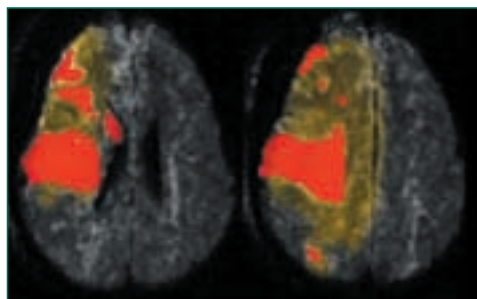


Figure 1. Composite diffusion and perfusion images of acute stroke. The ischemic core of dead and dying brain tissue is highlighted in red; the surrounding hypoperfused area is shown in yellow. This yellow area is thought to represent the "penumbra," which may be spared by timely reperfusion.

tential risks of thrombolysis are predictable from what is known of the pathophysiology of cerebral ischemia; reperfusion injury may occur when toxic free radicals and inflammatory cells enter an ischemic area following spontaneous reperfusion, and hemorrhagic transformation is commonly seen in patients with large infarcts. Certain groups of patients could be thought of as at higher risk of secondary intracerebral hemorrhage as a result of thrombolysis. Elderly patients already have a higher risk of spontaneous intracerebral hemorrhage, as

have hypertensives and patients with embolic rather than simple occlusive atherothrombotic strokes. Delayed thrombolysis may simply lead to reperfusion of already irreversibly infarcted tissue and increase the risk of hemorrhage. When trials of thrombolytics were devised, these issues were considered and are reflected in the design, entry, and exclusion criteria of the studies. All studies incorporated a variable "time window" out of which patients were ineligible, all patients underwent brain imaging with x-ray computed tomography (CT) to exclude intracerebral hemorrhage as the primary pathology, and some studies excluded large infarcts and hypertensive patients. The analysis of treatment efficacy is crucial in the design and

interpretation of any trial of stroke therapy. Most studies incorporated a validated functional outcome score such as the Barthel score.⁴ These scores describe the patients' ability to perform activities of daily living. More detailed assessments of neurological function were also made, using, for example, the Scandinavian Stroke Scale.⁵

A variety of thrombolytic agents and means of drug delivery have been investigated in the context of acute ischemic stroke. The first group of studies to be considered will be those that used systemic intravenous administration of a thrombolytic agent.

INTRAVENOUS STREPTOKINASE STUDIES

The MAST-E (Multicenter Acute Stroke Study–Europe)⁶ and ASK (Australian StreptoKinase trial in stroke)⁷ treated patients with streptokinase (1.5 M units over 1 hour) or placebo within 6 and 4 hours, respectively. In both studies, there

was an increase in early mortality sufficient to result in the safety committees abandoning both studies prior to completion. This correlated with a high incidence of complicating intracerebral hemorrhage. In the MAST-E study, 36% ($n=156$) patients treated with streptokinase vs 3% ($n=154$) placebo patients suffered a fatal hemorrhagic transformation of infarct.

The MAST-I (MAST-Italy) study evaluated treatment with streptokinase and aspirin compared with streptokinase or aspirin alone or placebo.⁸ Again the results suggested an increase in early mortality which was more marked in patients receiving both streptokinase and aspirin, while aspirin alone appeared to be safe, but of no clear benefit. Meta-analysis of all streptokinase results failed to reveal factors that predisposed to early mortality. Streptokinase significantly increased early mortality, while there may have been a trend towards improved outcome in survivors. To date, no randomized controlled trial has supported the use of intravenous streptokinase as therapy for acute ischemic stroke. Further studies of streptokinase using different patient selection criteria, lower doses of thrombolytic, and prohibition of antiplatelet or anticoagulant coadministration have been proposed, however, at present, no such trial is under way. Although there remains some debate,⁹ it is unlikely that streptokinase will have any role in the management of acute ischemic stroke.

INTRAVENOUS RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR STUDIES

Four major trials have evaluated the role of recombinant tissue plasminogen activator (rt-PA) in patients with acute stroke. There

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are theoretical reasons why rt-PA may be more effective:

- First, rt-PA is known to be more “clot-specific,” that is, it causes less generalized activation of plasminogen, instead having a more selective action at the site of the clot itself; this may make hemorrhagic complications less likely.
- Second, rt-PA is less antigenic than streptokinase and is not associated with a fall in blood pressure during the infusion. This may be of significance, as reducing blood pressure immediately after ischemic stroke has been associated with worse outcome.¹⁰
- Finally, angiographic studies in patients with acute myocardial infarction suggest rt-PA is more effective than streptokinase in reperfusing occluded coronary vessels.

ECASS 1 and 2 (European Cooperative Acute Stroke Study [first and second])^{11,12} and NINDS-TPAST (National Institute of Neurological Diseases and Stroke—Tissue Plasminogen Activator Stroke Trial)¹³ evaluated rt-PA at doses of 1.1 mg/kg, 0.9 mg/kg, and 0.9 mg/kg, respectively. Patients were treated within 6 hours in the ECASS studies and 3 hours in the NINDS-TPAST study. The Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study¹⁴ used a dosage of 0.9 mg/kg administered within an initial time window of 6 hours. The time window was altered twice during the study and the results were rather less encouraging.

ECASS 1. The higher dose of rt-PA used in the ECASS 1 study is equivalent to that used in the treatment of patients with myocardial infarction. Dose-ranging studies have shown an increasing incidence of complicating hematoma formation in patients receiving doses greater than 0.85 mg/kg, and this could

have contributed to the increased incidence of hemorrhages seen in the ECASS 1 study. The results of ECASS 1 are also notable for the large proportion of patients excluded from the target population analysis (109 out of 620 randomized). The protocol intended to exclude patients with greater than one-third middle cerebral artery (MCA) territory stroke on CT, ie, those with large infarcts. Sixty-six such patients were randomized, constituting the largest group of protocol violators. Survival in protocol violators was significantly worse than for those meeting the entry criteria. While analysis of the target population results suggested an improvement in functional outcome at 3 months ($P=0.03$), the more rigorous intention-to-treat (ITT) analysis was negative. Mortality was nonsignificantly higher in the rt-PA group in both ITT and target population (TP) analysis. In summary, the ECASS study did not show enough benefit to justify thrombolysis with rt-PA up to 6 hours after stroke onset although an improvement in functional outcome (Barthel⁴ and Rankin¹⁵ scores) was seen in the target population analysis of the rt-PA-receiving patients.

NINDS-TPAST. The National Institute of Neurological Disorders and Stroke—Tissue Plasminogen Activator Stroke Study Group assessed a lower dose of rt-PA (0.9 mg/kg) given within 3 hours of onset of CT-confirmed ischemic stroke. The results suggest an improvement in functional outcome at 3 months, with those in the treated group 30% more likely to have negligible disability at this time point. There was no difference in mortality in the actively treated patients, although there was an increase in symptomatic intracerebral hemorrhage (7% vs 1%; rt-PA vs placebo). Mortality ascribed to intracerebral hemorrhage was 3% vs 0.3%.

ECASS 2. The aim of the ECASS 2 study was to investigate the safety and efficacy of rt-PA given in a dose of 0.9 mg/kg within 6 hours of onset of ischemic stroke. Strenuous efforts to improve the quality of CT interpretation were made, and significantly fewer intracranial hemorrhages were seen in comparison with the original ECASS study. The primary outcome measure was the proportion of patients reaching modified Rankin¹⁵ scores (mRS) of 0 or 1 (ie, little or no disability) at 3 months. The study failed to demonstrate a statistically significant difference between treated and placebo groups; however when the outcome measure was redichotomized to define good outcome as mRS of 0 to 2, a beneficial effect of rt-PA was seen. The authors concluded that rt-PA treatment leads to a clinically relevant improvement in outcome without increased morbidity and mortality despite increased symptomatic hemorrhage. However, the failure of the trial to demonstrate efficacy using predetermined end points has led to the widespread interpretation of the trial as neutral. Incorporation of the ECASS 2 data into a meta-analysis of trials of rt-PA in acute stroke reveals a favorable odds ratio of 0.67 (95% confidence interval [CI] 0.56-0.80) with respect to death and disability.

ATLANTIS. The ATLANTIS study was designed to assess the safety and efficacy of intravenous rt-PA 0.9 mg/kg within 6 hours of ischemic stroke. Two years after recruitment commenced, the time window was changed to 0 to 5 hours due to adverse interim safety analysis in the 5-to-6-hour group. After a further 3 years, the time window was further modified (3 to 5 hours) due to the results of NINDS-TPAST. With the exception of the time window, entry criteria were very similar to those



employed by the NINDS-TPAST investigators. The ATLANTIS study was terminated prematurely in July 1998 following further interim safety analysis, which concluded that "treatment was unlikely to prove beneficial." The 90-day results in the placebo and rt-PA groups did not differ with regard to the primary outcome measure, and the use of intravenous rt-PA beyond 3 hours after stroke onset is not supported by the ATLANTIS study.

TRANSLATION OF TRIAL RESULTS INTO CLINICAL PRACTICE: THE STARS STUDY

Following publication of the NINDS-TPAST study, rt-PA was approved for use in acute ischemic stroke within 3 hours of onset of symptoms. Concerns were raised that the clinical benefit observed in the NINDS-TPAST patients would not be reproduced outside of the highly controlled atmosphere of a clinical trial. The Standard Treatment with Alteplase to Reverse Stroke (STARS) trial¹⁶ investigators addressed these concerns in a prospective, monitored, multicenter trial that evaluated outcome of patients thrombolysed in 57 hospitals in the USA. The results of this trial were reassuring—43% of treated patients were functionally independent at 30 days, early mortality was low (13%), and the overall rate of symptomatic intracerebral hemorrhage was comparable to that observed in NINDS-TPAST at 3.3%.

SUMMARY OF SYSTEMIC THROMBOLYTIC THERAPY FOR ISCHEMIC STROKE

NINDS-TPAST was the first trial to demonstrate that early intervention can improve the outcome for patients with acute ischemic stroke. The ECASS 2 study failed to repro-

duce the convincingly positive results of NINDS-TPAST; however, meta-analysis suggests a beneficial effect of intervention with rt-PA. The benefit of thrombolysis with intravenous rt-PA in patients with acute ischemic stroke has been demonstrated and the trial results appear to be reproducible when the treatment is implemented outside of the context of a clinical trial in the USA. Use of rt-PA can be justified when used judiciously within an experienced center. An application for use of rt-PA in acute stroke in the European Community is currently under consideration. It is likely that approval will be granted for use within 3 hours of ictus in patients with similar characteristics to those in NINDS-TPAST.

In contrast to the rt-PA trials, all studies that used streptokinase in stroke patients have yielded resoundingly negative results. Although it has been argued that the potential benefit of streptokinase has yet to be fully investigated,⁹ on the basis of current evidence its use cannot be justified in the context of acute ischemic stroke.

INTRA-ARTERIAL STUDIES

Intra-arterial thrombolysis involves administration of thrombolytic drugs distal to, directly within, and proximal to luminal thrombus within an occluded cerebral artery. The technique has a number of potential advantages over systemic administration, which may enable provision of treatment to a larger group of patients. Cerebral angiography can be performed immediately prior to instillation of a thrombolytic, hence precise characterization of the arterial occlusion is possible with documentation of the degree and extent of posttreatment reperfusion. Targeted delivery of thrombolytic

enables attainment of high concentrations of thrombolytic drug at its site of action and reduction in systemic exposure, hence bleeding complications are minimized and patients deemed unsuitable for systemic thrombolysis due to bleeding risk may still receive treatment.

Although no randomized comparative data exist, open clinical series^{17,18} have suggested a higher recanalization rate with intra-arterial (60% to 80%) than intravenous (20% to 60%) delivery of thrombolytics. Differences in recanalization rates are particularly marked in the context of internal carotid or proximal middle cerebral artery (MCA) occlusion; these vessels seem particularly resistant to intravenous thrombolysis.

The PROACT studies

A number of clinical trials have helped clarify the role of intra-arterial thrombolysis in the management of ischemic stroke. The first PROlyse in Acute Cerebral Thromboembolism trial (PROACT I)¹⁹ examined the effect of intra-arterial delivery of 6 mg of recombinant prourokinase upon arterial patency in 40 patients with MCA occlusion of less than 6 hours' duration. Recanalization rate was 57.7% in the actively treated group and 14.4% in the placebo recipients. Although the study was not designed to detect an effect of intra-arterial thrombolysis upon outcome, a trend towards benefit of prourokinase was observed. The second PROACT trial²⁰ followed up the suggestion of benefit obtained in the first study. In PROACT II, 180 patients with MCA occlusion of less than 6 hours' duration were randomized to receive 9 mg of intra-arterial prourokinase plus low-dose heparin or heparin alone. A 15% absolute benefit in the number of patients with minimal or no disabil-

ity at 90 days was seen, associated with similar rates of recanalization to those seen in PROACT I. The PROACT studies suggest a role for intra-arterial thrombolysis in the future management of acute stroke; however, that role is yet to be fully defined. Intra-arterial thrombolysis is an invasive procedure that is not without its drawbacks. Manipulation of catheters within the cerebral vessels confers risk of vasospasm or thrombus formation with potentially serious clinical sequelae; although the PROACT studies reported relatively low procedure-related complication rates, adverse events occurring outside of the context of a clinical trial may impinge upon the observed benefit of the intervention. Specialist facilities and expertise are required; at present, these are not widely available outside tertiary stroke centers in either the US or Europe, and hence, at present, relatively few patients will benefit from its use. The necessary preoperative preparation may extend "door-to-needle" time and reduce the benefit of reperfusion. These problems have prompted further investigation of combined thrombolytic strategies that aim to confer the advantages of the intra-arterial technique, but also enable provision of very rapid treatment.

The potential benefit of combined intravenous and intra-arterial thrombolysis has recently been explored in a small pilot study,²¹ in which low-dose intravenous rt-PA was administered prior to cerebral angiography and intra-arterial thrombolysis. The technique appeared safe and feasible, with high rates of arterial recanalization. The promising results of this small study will doubtless stimulate further work in the evolution of future acute strategies, including combination of thrombolytic agents with future neuroprotective drugs.

THE FUTURE

Improved patient selection

The trials discussed all used CT to exclude intracerebral hemorrhage prior to administration of thrombolytic agent. This technique is notoriously insensitive in the context of acute ischemic stroke, and will eventually be replaced by multimodal magnetic resonance imaging (mmMRI).²² This modality allows reliable identification, localization, and quantification of ischemic core of the infarct early after stroke using diffusion-weighted sequences (dwMRI), and in addition allows evaluation of cerebral perfusion with perfusion weighting (pwMRI).

Examination of the "mismatch" between diffusion and perfusion deficit (*Figure 1*) allows quantification of salvageable brain tissue, and serial imaging can assess the effect of reperfusion or neuroprotective strategies upon infarct maturation. Multimodal MRI may therefore reduce heterogeneity of stroke recruited into future efficacy studies and may provide useful surrogate end points for these trials.

Improved arterial recanalization

The combination of intra-arterial thrombolysis with other nonpharmacologic revascularization techniques is being studied and undoubtedly holds promise for the future. Acute balloon angioplasty of the cerebral vessels is already being used in some centers, although there are insufficient data to justify its widespread use.

A variety of newer mechanical clot disruption techniques such as umbrella and coil devices have been developed and may be employed as adjunctive strategies in the future.

Practical aspects

There is evidence supporting the benefits of rt-PA in selected stroke patients if administered within 3 hours of the onset of symptoms. Translation of these clinical trial findings into routine practice will not be easy. There are major challenges in educating patients, relatives, and doctors in primary care and hospitals to make all aware of the opportunities and urgency of referral of patients with focal neurological symptoms of cerebrovascular disease within the 3-hour time window. In addition, there are considerable logistic and resource issues in providing brain imaging (usually CT) 24 hours a day, 7 days a week, to exclude cerebral hemorrhage (or more rarely, noncerebrovascular diagnoses) within the 3-hour treatment window. Finally, there needs to be available clinical expertise to assess the scans and the patient's clinical state and to deliver thrombolysis in the time window and ongoing care of the patient.

New models of care, together with community education programs, need to be developed if the potential benefits of thrombolysis and stroke are to be realized in practice.

CONCLUSION

Thrombolytic therapy is the only proven treatment for acute ischemic stroke. Intravenous administration of rt-PA has been extensively evaluated in clinical trials and there is general agreement that this intervention is beneficial when used within 3 hours of onset of symptoms. Intra-arterial thrombolysis has been less thoroughly evaluated, but may be appropriate in the context of major arterial occlusion in a patient who will tolerate angiography, assuming the requisite facilities and expertise are available.



The advent of mmMRI, neuroprotective agents, and nonpharmacologic means of arterial reperfusion have the potential to improve current acute strategies. The evaluation and implementation of these novel techniques are the most important and exciting challenges in vascular neurology today.

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