TREATMENT OF ACUTE ISCHEMIC STROKE: PART I—RECANALIZATION STRATEGIES

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In 1994, a special writing group of the Stroke Council of the AHA published guidelines for the management of patients with acute ischemic stroke.1 The guidelines, based on the best available evidence, focused primarily on the prevention and treatment of the complications of acute stroke such as cerebral edema and increased intracranial pressure, aspiration pneumonia, urinary tract infections, deep vein thrombosis and pulmonary embolism, decubiti, and seizures. The authors further concluded that “until more data are available, the use of heparin remains a matter of preference for the treating physician” and “that thrombolytic therapy is not currently recommended for the treatment of patients with acute ischemic stroke.”1 No supportive recommendations were given for any neuroprotective strategy, nor therapies given to stimulate neurological recovery.

In the 8 years since these guidelines were published, a large number of randomized studies of treatment strategies for acute stroke have been completed. These trials have included thrombolytic agents given intravenously, intra-arterially, or both, antithrombotic and antiplatelet therapies, neuroprotective agents, pharmacological and mechanical therapies to stimulate neurological recovery, and the use of stroke units. In addition, many pilot studies of new therapies for acute stroke have been reported and are entering Phase II and Phase III studies.

The current state of knowledge regarding the treatment of acute ischemic stroke that are based on these randomized studies can be summarized as follows. (1) Intravenous thrombolytic therapy, if administered within the first 3 hours after stroke, improves functional outcome after acute ischemic stroke. Even within the first 3 hours, the likelihood of an excellent outcome increases with earlier treatment. The effectiveness of thrombolytic therapy after 3 hours has yet to be established. The use of thrombolytic therapy if administered within the first 3 hours of acute ischemic stroke remains a Holy Grail that has yet to be attained. However, several therapies, medical as well as surgical, are currently under study.

This article, as well as the companion article in a subsequent issue of Circulation, reviews the basis for these conclusions and the current recommendations for treatment of acute ischemic stroke. In the present article, we will review the use of thrombolytic agents and other recanalization strategies. In the subsequent article, we will discuss neuroprotective strategies such as hypothermia, the use of stroke units, general management of the acute stroke patient, and antithrombotic therapy.

UNIQUE CHALLENGES OF RECANALIZATION IN ACUTE ISCHEMIC STROKE

Successful techniques for treatment of acute myocardial infarction provide an excellent roadmap for physicians seeking better treatment of acute ischemic stroke. Very early recanalization of occluded arteries is the critical step for treatment of both diseases. Yet, although there are substantial parallels, major differences exist between acute myocardial infarction and acute ischemic stroke that make effective treatment of acute ischemic stroke particularly challenging.

Ischemia in myocardial infarction almost always results from acute platelet-rich thrombi that form on an atherosclerotic plaque. In contrast, many ischemic strokes are due to emboli from thrombi formed in a proximal extracranial artery or in the heart.2-3 These emboli likely vary substantially in composition and may consist of much older and harder clots that are less likely to respond to thrombolytic agents. Minimal data concerning clot composition in patients with embolic stroke are currently available.

Second, the volume of clot in some patients with ischemic stroke may be substantially greater that seen in acute myocardial infarction. For example, the extracranial internal carotid artery is one common site of symptomatic arterial occlusion in patients with ischemic stroke and has a substantially larger diameter than the main coronary arteries. Clot...
may occlude the internal carotid as well as the middle cerebral artery trunk and beyond. Such extensive clot is unlikely to be lysed by intravenous thrombolytic therapy alone during the first few critical hours after stroke onset in the large majority of cases.

Third, extracranial arteries to the brain can be quite tortuous, particularly in the elderly, and the intracranial carotid arteries traverse through bony canals. These factors can make intraarterial delivery of mechanical devices to remove clot, and even maneuvering of guide catheters, difficult and time-consuming. Finally, the large majority of ischemic strokes occur in patients over the age of 65. Very elderly patients have higher risks of intracerebral hemorrhage after reperfusion with recanalization therapies. However, all age groups, including the elderly, are more likely to have an excellent outcome with intravenous tissue-plasminogen activator (t-PA) begun within 3 hours of onset.

### Recanalization Strategies: Intravenous Therapy

**NINDS-Funded Studies of Intravenous t-PA for Acute Stroke**

In 1996, the Food and Drug Administration (FDA) approved the use of recombinant tissue-plasminogen activator (t-PA), a thrombolytic agent, for selected patients with ischemic stroke if begun within 3 hours of onset. This approval was based primarily on 2 studies funded by the National Institute of Neurologic Diseases and Stroke (NINDS) that were reported as the NINDS t-PA Stroke Trial.6–12 Patients in these 2 studies had to have t-PA administered within 3 hours of stroke onset and nearly half of patients had t-PA started within 90 minutes of onset.

The dose of t-PA used in these studies was 0.9 mg/kg administered intravenously over 1 hour, with 10% of the total dose given as a bolus. The maximum dose was 90 mg. This dose was determined by an NINDS-funded pilot dose escalation study in which 4 of the 5 symptomatic intracerebral hemorrhages occurred at a dose of 0.95 mg/kg or higher, one at dose of 0.89 mg/kg, and none at lower dose tiers (P<0.02).13 It should be noted that no difference in favorable outcome was detected between lower and higher dose tiers in this small nonrandomized pilot study.

In the subsequent randomized NINDS t-PA Stroke Trial, patients treated with t-PA were more likely to have an excellent functional outcome at three months as determined by 1 of 4 neurological or functional rating scales (absolute difference of 11% to 13%). A subsequent report from the NINDS t-PA Stroke Trial showed that the benefit seen for t-PA–treated patients was maintained at 1 year.12 t-PA was also cost-effective overall because patients treated with t-PA were likely to be discharged earlier and to home and were less likely to require nursing home care or extensive rehabilitation.

The major risk of t-PA is bleeding into the damaged brain. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4% of patients given t-PA in the NINDS t-PA Stroke Trial and 0.6% of the placebo group (P<0.001), but there was no significant difference in overall 90-day mortality between t-PA (17%) and placebo groups (21%, P=0.30). Patients with very severe neurological deficit and with acute hypodensity or mass effect on the baseline CT were more likely to have a symptomatic ICH. However, patients with severe neurological deficit or CT findings of hypodensity or mass effect who received t-PA were more likely than placebo-treated patients to have a favorable 3-month outcome and were equally likely to be dead or severely disabled. The authors concluded that despite a higher rate of intracerebral hemorrhage, patients with very severe neurological deficit strokes or hypodensity or mass effect on the baseline CT are reasonable candidates for t-PA if administered within 3 hours of stroke onset.

A subsequent report from the NINDS t-PA Stroke Trial indicated that the beneficial effect of t-PA is time-dependent, even within the first 3 hours of onset. In addition, t-PA appears to be effective for all ischemic stroke subtypes and patient subgroups in those patients who met all of the inclusion and exclusion criteria of the trial.

### Other Randomized Trials of Intravenous t-PA

There have been 3 other major randomized trials of intravenous t-PA for acute ischemic stroke. Two randomized trials evaluated the safety and efficacy of t-PA in stroke patients treated within 0 to 6 hours (European Cooperative Acute Stroke Study (ECASS) and ECASS II). None of these 3 other t-PA studies were positive as defined by a statistically significant difference between t-PA and placebo with regards to the a priori primary clinical endpoint, although the direction of benefit was in favor of t-PA. Several predefined secondary analyses and post hoc analyses, including those using the defined primary endpoint from the NINDS t-PA Stroke Trial, did indicate a positive benefit for patients treated with t-PA in the two European Studies. The risk of symptomatic ICH in the 3 trials was similar to, but nonsignificantly higher, than that reported for the NINDS t-PA Stroke Trial.

### Community Use of Intravenous t-PA for Acute Stroke

Since the approval of t-PA for ischemic stroke by the FDA in 1996, community use of t-PA has resulted in a similar percentage of successful outcomes and a similar rate of symptomatic ICH when the NINDS treatment protocol has been followed. Deviations from the NINDS treatment protocol have been associated with higher rates of symptomatic ICH. Currently only 1% to 2% of all ischemic stroke patients are estimated to be treated with intravenous t-PA within 3 hours of onset. At selected centers, this may approach 5% or greater. The major reason for failure to treat is that the majority of patients arrive beyond the 3-hour window.
Intravenous Medications

Experimental Studies of Other Intravenous Medications

### Studies of Intravenous Streptokinase for Acute Stroke

Three randomized trials of intravenous streptokinase for acute ischemic stroke have been reported. Two studies, the MAST-I and the MAST-E, treated patients within 6 hours and the Australian Streptokinase Trial treated patients within 4 hours.

The dose of streptokinase was 1.5 million units, the full cardiac dose. No dose-escalation pilot safety studies preceded the Phase III trials. All studies were stopped prematurely because of excess mortality and intracranial hemorrhage. The Australian Streptokinase Trial did find a trend toward benefit in patients treated within 3 hours of onset.

Why are both intravenous streptokinase and t-PA effective treatments for acute myocardial infarction whereas only intravenous t-PA has been proven effective for acute ischemic stroke? The answer probably relates more to study design than activity of the medications. First, the major difference in the NINDS t-PA Stroke Study was 1 hour. Lower-dose protocols for intravenous t-PA have been reported in the context of intraarterial therapies.

In summary, intravenous t-PA is effective if administered to appropriate patients within 3 hours of onset and its effectiveness increases even within the first 3 hours when given as soon as possible. t-PA is reasonably safe if used in a carefully defined manner, including close attention to blood pressure, careful monitoring of the patient, no use of heparin and aspirin during first 24 hours, and appropriate selection of patients. It is still unclear whether a lower dose of t-PA administered within 3 hours could be as effective but safer than the current approved intravenous dose of 0.9 mg/kg over 1 hour. Lower-dose protocols for intravenous t-PA have been used in some communities with similar reported rates of effectiveness as in the NINDS t-PA Stroke Study.

The effectiveness and safety of intravenous t-PA beyond 3 hours has yet to be conclusively demonstrated. One attractive development is the potential use of imaging, such as diffusion/perfusion MRI to determine if salvageable brain remains and if t-PA should be given in patients who are beyond the 3-hour time window. The drawback to MR imaging is the additional time that is required before the start of recanalization therapy. Advanced MR and CT imaging to select patients for recanalization therapy is an area of intense study.

Streptokinase cannot be recommended as a viable therapy for acute ischemic stroke. Other newer thrombolytic agents, such as the t-PA molecule, is currently being tested within 3 hours of stroke onset in an NINDS-funded Phase I pilot study (Clark Haley, MD, oral communication, 2001). Reteplase has also been used in small series of patients with acute stroke but has yet to be evaluated in a controlled trial. One pilot study of ReoPro, a GIIb/IIIa receptor antagonist has been completed and a subsequent randomized Phase II Study is ongoing. Small series of patients with a combination of GIIb/IIIa receptor antagonists and t-PA or reteplase have been reported in the context of intraarterial therapies.

### TABLE 1. Randomized Trials of Thrombolytic Therapy for Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Name of Study</th>
<th>Treatment Window</th>
<th>Medications Tested</th>
<th>Delivery</th>
<th>Dose of Agent</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS t-PA Stroke Trial (Parts 1 and 2)*</td>
<td>≤3 h, 1/2 ≤90 min</td>
<td>t-PA</td>
<td>IV</td>
<td>0.9 mg/kg over 1 h</td>
<td>624</td>
</tr>
<tr>
<td>ECASS I</td>
<td>≤6 h</td>
<td>t-PA</td>
<td>IV</td>
<td>1.1 mg/kg over 1 h</td>
<td>620</td>
</tr>
<tr>
<td>ECASS II</td>
<td>≤6 h</td>
<td>t-PA</td>
<td>IV</td>
<td>0.9 mg/kg over 1 h</td>
<td>800</td>
</tr>
<tr>
<td>Atlantis A1,2,3</td>
<td>≤6 h</td>
<td>t-PA</td>
<td>IV</td>
<td>0.9 mg/kg over 1 h</td>
<td>142</td>
</tr>
<tr>
<td>Atlantis B</td>
<td>0 to 5 h</td>
<td>t-PA</td>
<td>IV</td>
<td>0.9 mg/kg over 1 h</td>
<td>613 (31 ≤3 h)</td>
</tr>
<tr>
<td>PROACT II*</td>
<td>≤6 h</td>
<td>Prourokinase plus IV heparin</td>
<td>IA</td>
<td>9 mg over 2 h</td>
<td>180</td>
</tr>
<tr>
<td>ASK</td>
<td>≤4 h</td>
<td>Streptokinase**</td>
<td>IV</td>
<td>1.5 million units over 1 h</td>
<td>340</td>
</tr>
<tr>
<td>MAST I</td>
<td>≤6 h</td>
<td>Streptokinase***</td>
<td>IV</td>
<td>1.5 million units over 1 h</td>
<td>622</td>
</tr>
<tr>
<td>MAST E</td>
<td>≤6 h</td>
<td>Streptokinase</td>
<td>IV</td>
<td>1.5 million units over 1 h</td>
<td>310</td>
</tr>
</tbody>
</table>

*Positive study as determined by predefined primary study endpoint; **Streptokinase plus aspirin (100 mg) versus aspirin (100 mg) alone; ***Four randomized groups: streptokinase plus aspirin (300 mg), streptokinase without aspirin, aspirin alone, and neither aspirin nor streptokinase.
Intraarterial administration of thrombolytic agents appears to have higher rates of recanalization than intravenous t-PA, and the rate of intracerebral hemorrhage is similar to that seen in the NINDS t-PA Stroke Trial. However, the intraarterial approach also has limitations. The most important limitation of intraarterial therapy has been the time from onset of symptoms to initiation of therapy and the time to recanalization once therapy has begun. For example, in the PROACT II study, the median time from onset of symptoms to initiation of intraarterial therapy was >5 hours and only 4 patients had prourokinase started within 3 hours (Tony Furlan, MD, P.I. PROACT II Study, oral communication, 2002). In addition, the median time for recanalization after start of thrombolytic therapy in intraarterial studies is about 2 hours. Several published reports of intraarterial thrombolytic therapy indicate that treatment begun within 3 to 4 hours of symptom onset is associated with higher rates of recanalization and better outcome. The rate of symptomatic intracerebral hemorrhage in the group that was treated with 6 mg of prourokinase plus, a 100 u/kg bolus of heparin followed by 1000 U of heparin/hour for four hours, was 27%. For this reason, the heparin dose was decreased to a 2000 U bolus followed by a 500 U/hour infusion of heparin for 4 hours. The rate of symptomatic ICH in the patients treated with 6 mg of prourokinase and lower dose heparin was 7%. Although the recanalization rate in the prourokinase-treated group was significantly greater than in placebo-treated patients, neurological outcome was not significantly different between the small number of prourokinase and placebo-treated patients.

The PROACT II Study was published in December 1999. One hundred eighty patients with M-1 or M-2 occlusions by angiography were randomized within 6 hours of symptom onset to receive 9 mg of prourokinase plus heparin (low-dose) (n=121) versus placebo plus low-dose heparin (n=59). Of patients in the prourokinase group, 40% had a Rankin of 0 to 2 (mild or no significant disability) at 3 months compared with 25% of control patients (P=0.04). Only 19% of patients who received prourokinase had complete reperfusion of the arterial occlusions after 2 hours of therapy as compared with 2% of placebo patients. But, 66% of patients who received prourokinase did have complete or partial reperfusion.

The symptomatic rate of ICH in the prourokinase group was 10.9% as compared with 3.1% in the heparin-only group. Only elevated baseline serum glucose was significantly associated with symptomatic ICH. Patients with a baseline serum glucose of >200 mg/dL experienced a 36% risk of symptomatic ICH as compared with 9% in patients with serum glucose of ≤200 mg/dL (P=0.02). Possible biological explanations for the relationship between elevated glucose and ICH, such as elevated levels of lactic acid due to anaerobic glycolysis, remain speculative.

Although the absolute benefit for patients treated with prourokinase was at least moderate in effect, the FDA requested an additional confirmatory study. The small number of control patients in the PROACT II Study makes it difficult to adjust for differences in baseline variables between the 2 groups that may affect the interpretation of the study results.
Other Experimental Intraarterial Strategies

Other intravascular interventional approaches are under study. These have included lower-dose intravenous t-PA begun within 3 hours of onset followed by intraarterial t-PA and mechanical disruption (The EMS Study), angioplasty with intraarterial thrombolytic agents, devices that deliver laser energy, ultrasound devices, the Neurojet (a modified version of the Angiojet catheter currently approved for removal of clot in the coronary circulation and in the pulmonary veins), and angioplasty. Administration of small doses of thrombolytic agents or platelet receptor antagonists with these mechanical devices has also been reported in a small number of cases.

Whatever combination of agents or methods is tested, the primary goal remains to shorten the time from onset of symptoms to recanalization of the artery. Recent reports using transcranial doppler and MR angiography have demonstrated that these techniques can be used to monitor the time to recanalization after treatment with intravenous t-PA and have shown that earlier recanalization is associated with a greater likelihood of a good outcome (Figure 2). Stenotic flow signal: Low resistance flow with a significant focal velocity increase; may also be seen in hyperemia. Normal flow signal: Low resistance flow with no significant difference in velocities compared to the normal side.

Current Guidelines for Use of t-PA in Clinical Practice

Currently, the only FDA-approved indication for thrombolytic therapy is intravenous rt-PA given to appropriately selected patients with ischemic stroke within 3 hours of onset. A list of eligibility criteria in patient selection is summarized in Table 2. One of the remaining questions in the use of t-PA is whether patients with early ischemic changes on the baseline CT are eligible for t-PA during the first 3 hours after onset. Early ischemic changes on the baseline CT were not an exclusion for treatment with t-PA in the NINDS t-PA Stroke Trial. A recent publication from the NINDS t-PA Stroke Study Trial in JAMA December, 2001, reported a detailed reevaluation of all baseline CT scans for early ischemic changes. That study showed that early ischemic changes on the baseline CT scan are prevalent within the first 3 hours of stroke onset and correlate with severity. However, these early changes were not independently associated with an increased risk of adverse outcome after t-PA treatment. Patients treated with t-PA did better, whether or not they had these early ischemic changes.
TABLE 2. Suggested Guidelines for Use of t-PA in Patients With Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Eligibility for IV treatment with t-PA</th>
<th>Clinical diagnosis of ischemic stroke causing a measurable neurological deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of symptom onset well established to be less than 180 minutes before treatment would begin</td>
<td></td>
</tr>
</tbody>
</table>

Patient selection: contraindications

- Evidence of intracranial hemorrhage on pretreatment CT*
- Clinical presentation suggestive of subarachnoid hemorrhage, even with normal CT*
- Active internal bleeding*
- Platelet count less than 100 000 per mm³ (100 × 10⁹ per L)*
- Patient has received heparin within 48 hours and has an elevated aPTT (greater than upper limit of normal for laboratory)*
- Current use of oral anticoagulants (eg, warfarin [Coumadin]) with an elevated INR of 1.5 or greater†
- Within 3 months: any intracranial surgery, serious head trauma, or previous stroke*
- On repeated measurements, systolic blood pressure is greater than 185 mm Hg or diastolic blood pressure is greater than 110 mm Hg at the time treatment begins or patient requires aggressive treatment to reduce blood pressure to within these limits* |
- History of intracranial hemorrhage*
- Known arteriovenous malformation or aneurysm*
- Patient was observed to have seizure at the same time the onset of stroke symptoms was observed†
- History of gastrointestinal or urinary tract hemorrhage within 21 days†
- Recent arterial puncture at a noncompressible site†
- Recent lumbar puncture†
- Abnormal blood glucose level (<50 or >400 mg/dL [<2.8 or >22.2 mmol/L])†
- Only minor or rapidly improving stroke symptoms†
- Postmyocardial infarction periadmittance†

†-PA indicates tissue-plasminogen activator; IV, intravenous; CT, computed tomography; aPTT, activated partial thromboplastin time; and INR, international normalized ratio.

*Contraindication. †Relative contraindications. ‡In patients without recent use of oral anticoagulants or heparin, treatment with t-PA can be initiated before availability of coagulation study results but should be discontinued if the INR is greater than 1.5 seconds or the partial thromboplastin lasting time is elevated by local laboratory standards.

References


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