Intra-arterial thrombolysis for acute stroke

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In the 1980s, several reports of intra-arterial (IA) thrombolysis therapy in acute ischemic stroke were published.[1–3] The thrombolytic agents used in these early case series were urokinase or streptokinase. Studies of IA thrombolysis for acute ischemic stroke were initially limited to uncontrolled protocols.[4,5] There was great variability in technique, and efficacy and complication rates varied among the reported series. As a result, in 1996 an American Heart Association Special Writing Group published its recommendations for the use of thrombolytics in acute ischemic stroke. Based on the strength of the scientific evidence at that time, this group concluded that IA thrombolysis "should be considered investigational and only used in the clinical trial setting" and recommended "further testing of" IA thrombolysis.[6]

Subsequently, the results of the first randomized multicenter controlled trials of IA thrombolysis, the Prolyse in Acute Cerebral Thromboembolism trials (PROACT I[7] and PROACT II[8]), were reported in 1998 and 1999, respectively. PROACT II remains the only randomized, controlled, multicenter trial to demonstrate the efficacy of IA thrombolysis in patients with acute ischemic stroke of less than 6 hours' duration due to middle cerebral artery (MCA) occlusion. Trials comparing the IA and the intravenous (IV) modes of application are not available and are not very likely to be performed in the future.

IA THROMBOLYSIS: GENERAL TECHNIQUE

Diagnosis and access

In advance of any procedure, the basic and crucial CT criterion is to rule out hemorrhage. A complete four-vessel cerebral angiogram, from a transfemoral approach, is necessary to evaluate the site of vessel occlusion, extent of thrombus, number of territories involved, and collateral circulation. An MRA or CTA can first be done to identify the primary site of occlusion. A diagnostic catheter is guided into the high cervical segment of the vascular territory to be treated, followed by a 2.3-French coaxial microcatheter with a steerable microguidewire. Under direct fluoroscopic visualization, the microcatheter is gently navigated through the intracranial circulation until the tip is embedded within or through the central portion of the thrombus.

Many variations in catheter design and delivery technique have been described.[9] Two types of microcatheters are used most often for local cerebral thrombolysis, depending on the extent of clot formation. For the majority of intra-arterial cases, a single end-hole microcatheter is used, while for longer segments of clot formation, multiple side-hole infusion microcatheters are used. Superselective angiography through the microcatheter is performed at regular intervals to assess for degree of clot lysis and to adjust the dosage and volume of the thrombolytic agent. A superselective angiogram is performed, and if there is partial clot dissolution, the catheter is advanced into the remaining thrombus, where additional thrombolysis is performed. Infusion of the thrombolytic agent distally into a vessel with no flow should be avoided. The goal is to achieve rapid recanalization with as little thrombolytic agent as possible to limit the extent of brain infarction and to reduce the risk of hemorrhage. However, common experience indicates that it can take up to 2 hours to achieve recanalization after the procedure begins, that thrombolytic agents alone (ie, without mechanical manipulation) rarely achieve recanalization in less than 30 minutes, and that recanalization is often incomplete. Among other factors, clot composition plays a key role in the rapidity and degree of recanalization achieved with IA thrombolysis. Advances in microcatheter technology have allowed superselective catheterization of even distal branches of occluded intracranial vessels.

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Thrombolytic agents

Recombinant pro-urokinase (r-pro-UK), the thrombolytic agent used in PROACT II (see below), is currently not approved by the US Food and Drug Administration (FDA) and not commercially available. Although some thrombolytic agents have theoretical advantages over others, there is no proof that one is superior to another in terms of safety, recanalization, or clinical efficacy in acute ischemic stroke. Therefore, it is not clear if the results of PROACT II are applicable when agents other than r-pro-UK are used for IA thrombolysis.

Commercially available agents include urokinase (UK), recombinant tissue-plasminogen activator (rt-PA), reteplase (r-PA), and tenecteplase (TNKase). These thrombolytic agents differ in stability, half-life, and fibrin selectivity. UK is not fibrin-selective and thus can result in systemic hypofibrinogemia. rt-PA and r-pro-UK are fibrin-selective and are only active at the site of thrombosis. However, r-pro-UK requires heparin for maximal thrombolytic effect. Newer agents like r-PA have long half-lives, allowing bolus administration, or are more fibrin-selective, like TNKase.

Local fibrinolysis makes it possible to monitor not only the frequency of recanalization but also how fast it occurs. All current single thrombolytic agents often require 30 to 60 minutes for recanalization, even with direct IA application. Even 325,000 IU urokinase or 40 mg rt-PA takes 100 minutes to recanalize, based on our experience with 140 patients.[10] A very promising concept involves using Lys-plasminogen with rt-PA during local IA infusion.[11] Compared with rt-PA and urokinase alone, adjunctive Lys-plasminogen increased the frequency of recanalizations and reduced recanalization time.

The efficacy of second- and third-generation thrombolytic agents in acute ischemic stroke has not been demonstrated in a randomized controlled trial.

Intravenous heparin

IV heparin is given by most neurointerventionalists during IA stroke thrombolysis. Systemic anticoagulation with heparin reduces the risk of catheter-related embolism. Also, the thrombolytic effect of some agents, such as r-pro-UK, is augmented by heparin. Another rationale for antithrombotic therapy is to prevent early reocclusion, which is more common with atherothrombosis than with cerebral embolism. These indications are counterbalanced by the increased risk of brain hemorrhage when heparin is combined with a thrombolytic agent.

The optimal dose of heparin during IA stroke thrombolysis has not been established. PROACT I[7] reported a 27% rate of symptomatic brain hemorrhage when a conventional non–weight-adjusted heparin regimen (bolus of 100 U/kg followed by 1,000 U/hr for 4 hours) was employed with IA r-pro-UK. Subsequently, a low-dose heparin regimen was used (bolus of 2,000 U followed by 500 U/hr for 4 hours), which reduced the symptomatic brain hemorrhage rate with IA r-pro-UK to 7% in PROACT I and 10% in PROACT II. Unfortunately, low-dose heparin also cut the recanalization rate in half with IA r-pro-UK. Some neurointerventionalists now employ the PROACT low-dose heparin regimen during IA thrombolysis. However, this heparin regimen does not prolong the activated partial thromboplastin time or the activated clotting time. Other neurointerventionalists employ weight-adjusted heparin, keeping the activated clotting time between 200 and 300 seconds.

Other factors influencing thrombolysis outcomes

Hacke has described an ideal patient for thrombolysis: a young person with good collaterals who has an MCA occlusion distal to the lenticulostriates due to a fresh fibrin-rich thrombus that passed through a patent foramen ovale.[12] The presence of collateral flow is one of the prime determinants of outcome.[13,14] Good leptomeningeal collaterals may limit the extent of ischemic damage and prolong the therapeutic window. Good collateral flow is also associated with higher rates of reperfusion, presumably by allowing a greater amount of thrombolytic to reach the clot by means of redistribution. Clot composition is a neglected factor in recanalization success rates.[15] Fresh thrombi, which are rich in fibrin and plasminogen, are easier to lyse than aged atherothrombi, which are more organized and have low fibrin and plasminogen contents and high amounts of platelets and cholesterol. Fresh cardiac emboli may therefore respond better to thrombolyis than atherothrombotic occlusion or calcific embolism.

■ RISK FACTORS FOR HEMORRHAGIC TRANSFORMATION

Several series have found no relationship between recanalization and hemorrhage risk.[16–18] However, these series do not address delayed recanalization or the status of recanalization at the time of brain hemorrhage. The amount of ischemic damage is a key

factor in the development of hemorrhage after thrombolysis. Early extensive CT changes and severity of the initial neurologic deficit, both indicators of the extent of ischemic damage, are the best predictors of hemorrhagic transformation risk.[18,19] In the first European Cooperative Acute Stroke Study (ECASS I),[20] early CT changes in greater than one third of the MCA territory correlated well with the frequency of hemorrhagic infarction. However, the so-called ECASS CT criteria are not present in all cases of hemorrhage, and there is considerable interreader variability in the interpretation of early CT changes. A recent analysis of the PROACT II data indicates that patients with early (< 6 hours) CT infarct volumes greater than 100 mL do poorly.[21] However, estimated early CT changes (ie, ECASS criteria) appear less predictive of outcome among homogeneous patients with MCA occlusion relative to patients with mixed sites of arterial occlusion.[21]

Given the somewhat conflicting data, it would be prudent either to avoid thrombolysis in patients with clear-cut extensive early signs of infarction on CT and a National Institutes of Health Stroke Scale (NIHSS) score greater than 20 (especially if the patient is older than age 75) or to emphasize to the patient's family a greatly reduced benefit:risk ratio, even for patients who present within 3 hours of onset.

The amount of ischemic damage depends on the duration of occlusion and the degree of collateral blood flow. Both of these factors have been associated with increased hemorrhage risk. Ueda et al[22] found that the amount of residual blood flow, as determined by SPECT scanning, was associated with hemorrhagic transformation, but they also used SPECT results to extend the thrombolytic time window beyond 6 hours in 3 patients. Improved perfusion after 3-hour IV rt-PA has also been demonstrated with SPECT.[22,23] Apparent diffusion coefficient (ADC) mapping on MRI has also been used to predict hemorrhagic risk.[24]

Several other factors have been associated with hemorrhage after thrombolysis for both stroke and myocardial infarction, including thrombolytic dose, blood pressure, advanced age, prior head injury, and blood glucose.[25–31] A strong relationship between advanced age and hemorrhage was also demonstrated in the NINDS t-PA Stroke Trial[32] and the ECASS trials. Although there is no strict age cutoff, physicians need to account for the increased risk of hemorrhage in patients aged 75 or older when deciding about thrombolysis for stroke.

Intracerebral hemorrhage after thrombolysis for stroke can occur at sites distant from the ischemic region.[32] Cerebral amyloid angiopathy has been implicated as a causative factor for brain hemorrhages after thrombolysis for myocardial infarction.[30]

The PROACT trials

PROACT I. Patient enrollment in the first placebo-controlled, double-blind, multicenter trial of IA thrombolysis in acute ischemic stroke, PROACT I, began in February 1994. The results were published in 1998.[7] The thrombolytic agent used in this study was r-pro-UK, which is, as noted above, not yet commercially available. r-pro-UK is a recombinant single-chain zymogen of an endogenous fibrinolytic, UK or u-PA.[33] Infusion of r-pro-UK does not result in a systemic dysfibrinogenemia with its associated higher risk of hemorrhagic side effects. Another clinically relevant characteristic of r-pro-UK is the facilitatory effect of coadministered heparin, which improves the fibrinolytic efficacy of r-pro-UK.

The study compared safety and recanalization efficacy between 6 mg IA r-pro-UK and IA saline placebo in 40 patients with acute ischemic stroke of less than 6 hours' duration due to MCA occlusion. Only patients with Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 occlusion of the M1 or M2 MCA on diagnostic cerebral angiography were included. Additional major inclusion criteria were a minimum NIHSS score of 4 (except for isolated aphasia or hemianopsia) and a maximum score of 30. Major exclusion criteria were uncontrolled hypertension (> 180/100 mm Hg), a history of hemorrhage, recent surgery, or trauma. Early CT changes were not an exclusion criterion. Mechanical disruption of the clot was not permitted since the trial's goal was to demonstrate the efficacy and safety of r-pro-UK. Patients also received heparin in addition to r-pro-UK. The first 16 patients received "high-dose" heparin consisting of a bolus of 100 IU/kg followed by infusion of 1,000 IU/hr for 4 hours; anticoagulation was prohibited for the following 24 hours. Based on a recommendation from the external safety committee, the heparin regimen was changed after the first 16 patients to a 2,000-IU bolus followed by 500 IU/hr for 4 hours.

The recanalization rate was 57.7% in the r-pro-UK group and only 14.3% in the placebo group. In the "high-dose" heparin group, the recanalization rate was 81.8% in the r-pro-UK recipients but the symptomatic intracranial hemorrhage (ICH) rate was 27%. In contrast, in the "low-dose" heparin

group the recanalization rate was 40% in the r-pro-UK recipients but the ICH rate decreased to 6%. Overall, symptomatic ICH occurred in 15.4% of treated patients and in 14.3% of placebo recipients. Although this was not a clinical efficacy trial, there appeared to be a 10% to 12% increase in excellent outcomes in the IA r-pro-UK group as compared with the control group.

PROACT II. The follow-up clinical efficacy trial, PROACT II, was launched in February 1996 and the results published in December 1999.[8] This was a randomized, controlled, multicenter trial but differed from PROACT I in that it used an open-label design with blinded follow-up. Patient selection was essentially the same as in PROACT I, with the major exception being that patients were excluded if they had early signs of infarction in greater than one third of the MCA territory (the so-called ECASS criteria[17]) on the initial CT scan. Additionally, a 9-mg dose of r-pro-UK was used instead of 6 mg and "low-dose" heparin was used in the treatment and control groups. A total of 180 patients were randomized to receive either 9 mg of IA r-pro-UK plus low-dose IV heparin or low-dose IV heparin alone. The patients in PROACT II had a very high baseline stroke severity (median NIHSS score of 17). The median time from symptom onset to initiation of IA thrombolysis was 5.3 hours.

The primary outcome measure was the proportion of patients who achieved a modified Rankin score of 2 or less at 90 days, which signifies slight or no neurologic disability. For the r-pro-UK group there was a 15% absolute benefit (P = .043). The benefit was most noticeable in patients with a baseline NIHSS score between 11 and 20. On average, 7 patients with MCA occlusion would require IA thrombolysis for 1 patient to benefit. Recanalization rates at 2 hours were 66% for the treatment group and 18% for the placebo group (P < .001). Symptomatic brain hemorrhage occurred in 10% of the r-pro-UK group and in 2% of the control group.

Considering the later time to treatment and greater baseline stroke severity in PROACT II, the symptomatic brain hemorrhage rate compared favorably with the rates in the IV rt-PA trials (6% in the NINDS t-PA Stroke Trial, 9% in ECASS II, and 7% in ATLANTIS). As in the NINDS trial, in PROACT II patients benefited overall from therapy despite the higher brain hemorrhage rate, and there was no excess mortality (24% in the r-pro-UK group vs 27% in the control group).

■ CAROTID TERRITORY IA THROMBOLYSIS: SPECIAL FEATURES

The majority of hemispheric vessel occlusions are due to embolism. In thrombolysis trials, the 30-day mortality rate in hemispheric stroke is between 15% and 20% and does not differ significantly between treatment and placebo. Thrombolytic treatment has had no impact on survival but rather improves the clinical outcome of patients with less than massive strokes. Most successful recanalizations of the carotid circulation involve the MCA. Recanalization of the internal carotid artery origin is seldom achieved even with direct IA approaches. Some interventionalists advocate passing the catheter through the obstructing thrombus to access the MCA. Occlusion of the carotid "T" eliminates the posterior communicating artery and ophthalmic artery collaterals, so that leptomeningeal collaterals and the anterior communicating artery often are not sufficient to save major parts of the hemisphere even for a short period of time.[34,35] Recanalization of the carotid "T" is difficult and rarely leads to good clinical results; such patients are commonly excluded from clinical trials.

■ VERTEBROBASILAR IA THROMBOLYSIS: SPECIAL FEATURES

In the posterior circulation, two special conditions have to be kept in mind: the natural history of acute basilar occlusion is extremely poor, with mortality rates ranging from 83% to 91%,[36,37] and atherothrombotic occlusions of the basilar artery are relatively more common than embolic occlusions.[35] Hence, there is often need for angioplasty of an underlying basilar artery atherostenosis. Accordingly, IA thrombolysis is preferred in patients with acute basilar artery occlusion. In a compilation of reported cases of vertebrobasilar thrombolysis, mortality was 90% in patients not responding to recanalization compared with 31% in patients achieving at least partial reperfusion.[36] Approximately 278 cases have been reported, with an overall basilar recanalization rate of 60%. Good outcomes are strongly associated with recanalization after thrombolytic therapy. The majority of patients with successful vertebrobasilar recanalization have only mild or moderate disability, compared with less than 14% of patients whose vessels remained occluded.[38]

Distal basilar artery occlusions have a higher recanalization rate because they often consist of soft emboli, which are easier to lyse than atherosclerosis-

related thrombi.[39] In addition, the high rate of reocclusion worsens the prognosis of mid- or lower basilar atherothrombosis. Recent excellent experience supports the use of angioplasty for stabilizing atherothrombotic recanalization.[40–42] Short-segment occlusions are easier to lyse than longer-segment occlusions. Patients who are younger have higher recanalization rates, probably because of the increased incidence of embolic occlusions in this age group.

The time window for thrombolysis was thought to be longer in the posterior circulation. Many series have included patients up to 72 hours after symptom onset.[42] However, thrombolysis with such prolonged time windows makes sense only in patients with prolonged stuttering courses, such as vertebrobasilar patients with chronic atherothrombotic disease in whom collaterals have developed over time. Except in such cases with favorable hemodynamic conditions, treatment beyond the 6-hour window has a very poor prognosis, especially in the presence of coma or tetraparesis for several hours.[35]

The importance of signs of infarction on CT in the brainstem and other posterior circulation locations is controversial.[43] The decision must be made individually regarding the lethal thread and the clinical status related to the CT findings. A clearly hypodense, destructed brainstem in a comatose, reflexless individual is for sure not an indication.

■ INVESTIGATIONAL ENDOVASCULAR THERAPIES FOR ACUTE STROKE

Combined IV and IA thrombolysis

It may be feasible to combine IV and IA thrombolysis to take advantage of the early infusion possible with IV administration and the greater recanalization efficacy of IA therapy. This approach was studied in the pilot Emergency Management of Stroke (EMS) Bridging Trial.[44] Patients with stroke of less than 3 hours' duration were given a loading dose (0.6 mg/kg) of IV rt-PA or placebo followed by angiography and IA thrombolysis if a vascular occlusion remained. Of all patients, 70% still had clot on angiography after IV therapy. There was improved MCA recanalization in patients who then received IA rt-PA, but there also was an increased risk of life-threatening bleeding complications. The results of the follow-up IV plus IA rt-PA trial (Interventional Management of Stroke [IMS]) were recently reported.[45] Among 62 patients with a baseline NIHSS score greater than 10 enrolled in the IMS trial, 44 (71%) required both IV (0.6 mg/kg) and IA rt-PA. The symptomatic brain hemorrhage rate was 6.2% in patients receiving combination IV/IA thrombolysis, and 90-day outcomes appeared to be favorable compared with historical controls from the NINDS IV t-PA trial.[32]

Combined platelet and fibrin thrombolysis

Dissected atherothrombotic plaques in the coronary artery and in the basilar artery often carry platelet-rich thrombi. The platelet glycoprotein (GP) IIb/IIIa receptor inhibitors abciximab and eptifibatide improve the speed and completeness of recanalization in acute coronary interventions and have also been used in patients undergoing cerebrovascular interventions.[46] Coronary doses of IV abciximab appear to be relatively safe in patients with acute ischemic stroke.[47] Because of underlying atherostenosis, GP IIb/IIIa inhibitors may play a significant role in basilar artery endovascular intervention. Many interventionalists initiate an abciximab bolus and infusion as soon as a basilar thrombosis is demonstrated on CTA or MRA.[35] Whether GP IIb/IIIa inhibitors speed up recanalization with emboli in advance of or during local rt-PA fibrinolysis is also under study.

Mechanical procedures

The speed and completeness of recanalization are suboptimal with thrombolytic agents alone. Thus, new technologies for mechanical clot removal are in early feasibility and safety trials in both the United States and Europe. Reports have all been individual case series from single institutions. The techniques include treatment of acute ischemic stroke by direct mechanical balloon angioplasty of the thrombus, mechanical snaring of clot from the MCAs, and use of suction thrombectomy devices for establishing reperfusion, all of which require relatively coarse manipulation.[48–52] Techniques employing a power-assisted endovascular Doppler probe (EKOS®) for clot destabilization or the EPAR® probe, which transforms laser energy into photoacoustic energy to vaporize the clot,[53] allow a more gentle approach to the clot and reduce the recanalization time.

■ CURRENT STATUS AND FUTURE OF IA THROMBOLYSIS: PERSONAL PERSPECTIVES

Since a clinical trial comparing IV with IA or combination thrombolysis will be difficult to perform, and since IV rt-PA within 3 hours of stroke onset

remains the only FDA-approved acute stroke therapy, decisions on the best approach to reperfusion in an individual patient must take into account numerous factors discussed above.[54,55] The advantages of local fibrinolysis include precise angiographic information, control of the progress of recanalization (including the option to use mechanical devices), lower systemic thrombolytic activity, and higher recanalization rates for large-vessel occlusions. The fear of serious procedural complications was not borne out in the PROACT I and II trials, in which cerebral angiography was associated with a 0.1% rate of permanent complications and a 0.02% death rate.

On the other hand, IA thrombolysis requires access to a team of physicians (an interventionalist and tertiary stroke team) capable of performing IA thrombolysis. Such expertise is not readily available in many developing countries or in many communities across Europe and the United States, as it is usually limited to large academic centers. Treatment delays are also inherent to IA thrombolysis. In PROACT II, the median time to drug infusion from stroke onset was 5.3 hours, and the average time from arrival at the hospital to the initiation of IA r-pro-UK was 3 hours. IA thrombolysis also involves costs and procedural risks not inherent to IV thrombolysis. As the total number of intra-arterially treated patients is small, not much is known about drug and dose-efficacy relations. Recently an IA Web registry was established to gather more information.[56]

Relative merits and drawbacks of IV thrombolysis

IV thrombolysis has the important advantages of time, ease of administration, and widespread availability. However, currently less than 5% of acute stroke patients receive IV rt-PA, mainly because of the 3-hour treatment window. The difficulty in demonstrating a benefit from IV thrombolysis beyond 3 hours from stroke onset arises from a number of factors. The proportion of patients with major stroke who have salvageable brain decreases with time, while the brain hemorrhage rate with thrombolysis increases. A worse than expected outcome due to the inclusion of patients with early signs of infarction on CT contributed to the negative results of ECASS I. Conversely, a better than expected outcome made it difficult to demonstrate a benefit in ECASS II when such patients were excluded. Vascular imaging studies were not done in the IV thrombolysis trials, so that neither the sites of arterial occlusion nor the recanalization rates are known. Patients with ischemic stroke of less than 6 hours' duration have a wide variety of occlusion sites, and 20% have no visible occlusion, despite similar neurologic presentations.

Rapid and complete recanalization is the key

The key issue is to achieve complete recanalization as quickly as possible. A good clinical outcome is significantly related to recanalization regardless of how it is achieved. The factors that determine individual susceptibility to ischemia are not completely understood, and there clearly is a great deal of variability in time to irreversible damage among individuals—ie, there are many therapeutic windows. Greater recanalization efficacy is taken as an explanation of why the time window for successful IA thrombolysis may be longer than for IV administration. Based on PROACT II, a 6-hour window appears to be a realistic goal for IA therapy in anterior circulation ischemia. However, in PROACT II only patients with MCA occlusions were treated, an occlusion type in which the probability of good collateralization is high, recanalization occurs frequently, and a chance of recanalization "in time" is most probable. Patient selection contributed highly to the degree of efficacy in PROACT, and this is now a central challenge in acute reperfusion therapy.

Progress linked to improved patient selection

It is increasingly obvious that selecting reperfusion therapy based only on time from stroke onset, a neurologic examination score, and a routine CT scan is inadequate. Since the evolution of new-generation MR devices, and partially also after the development of multislice spiral CT, a great variety of information can now be made available within minutes to describe the anatomic and pathophysiologic status of the brain tissue. This enables clinicians to make highly selective treatment decisions.[57–59] With this in mind, the *Kompetenznetzwerk Schlaganfall* (B5) Study Group has investigated in a multicenter, prospective trial stroke patients with and without IV fibrinolytic treatment who were selected by MRI protocol that included diffusion-weighted and perfusion-weighted imaging (DWI and PWI), T2*-weighted imaging, time-of-flight MRA, and, if necessary, contrast-enhanced MRA.[60] The trial used a 6-hour treatment window. Only patients exhibiting at least 20% DWI/PWI mismatch in a hemispheric infarct of not more than one third of the MCA ter-

ritory were included. Calculating the number needed to treat for the major trials with a 6-hour window using a dichotomized modified Rankin score of 0–2/>3 shows that 12 patients were needed for ECASS II and 7 patients for PROACT II. The number needed to treat in the B5 Study Group cohort was 5 patients. This again shows that, as in PROACT II, more precise and pathophysiologic patient selection may translate into greater efficacy regardless of the thrombolytic method.

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