Cerebrovascular Disease III. Acute Ischemic Stroke

Use of Intravenous Alteplace in Acute Ischemic Stroke

Louis R Caplan MD

Thrombolysis was abandoned as a stroke treatment in the 1960s due to an unacceptable rate of brain hemorrhage. During the ensuing 3 decades, clinicians and researchers explored various thrombolytic (fibrinolytic) agents (streptokinase, urokinase, plasminogen activator) to treat patients with myocardial infarction and pulmonary embolism. In 1947, an agent extractable from animal tissue was found that activated plasminogen. During the 1960-1980s this agent, tissue plasminogen activator (tPA), was purified and posited to be a fibrin -specific agent that would activate the bodies plasminogen. When plasminogen was converted to plasmin, the active agent would disrupt the fibrin bonds within blood clots. Recombinant tPA (rtPA) was synthesized and tried on animals and patients with pulmonary embolism and myocardial infarction during the 1970-80s decades.

Fibrinolytic drugs degrade the fibrin network mesh of red erythrocyte-fibrin clots. They do not lyse white platelet-fibrin thrombi but instead may activate platelets. Endogenous formation of plasmin is probably responsible for some examples of spontaneous recanalization of thrombosed arteries. The ideal thromolytic agent would adhere specifically to fibrin in clots and would not cause

systemic fibrinogenolysis. Lowering fibrinogen levels excessively can promote systemic bleeding.

During the 1980s, stimulated by success in treating coronary artery thrombosis, clinicians turned again to "clot busters'' to treat cerebrovascular thromboembolism. My colleagues and I in Boston were involved in some of the early studies with American, German, and Japanese colleagues. Streptokinase, Urokinase, and rt-PA were the most common agents used. In these early studies, acute stroke patients were screened clinically and by CT, and then angiography was performed. If an intracranial arterial occlusion was shown, thrombolytic drugs were given either intra-arterially (IA) into the clots, or intravenously (IV). Follow-up angiography was performed after treatment to assess recanalization. Both anterior and posterior circulation thromboembolism were treated. These studies were observational only since controls were not used and patients were not randomized but successive patients meeting protocol requirements were treated.

Among patients treated using IA thrombolytic agents under angiographic control the agents were given within 24hrs. The presence and extent of reperfusion depended mostly on the location of the occluded artery and the mechanism of the stroke. Among 449 patients treated in 17 studies, 64% had effective recanalization after therapy. Mainstem and divisional middle cerebral artery (MCA) occlusions responded best, while ICA occlusions responded poorly. Distal MCA branch occlusions did not respond as well as more proximal MCA lesions probably because the blockage was beyond the reach of interventional catheters. Basilar artery occlusions were

recanalized in 69% of patients. Thrombolysis of occlusions of the intracranial carotid artery (ICA) bifurcation (the carotid “T” portion) was almost invariably unsuccessful. Embolic occlusions were more successfully recanalized than thrombosis engrafted upon in-situ atherosclerosis. Intra-arterial delivery was more effective than intravenous. IV therapy caused more bleeding than intra-arterial.

The results of these early studies were not included in the publications of the results of the later randomized trials. In all of these early angiographic studies, and in angiographically controlled trials since release of rt-PA, recanalization heavily correlated with outcome. As far as is known thrombolytic agents act only by lysing clots. If arteries are not opened the drugs do not facilitate recovery. Knowing the recanalization rate of agents given IV and IA in patients with various occlusive arterial lesions is extremely helpful in choosing appropriate therapy.

The first randomized thrombolytic trials of IV rtPA, ECASS 1 and ECASS 2 in Europe, and the NINDS trial in the USA were pragmatic and chose brain imaging readily available at that time- CT scanning. No vascular imaging was required or reported. In the NINDS trial two time periods were reported 90 min and 180 minutes. IN E$CASS 1, a 3hr period was reported and in ECASS 2, 3 hr and 6 hr periods were studied.

In ECASS l, among rt-PA treated patients in the target population (those patients who had no protocol violations) there was a significantly better outcome and hospital stay was significantly shorter. Intracerebral hemorrhages and death were more common in

rt-PA treated patients but these differences were not statistically significant. Large parenchymal hematomas were more often found in rt-PA treated patients. Patients treated with rt-PA within 3 hours did better than controls and those treated with rt-PA between 3 and 6 hours.

The NINDS study in the USA was planned in 1990 and reported in 1995. The major study differences compared to ECASS were: lower rt-PA dose, earlier treatment (302 patients were treated within 90 minutes and 322 between 90 and 180 minutes), and no exclusion of patients because of brain ischemia on entry CT scans. Patients who received intravenous rt-PA were at least 30% more likely to have minor or no disability at 3 months. Symptomatic intracerebral hemorrhages were more common in the rt-PA treated patients (6.4% vs 0.6%) and more often developed in patients who had more severe neurological deficits at entry and in patients 75 years or older. The mortality at 3 months was 17% in the rt-PA group vs 21% in the placebo group. There seemed to be no important difference in outcome in the groups with varying etiologies but the quick entry and absence of vascular and cardiac imaging made the clinical diagnosis of stroke etiology and mechanism tentative at best. A committee that reviewed the NINDS results reported that the stroke subtype results were not valid.

Three studies of IV streptokinase were launched but all showed excessive bleeding.

Release of the results of the NINDS trial gave momentum to a movement in the USA to quickly introduce IV thrombolysis widely into the community. During the summer of 1996, about one-half year after

the publication of the NINDS trial, the FDA approved the use of rt-PA for the treatment of stroke patients when the drug was given within the first 3 hours. The American Heart Association and American Academy of Neurology published treatment recommendations that exactly followed the inclusion and exclusions and the treatment protocols of the NINDS trial. The recommendations suggest that a CT scan done before thrombolysis should not show major infarction, mass effect, edema, or hemorrhage. The guidelines did not require or suggest MRI or vascular tests before treatment. American Heart Association/American Stroke Association Guidelines published in 2007 concerning early management of adults with ischemic stroke did not substantially alter the original guidelines concerning IV tPA administration. I and others (Mohr, Kistler and Koroshetz) argued that the results of the NINDS trial were preliminary and that research should continue using patients with known vascular lesions and studying groups of patients excluded in the NINDS trial.

After publication of the NINDS trial few (1-2% of patients were treated with IV tPA in the USA. Hospitals were unprepared; Emergency physicians balked; they were unused to treating stroke patients and felt tPA was potentially dangerous.

During the next decades- 1997-2017, many observational studies especially the SITS-MOST Registry in Europe and the IST-3 trial centered in the UK showed that tPA given intravenously was safe and efective even in elderly patients. ECASS -3 results showed that IV tPA was effective and safe up to 4.5 hours after the onset of acute ischemic stroke symptoms. Data accumulated among patients with minor deficits, those who awakened with stroke, those who had

seizures at onset, and those with various vascular lesions shown by MRangiography and CT angiography. Also explored was the use of modern technology- MRI (diffusion-weighted, susceptibility-weighted, and MRA and MRI perfusion) and CT, CTA and CT perfusion to choose candidates by tissue findings rather than by time alone.

Studies in patients who had vascular imaging later showed that IV tPA treatment resulted in less than 25% improved outcome in patients with large intracranial arterial occlusions. Intracranial ICA and mainstem MCA and Basilar artery occlusions opened only about 20-30% of time after IV tPA. Catheter-based mechanical thrombectomy techniques to reopen acutely occluded arteries made rapid technical advances during the past decade. Endovascular mechanical therapies offer several distinct advantages over both IV and IA delivery of thrombolytic drugs. Catheter-based mechanical therapies typically work more rapidly, achieving recanalization within a few minutes, rather than the up to 120 minutes required with lytic drug administration. Mechanical techniques may have lower intracerebral and systemic hemorrhage risk, due to the avoidance of pharmacologic lysis. Catheter-based mechanical therapies are more effective removing large clot burdens in proximal vessels, such as carotid T occlusions, where the sheer volume of clot to be digested retards pharmacologic lysis. The most recently developed catheter-based mechanical thrombectomy devices are more effective at achieving substantial reperfusion than pharmacologic approaches.

The variety of target vascular lesions in acute ischemic stroke has fostered development of a range of mechanical treatment options. In many patients, the intracranial occlusion is an embolus

that has arisen from the heart or an arterial source, such as the aorta or the cervical carotid artery, and landed in a relatively normal recipient brain artery. Such target thrombi respond well to devices that fish the clot out (retrieval devices) or suck the clot out (aspiration devices). In other patients, the occlusive lesion is comprised largely of a local atherosclerotic plaque with small thrombus on top of it. Retrieval and aspiration devices may be able to remove the small thrombus component of these blockages, but not the atherosclerotic plaque.

During the 21st century, primary stroke centers and comprehensive stroke centers with advanced treatment capabilities were developed and certified. Stroke units proliferated especially in Europe. Telemedicine developed and connected centers with less capability with more experienced stroke centers. During the past several years treatment trials showed that intra-arterial interventions (thrombectomy and/or intra-arterial thrombolytic administration) clearly provided better outcomes than IV tPA alone in patients with large artery occlusions.

As a result of the studies on mechanical thrombectomy, there were available 2 different strategies. Take patients directly toi comprehensive stroke centers or have them go to the nearest center-often a primary stroke center for IV tPA. But which patients, with which clinical symptoms and signs, and what distances from the primary and comprehensive centers?

References

del Zoppo GJ. Thrombolytic therapy in cerebrovascular disease. Stroke 1988; 19:1174-1179.

Pessin MS, del Zoppo GJ, Furlan AJ. Thrombolytic Treatment in Acute Stroke: Review and Update of Selected Topics. In Cerebrovascular diseases, 19th Princeton Conference, 1994. Boston: Butterworth-Heinemann, 1995; 409-418.

Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA 1995; 274:1017-1025.

The National Institute of Neurological Disorders and Stroke rt-PA Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.

Ingall TJ, O'Fallon WM, Asplund K, Goldfrank LR, Hertzberg VS, Louis TA, Christianson TJ. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. Stroke. 2004; 35:2418-2424.

Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous

alteplase in acute ischaemic stroke (ECASS ll). Lancet 1998;352:1245-1251.

Adams HP, Brott TG, Furlan AJ, et al. Use of thrombolytic drugs. A suppement to the guidelines for the management of patients with acute ischemic stroke. A statement for Health Care Professionals from a special writing group of the Stroke Council American Heart Association. Stroke 1996; 27:1711-1718.

Quality Standards Subcommittee of the American Academy of Neurology. Practice advisory: Thrombolytic therapy for acute ischemic stroke-summary statement. Neurology 1996; 47:835-839.

Hacke W, Kaste M, Blumki E et al for the ECASS Investigators. . Thrombolysis with Alteplese 3-4.5 hours after acute ischemic stroke. N Engl J Med 2008; 359:1317-1329

Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: An updated systematic review and meta-analysis. *Lancet*. 2012;379:2364-2372

Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in stroke-monitoring study (sits-most): An observational study. *Lancet*. 2007;369:275-282

#

Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [ist-3]): A randomised controlled trial. *Lancet*. 2012;379:2352-2363

Davis SM, Donnan GA, Butcher KS, Parsons M. Selection of thrombolytic therapy beyond 3 h using magnetic resonance imaging. *Curr Opin Neurol*. 2005;18:47-52

Schellinger PD, Thomalla G, Fiehler J, Kohrmann M, Molina CA, Neumann-Haefelin T, et al. Mri-based and ct-based thrombolytic therapy in acute stroke within and beyond established time windows: An analysis of 1210 patients. *Stroke*. 2007;38:2640-2645

Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al. Endovascular therapy after intravenous t-pa versus t-pa alone for stroke. *N Engl J Med*. 2013;368:893-903

Bhatia R, Hill MD, Shoba N et al. Low rate of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke real- world experience and a call for action. Stroke 2010; 41(10) 2254-2258.

#

Caplan LR, Furlan AJ, Hacke W. Acute ischemic stroke therapy: the way forward. JAMA Neurology 2015;72(12) 1405-1406.

#