Editorial

Stroke Thrombolysis
Slow Progress

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During the past decade, few topics have prompted as much controversy as stroke thrombolysis. Although there is general agreement that thrombolysis of stroke patients is effective, the major issue is case selection: Who should give what drug at what dose? Where, how, and to which patients? Like many potent treatments, there is great potential for effectiveness but also important risk of harm. In this issue of Circulation, Georgiadis and his Swiss colleagues analyze some aspects of potential harm.

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Background
Stroke thrombolysis was jump-started during the summer of 1996, when the US Food and Drug Administration approved the use of tissue plasminogen activator (tPA) for treatment of patients with stroke when the drug was given within the first 3 hours. Approval was based on publication of the results of a National Institute for Neurological Disorders and Stroke (NINDS)—sponsored trial. Soon after that trial was reported, committees of the American Heart Association and the American Academy of Neurology published treatment protocols recommending intravenous tPA use according to the NINDS trial protocol. These guidelines (which have never been updated) recommend that patients be treated within 3 hours of symptom onset and that a computed tomography (CT) scan done before thrombolysis should not show major infarction, mass effect, edema, or hemorrhage. Treatment is not recommended in patients who wake up with a deficit, in those with minor signs, or those who are improving. The guidelines do not require or suggest magnetic resonance imaging (MRI) or vascular tests before treatment. Stroke neurologists were enthusiastic about the Food and Drug Administration approval. Before tPA, therapeutic nihilism prevailed. Approval of tPA was a wake-up call. Stroke can be treated. Patients with stroke should be hurried into medical centers, and doctors and hospitals must become prepared and able to treat them. The media, politicians, and authorities called the attention of the public and of doctors to which patients? Like many potent treatments, there is great potential for effectiveness but also important risk of harm. In this issue of Circulation, Georgiadis and his Swiss colleagues analyze some aspects of potential harm.

Only 3% to 8% of eligible patients in the United States receive the treatment. Reasons for this dismal record vary and include poor public knowledge about stroke; ineffective public systems to deliver patients with stroke to capable centers; excessive fear of harm, especially by emergency physicians who first see the patient with stroke; lack of preparedness technology and personnel in many community hospitals; and fear of litigation. Part of the problem is the fact that we still have much to learn about stroke thrombolysis. There is a large mismatch between what we have learned from new technology and recent therapeutic trials and observations and the present guidelines.

The NINDS trial was planned nearly 20 years ago. The trial was ancient history in medical terms. Major determinants of treatment in the NINDS trial were a clock and rather primitive technology: a plain CT scan. It should be obvious to thinking doctors and the public that a patient does not automatically change from a good treatment candidate to a bad candidate when the clock passes 3 hours. The other rules (awakening with a deficit, minor and/or improving deficits) are poor surrogates for the information that doctors need to treat. For logical treatment of patients with stroke, doctors optimally would like to know (1) whether arteries supplying the ischemic brain tissue are occluded by thrombi and if so, where; (2) how much brain is already infarcted; (3) how much brain is still at risk for further infarction; and (4) whether there are important systemic and local risks for harm related to thrombolysis.

Diagnostic and Treatment Gains Since 1996
There has been a dramatic upgrade in MRI, CT, and ultrasound technology during the past decade. Diffusion-weighted MRI (DWI) can now predict with reasonable accuracy the location and amount of irreversible ischemic damage soon after symptom onset. T2*-weighted (susceptibility) images are able to show acute brain and subarachnoid hemorrhages. Magnetic resonance angiography (MRA) is able to show occlusions of neck and large intracranial arteries. Perfusion-weighted MRI (PWI) can show brain regions that are underperfused. When DWI, PWI, and MRA are combined, clinicians can quickly and safely learn the presence and location of arterial occlusions, the amount of brain that is probably already infarcted, and the amount of brain threatened by hypoperfusion.

CT capability has also developed. Helical CT scanners are now more widely available. They can provide films more quickly and accurately than older scanners. Contrast injection leads to vascular opacification and generation of vascular data. Software allows rapid reformating showing a CT

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Abbreviations and Acronyms
CT = computed tomography
DWI = diffusion-weighted imaging
MRA = magnetic resonance angiography
PWI = perfusion-weighted imaging
T2* = T2 asterisk
tPA = tissue plasminogen activator
UCLA = University of California, Los Angeles
WBC = white blood cell

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
angiogram (CTA), and late films show perfusion data because underperfused areas show less contrast density.

Clinicians have also gained experience with duplex ultrasound scans of the neck arteries and transcranial Doppler ultrasound of the intracranial arteries. In Germany and elsewhere, clinicians became adept at using Doppler ultrasound at the bedside and in the emergency room. Neck and transcranial Doppler ultrasound are able to reliably show complete occlusions of large arteries in the neck and head. Ultrasound testing is inexpensive and portable and may even improve the effectiveness of thrombolysis when it is used to monitor arterial recanalization during thrombolysis.

The potential menu available for clinicians and interventionists to open occluded arteries has also greatly expanded. Thrombolytic drugs are now being given intravenously, intra-arterially, and in a bridging fashion: first intravenously and then intra-arterially if the occluding artery has not recanalized. Mechanical clot retrievers are sometimes used alone or as an adjunct to thrombolysis. Angioplasty and/or stenting are sometimes used primarily or after successful thrombolysis to prevent thrombi from reforming in areas of severe atherostenosis.

In the years since the NINDS trial was reported, doctors became able to determine safely and quickly the information needed to make logical choices for acute and subsequent therapy for their patients with acute stroke, if they had available modern technology and could quickly interpret the results. Since brain imaging was mandated, additional CTA or MRA and DWI images add only a few minutes of time to the testing. The technology greatly aids experienced stroke clinicians. It does not replace the clinical encounter; it merely refines and quantifies the anatomy, pathology, and pathophysiology of the stroke. The improved imaging has facilitated knowledge about the risks and benefits of thrombolysis in specific individual patient situations.

Risks of Thrombolysis: Potential Harm

Producing Emboli That Cause New Brain Infarcts

The major purpose of the study by Georgiadis and colleagues was to analyze the frequency of new acute ischemic deficits that developed during the first day in a large group of patients treated in Switzerland with tPA, according to the existing guidelines. One potential posited complication is thrombolytic-induced breakup of thrombi (mostly in the heart or aorta), which could cause fragments to move distally and block major coronary and brain-supplying arteries, leading to new strokes and myocardial damage. Such complications have been reported in isolated single case reports. Only 2 of 341 patients (0.6%) had new brain infarcts. Each patient worsened during the first hour after tPA infusion; brain infarcts (and renal infarcts in 1 patient) were scattered among different vascular territories. The source of the thromboemboli must have been the heart or aorta, but echocardiography did not define the source in 1 patient and was not performed in the other. The limitations of the study are that a rather severe worsening (4 points on the National Institutes of Health Stroke Scale) was used to screen patients, and only those patients meeting this criteria had follow-up brain scanning. Scanning was performed with CT, a modality not as sensitive as MRI for new brain infarcts. There might have been more patients with new brain infarcts if all patients with acute stroke were systematically scanned with MRI.

I agree with the authors’ conclusion that routine screening for cardiac and aortic thrombi is not warranted before stroke thrombolysis because the yield is low. Also, even if many small emboli are formed, they are usually efficiently washed out and cleared if the major large arteries are not occluded. Derex et al studied 5 patients with cardiac thrombi who had stroke thrombolysis; none had clinical or imaging evidence of new brain or myocardial infarction.

Brain Hemorrhage

Bleeding into the brain is the most important and feared complication of thrombolysis. In the Georgiadis et al study, only 15 patients (4.4%) had intracerebral hemorrhage (ICH), 13 in the same territory as the brain infarct. Hemorrhages occurred 2 to 22 hours after termination of thrombolysis, later than the occurrence of new brain ischemia. No clinical, imaging, or hematologic feature predicted which patients would have ICH in this study. Others have shown that high serum glucose levels, severe neurological deficits before treatment, and the presence of brain edema or mass effect on pretreatment CT scans predict an increased risk of hemorrhage after intravenous thrombolysis. Several MRI findings also predict increased bleeding risk: large tissue volumes on DWI and PWI, severe neurological deficits before treatment, and the presence of brain edema or mass effect.

Brain Edema

Recanalization allows flooding of previously ischemic brain tissue with blood under arterial pressure. Often the capillaries and small blood vessels within the ischemic tissue have been damaged by the ischemia, especially if the duration of reduced perfusion was long and or severe. This reperfusion can lead to bleeding, causing a circumscribed hematoma, or to diapedesis of red cells into dead tissue (so-called hemorrhagic infarction). Sometimes the reperfusion leads to significant brain edema that can cause mass effect and further increase morbidity and mortality.

Less Common Complications

Occasional patients with stroke who had cardiac symptoms before thrombolysis for acute strokes had development of hemopericardium and cardiac tamponade after treatment. Edema of the lips, tongue, and oropharynx has also been noted after thrombolysis with tPA, especially in patients given angiotensin-converting enzyme inhibitors. Anaphylaxis is a rare complication.
Potential Benefit of Thrombolytic Treatment

Many researchers have studied predictors of benefit. Severity of the clinical deficit and time do not seem to reliably predict improvement after thrombolysis. Patients with both slight and severe deficits often improve meaningfully. Modern MRI and CT protocols that include vascular data (CTA or MRA) and perfusion information have been shown to be very useful. When the major brain arteries are open on MRA, the size of brain infarcts (as judged by DWI) do not expand, and patients do not worsen clinically.34,35 Emboli often spontaneously pass. Because the only function of thrombolytic drugs is to lyse clots, giving them to patients without occluding thrombi makes little sense. The exception might be blockage of a small artery that supplies a critical cortical region, for example, related to speech. When much of the brain is already infarcted, there is also little to gain, and the risk of hemorrhage and edema is substantial. The ideal patient for thrombolysis is one with a blocked intracranial artery, who has no infarction or a small region of infarction and substantial at-risk brain tissue that is underperfused and probably would become infarcted if the vascular occlusion is not opened.

Several recent studies showed that choosing patients by using modern MRI protocols improves selection of patients beyond the present 3-hour time limit. The tissue still at risk for infarction (often referred to as the ischemic penumbra) is estimated accurately when the area underperfused on PWI is significantly larger than the area already damage on DWI (the so-called perfusion-diffusion mismatch).36 Two studies showed that giving tPA between 3 and 6 hours after onset to patients with considerable at-risk tissue was an effective strategy (G.W. Albers et al, manuscript submitted for publication, 2006).37 Improvement was equivalent to that in the NINDS trial, and the hemorrhage rate was not increased over pooled 3-hour tPA data. Patients with large infarcts did have less improvement and more intracerebral bleeding (G.W. Albers et al, manuscript submitted for publication, 2006). In 2 other trials, a novel thrombolytic agent, desmoteplase—an agent derived from bat wings—was given to patients who had perfusion-diffusion mismatches as determined by MRI between 3 and 9 hours after symptom onset.38,39 The results were comparable to those reported in the NINDS trial.

Conclusions

Research, experience, and therapeutic alternatives have come a long way since the NINDS trial was planned and reported. The present guidelines badly need to be updated to reflect these advances. The Swiss study1 reported in this issue of *Circulation* adds information about one aspect of the potential risks of thrombolysis. Whenever possible, patients with brain ischemia should be treated at stroke centers that have experienced stroke clinicians and interventionalists; up-to-date technology; and systems that ensure rapid diagnosis, treatment, and throughput of patients. Advanced MRI, CT, and ultrasound are very important in patient selection and estimating the benefit versus the risk of thrombolytic treatment of patients with stroke.

Disclosures

None.

References


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