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Thrombolysis for acute ischemic stroke: Update on the beginning of a revolution

ABSTRACT

Now, acute stroke is a medical emergency similar to a myocardial infarction, but much will have to change for the medical system to be able to diagnose and treat acute stroke more effectively.

KEY POINTS

The goal of stroke treatment is to let no more than 60 minutes elapse from the time the patient enters the hospital until the t-PA infusion is started. Hospitals need to draw up plans for meeting this goal.

To receive tissue plasminogen activator (alteplase, t-PA), a patient must have had the onset of stroke symptoms within 3 hours of when the infusion will be started, have no evidence of hemorrhage on computed tomography of the head, and have no risk factors for hemorrhage.

Patients with risk factors for stroke, and the physicians who treat them, should find out in advance which of their area hospitals are prepared to treat acute stroke.

Research to improve stroke outcomes is proceeding along several lines: tighter inclusion criteria, better imaging techniques, intra-arterial therapy, antiplatelet drugs, cytoprotective drugs, and mechanical reperfusion.

A REVOLUTION IS UNDERWAY in the treatment of acute ischemic stroke, brought about by the FDA's approval of tissue plasminogen activator (alteplase, t-PA) for this indication in June 1996. Previously, a nihilistic attitude prevailed, as there was no effective therapy for stroke.

All this changed with publication of a study from the National Institute of Neurological Disorders and Stroke (NINDS),[1] which showed t-PA to be beneficial in acute ischemic stroke. The study showed that patients who received t-PA within 3 hours of the onset of stroke symptoms were 30% more likely to have minimal or no disability 3 months subsequently, as compared with patients who received placebo.

Now, acute stroke is a medical emergency similar to a myocardial infarction. But much will have to change for the medical system to be able to diagnose and treat acute stroke more effectively. Patients will need to be educated to recognize stroke symptoms and to seek help immediately. Physicians, hospitals, and emergency medical service (EMS) units are revising their procedures, with an eye to speeding the diagnosis and treatment of stroke patients, but much more remains to be done.

Finally, we need to better define which patients should be treated and which should not, improve the diagnostic procedures, optimize delivery of t-PA, and determine whether other drugs might improve outcomes.

DELAY IS THE ENEMY

Currently, only 5% of acute stroke patients receive t-PA, and the main reason is time delay. From the onset of stroke symptoms, there is a

TABLE 1

Treatment goals for acute stroke treatment: Increasing the speed of care

ELAPSED TIME (MINUTES)	ACTION
0	Patient arrives at hospital
10	Physician examines patient
15	Physician consults neurologist*
25	CT scan done
45	CT scan read
60	Infusion of t-PA started
120	Physician consults neurosurgeon*
180	Patient placed in monitored bed

*Consultation can be by phone call or teleconferencing

SOURCE: FROM THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE, REFERENCE 5

Acute stroke is an emergency similar to an MI

window of opportunity for using t-PA of only 3 hours. The 3-hour figure may be somewhat arbitrary, chosen because it was an inclusion criterion in the NINDS study. However, it has a basis in physiology: deprived of oxygen, neurons begin to die, and after a certain period of time—probably in the neighborhood of 3 to 6 hours—reperfusion will do little good. With most patients this time is squandered, for many reasons.

Getting to the hospital

Only approximately one fourth[2] to one half[3] of stroke patients arrive at the hospital within 3 hours of the onset of symptoms.

Recognizing stroke symptoms. The first challenge in reducing the delay is to get people to recognize when they are having a stroke. Surveys have found that many members of the general public are unaware of the warning symptoms of stroke, although this awareness can be improved with public education campaigns.[4]

911 fastest. In two studies that examined time to arrival, the fastest way to get to the hospital was by calling 911, and in fact approximately half of stroke patients get to the hospital this way. Barsan et al[3] found that the median time to arrival was 84 minutes when patients called 911, vs 270 minutes when they called their personal physician or 212 minutes when they called the hospital ($P < .0001$).

Make stroke calls a priority. EMS units may be able to cut this time even further. Up to now, acute stroke has been a second- or third-level dispatch priority. After area hospitals held meetings with Cleveland EMS services, dispatch time for stroke victims in Cleveland has gone from 45 minutes to 15 minutes (J. Duldner, personal communication).

Identify hospitals that treat stroke. But once the ambulance comes, where does it go? Most units have a policy of taking patients to the nearest emergency room. However, not all hospitals are prepared to give t-PA for acute stroke, largely out of fear of causing intracerebral hemorrhage. Patients with risk factors for stroke, and physicians who treat them, would be wise to find out in advance which area hospitals are prepared to treat acute stroke.

Delays in getting a CT scan and seeing a neurologist

Because t-PA therapy is only indicated in ischemic stroke and would worsen an intracerebral hemorrhage, a patient faces further delays at the hospital. A computed tomographic (CT) scan is necessary to rule out hemorrhage, but the median waiting time is 90 minutes just to get a scan, not including time to read it (unpublished data, National Stroke Association, University of Cincinnati). Then, if a neurologist or specially trained physician is not available in the emergency department to interpret the scan, further delays are introduced.

STROKE TREATMENT GOAL: 60 MINUTES "FROM DOOR TO NEEDLE"

In an unprecedented meeting in Washington in December 1996, 50 organizations came together to establish new standards of care for stroke. Out of this meeting came the first-ever time goals for stroke treatment, including a 60-minute "door-to-needle" time—the time from when the patient enters the hospital, all the needed tests are performed, and t-PA infusion is started (TABLE 1).[5]

INTRAVENOUS T-PA PROTOCOL

(Front)

Inclusion criteria

- Screening NIH stroke score ❑
- Onset < 3 hours ❑
- CT shows no hemorrhage ❑
- Early infarct not > 1/3 middle cerebral artery territory ❑

Exclusion criteria

- Systolic blood pressure > 185 or diastolic blood pressure > 110 mm Hg ❑
- Aggressive treatment required to reduce blood pressure to specified limits ❑
- Rapidly improving or minor symptoms ❑
- Seizure at onset ❑
- Stroke within prior 3 months ❑
- History of head trauma within 3 months ❑
- GI hemorrhage or urinary tract hemorrhage within 21 days ❑
- Arterial puncture at a noncompressible site within 7 days ❑
- Taking anticoagulants or receiving heparin within 48 hours ❑
- Elevated PTT, or PT > 15 ❑
- Platelet count < 100,000 ❑
- Glucose < 50 ❑
- Glucose > 400 ❑

Risks/benefits: discussed and documented in chart ❑

- Call NICU for bed ❑

Treatment

- Weight _____
- t-PA 0.9 mg/kg total or maximum 90 mg ❑
- Dose given_____ ❑
- Give 10% bolus over 1 minute ❑
- Give remaining 90% at a constant infusion over 60 minutes ❑

Follow-up

- No anticoagulants for next 24 hours ❑
- No antiplatelets for next 24 hours ❑
- Maintain blood pressure at < 185 systolic, < 110 diastolic ❑

(Back)

Post thrombolysis management

Vital signs and neurological checks every 15 minutes for 2 hours, then every 30 minutes for 6 hours, then every 60 minutes for 18 hours

If systolic blood pressure is 180–230 or diastolic blood pressure is 105–120 mm Hg on two consecutive readings 5 to 10 minutes apart, consider:

Labetalol 10 mg IV over 1–2 minutes
Dose may be repeated or doubled every 10–20 minutes up to total of 150 mg.
If satisfactory response is not obtained, use nitroprusside (0.5–10 µg/kg/minute)
Monitor blood pressure every 10 minutes during IV therapy, observe for hypotension

If systolic blood pressure is > 230 or diastolic blood pressure is 121–140 on two consecutive readings 5–10 minutes apart, consider:

Labetalol 10 mg IV over 1–2 minutes
Dose may be repeated or doubled every 10–15 minutes up to 150 mg total
If satisfactory response is not obtained, use nitroprusside (0.5–10 µg/kg/minute)
Monitor blood pressure every 10 minutes during therapy, and observe for hypotension
If labetalol is contraindicated (cardiac or pulmonary), may use enalapril 1.25–2.5 mg IV piggyback every 6 hours

If diastolic blood pressure is > 140:

IV sodium nitroprusside (100 µg/250 mL 0.9% normal saline) (0.5–1.0 µg/kg/minute)
Monitor blood pressure every 10 minutes; observe for hypotension

No antiplatelet or anticoagulant therapy for 24 hours after thrombolysis

Avoid blood draws or invasive lines or procedures for 24 hours after thrombolysis

If intracerebral hemorrhage is suspected:

Stop thrombolytic immediately.
Stat noncontrast head CT.

For life-threatening hemorrhage:

6–8 units platelets
4–6 units cryoprecipitated fibrinogen and plasma containing factor VIII
Labs: CBC, PT, PTT, fibrinogen

If blood transfusion is required:

Type and crossmatch 4 units packed red blood cells,
4–6 units of cryoprecipitate or fresh frozen plasma, and
1 unit of single-donor platelets

FIGURE 1. Pocket-sized card used by personnel in the Cleveland Clinic emergency department, outlining the inclusion and exclusion criteria and protocol for using t-PA to treat acute stroke.

As yet, most hospitals do not have a stroke plan for meeting this goal, but they need one. Such a plan should take a "systems approach," identifying all the actions that need to take place and all the persons involved, and then looking for ways to streamline the process.[6] Parts of the stroke plan should include:

- Community stroke awareness and education programs.
- A stroke team on call 24 hours a day, which works closely with emergency department physicians and nurses.
- Rapid and efficient communication systems and protocols.
- Standardized stroke examinations and protocols for blood pressure management, detection of intracranial hemorrhage, and nursing care.

The "point person" is often the emergency department physician, but to assume this role he or she needs training in reading CT scans, performing a standardized stroke assessment, and determining whether a given patient is a candidate for t-PA therapy. Access to neurological expertise is essential.

WHO IS A CANDIDATE FOR T-PA?

FIGURE 1 shows a pocket-sized card that we have distributed to all personnel in our emergency department. The front of the card outlines the

TABLE 2

National Institutes of Health stroke scale

ITEM	RESPONSE	SCORE
Level of consciousness	Alert	0
	Drowsy	1
	Stuporous	2
	Coma	3
Level of consciousness questions	Answers both correctly	0
	Answers one correctly	1
	Answers neither correctly	2
Level of consciousness commands	Obeys both correctly	0
	Obeys one correctly	1
	Obeys neither	2
Pupillary response	Both reactive	0
	One reactive	1
	Neither reactive	2
Gaze	Normal	0
	Partial gaze palsy	1
	Total gaze palsy	2
Visual fields	No visual loss	0
	Partial hemianopsia	1
	Complete hemianopsia	2
	Bilateral hemianopsia	3
Facial palsy	Normal	0
	Minor paralysis	1
	Partial paralysis	2
	Complete paralysis	3
Motor arm (left and right)	No drift	0
	Drift before 10 seconds	1
	Falls before 10 seconds	2
	No effort against gravity	3
	No movement	4
Motor leg (left and right)	No drift	0
	Drift before 5 seconds	1
	Falls before 5 seconds	2
	No effort against gravity	3
	No movement	4
Ataxia	Absent	0
	One limb	1
	Two limbs	2
Sensory	Normal	0
	Mild loss	1
	Severe loss	2
Language	Normal	0
	Mild aphasia	1
	Severe aphasia	2
	Mute or global aphasia	3
Dysarthria	Normal	0
	Mild	1
	Severe	2
Extinction/inattention	Normal	0
	Mild	1
	Severe	2
TOTAL (42 possible)		___

SOURCE: FROM THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE; FOR A COMPLETE DESCRIPTION OF THE ITEMS AND RESPONSES, SEE LYDEN ET AL, REFERENCE 7

inclusion and exclusion criteria for administration of intravenous t-PA. The criteria are based on those used in the NINDS trial.[1]

The inclusion criteria are designed to identify a stroke, rule out hemorrhage, and insure that the patient is treated within the 3-hour window. The exclusion criteria are designed primarily to minimize hemorrhage, the chief adverse effect of t-PA administration.

The back of the card outlines the Cleveland Clinic protocol for managing patients during the first 24 hours after the administration of t-PA.

FUTURE STRATEGIES FOR IMPROVING RESULTS

Amid the enthusiasm for the new therapy for ischemic stroke, it is important to examine the data from the NINDS t-PA stroke study[1] and be mindful of the modest gains of the current therapy. Of 312 patients who received t-PA, approximately 22% to 33% were free of neurologic symptoms 3 months later, depending on the rating scale used. In comparison, the numbers for patients who received placebo ranged from 13% to 24%.

The investigators calculated that the absolute benefit was 12%—not huge, but statistically significant and convincing. However, therapy for acute ischemic stroke is in its infancy; other strategies may improve outcomes in the future.

Tightening the exclusion criteria. Intracerebral hemorrhage is the most serious adverse effect of t-PA. In the NINDS trial, the rate of intracerebral hemorrhage was higher in t-PA patients with higher scores on the 42-point NIH stroke scale (higher scores reflect more severe neurologic deficits; TABLE 2)[7]: 2.7% in patients with stroke scores of 0 through 10, 4.3% in those with scores of 11 through 20, and 17.5% in those with scores higher than 20 (unpublished data, FDA Advisory Center, June 6–7, 1996). Even with this high rate of bleeding, patients with NIH stroke scores over 20 still did better with t-PA than with placebo. However, it may be that the ideal candidate for t-PA has an NIH stroke score between 4 and 20, because with scores lower than 4 the stroke may be too mild to treat, and with

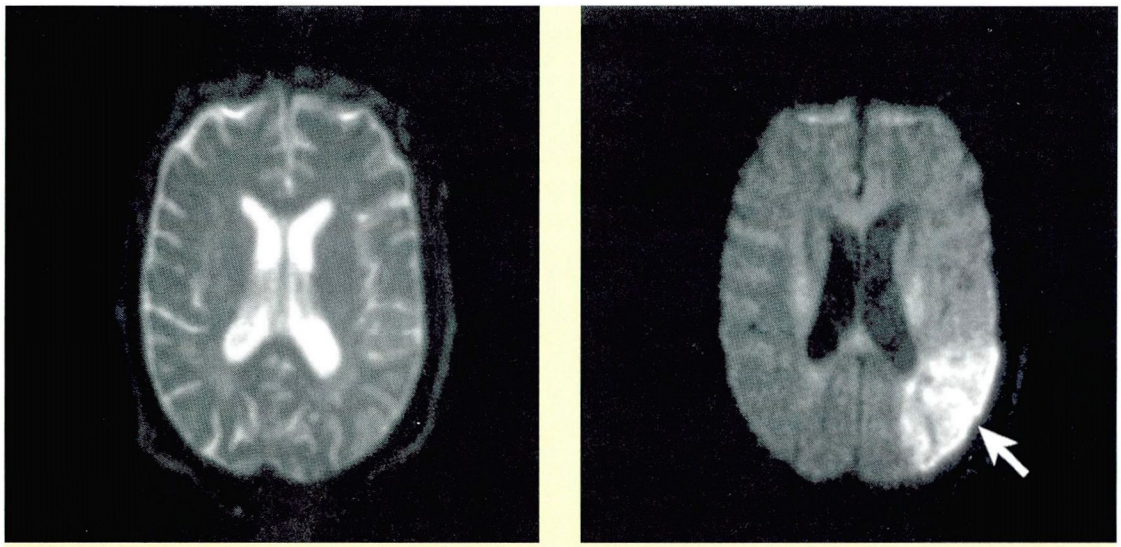

FIGURE 2. Left, a standard T2 magnetic resonance imaging scan appears normal in this patient 4 hours after the onset of stroke symptoms. Right, a diffusion-weighted MRI scan in the same patient reveals the area of ischemia (arrow).

scores higher than 20, the risk of intracerebral hemorrhage may be too great.

Better imaging techniques. In the NINDS trial, patients were selected on the basis of a neurologic examination and a *normal* CT scan. However, angiographic studies at our hospital and elsewhere are revealing some disturbing news about ischemic stroke patients. Approximately 20% of patients who would appear to be excellent candidates for t-PA have no visible occlusion at all on angiography.[8] The remainder have occlusions that vary widely in size and location—and chances of being reopened with t-PA. For example, carotid "T" occlusions (ie, at the junction of the internal carotid and middle cerebral arteries) are very difficult to reopen, even with intra-arterial therapy. Occlusions in small vessels have a greater likelihood of reopening than those in large vessels.

Using arteriography in deciding whether to give t-PA is not practical for most patients; we need a fast, noninvasive screening test. Advances in magnetic resonance imaging (MRI) show some promise. MRI angiography may reveal the location of the occlusion. Another technique, diffusion-weighted MRI,[9] detects movement of water across cell membranes and may prove useful in revealing ischemic areas that appear normal on standard T2 scans (FIGURE 2).

Improved techniques for administering fibrinolytics. In theory, infusing a fibrinolytic drug directly into the occluded artery should be more effective than giving it intravenously, but this approach is fraught with logistic problems. In the largest controlled study of this therapy to date, approximately 6,000 patients were screened for occlusions in the mainstem middle cerebral artery, but only 40 were treated.[10] Intra-arterial therapy reopened the blocked middle cerebral artery approximately 60% of the time, compared to a 14% rate of spontaneous recanalization in untreated patients.

Treated patients also received heparin in either a high or a low dosage. The recanalization rate was 82% with high-dose heparin—but the rate of intracerebral hemorrhage was more than 20%. With the low-dose heparin regimen, the bleeding rate dropped below 10%, but the recanalization rate was also cut in half.

Antiplatelet drugs. The antiplatelet drug abciximab or similar drugs might be used in conjunction with thrombolytic drugs to prevent rethrombosis.[11] At present, aspirin is recommended for all patients with ischemic stroke.

Occlusions in small vessels have a greater likelihood of reopening than those in large vessels

Intra-arterial therapy after intravenous therapy. In a small pilot trial, 35 patients received either a loading dose of t-PA (0.6 mg/kg) or placebo, then all underwent angiography and intra-arterial therapy. The loading dose seemed to soften the clot and result in more complete opening after intra-arterial t-PA. However, all the major hemorrhages that occurred were in the treated group (T. Brott, personal communication, EMS Bridging Trial).

Cytoprotective therapy of brain tissue. Certain drugs might protect ischemic brain tissue from further damage; examples include citicoline and lubeluzole. These could possibly be given by EMS crews in the ambulance and combined with thrombolytics.

Mechanical reperfusion. Just as angioplasty and stenting have shown great efficacy in the treatment of coronary artery disease, similar strategies might be useful in the treatment of acute ischemic stroke. Studies of percutaneous angioplasty, with or without stents, are being planned or underway. Mechanical clot removal is also under investigation.

CONCLUSION

Tissue plasminogen activator has ushered in a new era in acute stroke therapy. Patients, physicians, and hospitals must become more familiar with acute stroke care and develop systems to enhance access to new treatments. A number of tools have been developed by national organizations to assist in this process.

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