Thrombolysis for Acute Stroke: The Incontrovertible, the Controvertible, and the Uncertain

Arguments concerning the usefulness of thrombolytic treatments in the emergency treatment of patients with acute ischemic strokes have become commonplace. Unfortunately, much of the debate in the emergency medicine community has become mired in the posturing of critics and advocates, impeding a meaningful exploration of the issues involved. Positions on either side have become inflexible, transforming the debate into a ''win-lose'' proposition, without hope of identifying the truth. Approaching this debate with a review of what we know, and do not know, is thereby warranted. Furthermore, a consideration of how physicians adopt new therapies may provide insight into the limited acceptance fibrinolytic treatment in stroke has achieved.

THE INCONTROVERTIBLE

Much of the pathophysiology of stroke is well understood and incontrovertible. Acute stroke symptoms are most often caused by a focal impairment of blood flow in a specific cerebrovascular distribution. The impairment is usually caused by a mechanical obstruction of flow of a thromboembolic nature.[1] If blood flow is restored within a sufficiently early time frame, there is functional recovery of the ischemic territory; if not, the ischemic tissue fails to recover following reperfusion.[2–6] Lastly, tissue plasminogen activator (tPA) promotes lysis of thrombi and reperfusion following vascular occlusion.[7,8]

Each of these elements has been demonstrated extensively in animal research and in observational and interventional clinical research. Indeed, they are a part of most clinicians' everyday experience in patients they have cared for with transient ischemic attacks and in patients treated with thrombolytic agents for coronary occlusions. Thus, the use of rapid thrombolysis to reverse or ameliorate the effects of acute cerebrovascular occlusion is conceptually sound.

It would be incorrect, then, to consider the series of clinical trials of thrombolysis in stroke,[9–16] using different agents and different treatment protocols, as a cumulative attempt to prove the concept of thrombolytic therapy in stroke. Rather, the trials represent competing attempts to identify the details of implementation: the clinical parameters in which this concept might translate into patient benefit. In this context, it is expected that some trials would be negative and others positive. Hence, the conflicting data from these trials are not surprising and do not suggest ambiguity in the soundness of the underlying concept of thrombolytic use in stroke.

THE CONTROVERTIBLE

The question then is in the details of implementation. The purpose of clinical trials involving use of fibrinolytic treatment in stroke is to determine a set of specific conditions in which a therapy can be effective. Whether the existing National Institute of Neurological Disorders and Stroke (NINDS) clinical trial experience sufficiently defines such a set of details is potentially controvertible and therefore worthy of review.

In the NINDS trial, 624 patients with symptoms of acute ischemic stroke were randomly assigned to treatment with tPA or placebo within three hours of symptom onset. Three months later, 133 of the 312 patients (43%) treated with tPA were neurologically intact as compared with 83 of the 312 patients (27%) receiving placebo. Fifty-three patients (17%) treated with tPA and 66 patients (21%) receiving placebo had died. Twenty patients (6.4%) treated with tPA and two patients (0.6%) receiving placebo developed symptomatic intracranial hemorrhage within 36 hours of treatment.[9]

Thus, in the NINDS study, the effect of tPA treatment on improving neurologic outcome in the entire sample of 624 patients was positive and durable.[17] Patients with intracranial hemorrhage were included in the benefit analysis and the higher rate of good neurologic outcomes occurred in the treated group despite more hemorrhages, which is a point of frequent misunderstanding. Additionally, in response to study critics, the trial data underwent independent, external analysis, with the results presented at the 2003 Society for Academic Emergency Medicine annual meeting confirming benefit from treatment in the trial. Criticisms of the statistical analysis still exist but should not represent the core of the remaining controversy on the use of tPA in stroke.

Other trials evaluating different sets of conditions have not been found efficacious in improving outcome. Table 1 lists major differences in the reported randomized, double-blind, placebo-controlled studies of intravenous thrombolytic use in acute stroke.

In summary, the NINDS trial demonstrated one set of detailed circumstances in which a specific fibrinolytic treatment was successfully applied while differing

Table 1. Differences in Clinical Trial Protocols for Thrombolytic Use in Stroke

Study	Location	Drug	Dose	Time (h)	Exclusion Criteria
Atlantis A (1991–1993)[12]	United States	rtPA	0.9 mg/kg (maximum, 90 mg)	0–6	Blood pressure
NINDS (1991–1994)[9]	United States	rtPA	0.9 mg/kg (maximum, 90 mg)	0–3 (1:59)*	Blood pressure
MAST-I (1991–1995)[11]	Italy, United Kingdom, Portugal	Streptokinase	1.5 million units	0–6	
ECASS 1 (1992–1994)[13]	Europe	rtPA	1.1 mg/kg (maximum, 100 mg)	0–6 (4:24)*	Computed tomographic evidence of early infarct; age
MAST-E (1992–1994)[10]	France, United Kingdom	Streptokinase	1.5 million units	0–6 (4:36)†	Mild stroke
ASK Trial (1992–1994)[16]	Australia	Streptokinase	1.5 million units	0–4 (3:28)*	Age; minor stroke
Atlantis B (1993–1998)[15]	United States	rtPA	0.9 mg/kg (maximum, 90 mg)	3–5 (4:36)†	Blood pressure; age
ECASS 2 (1996–1998)[14]	Europe, Australia–New Zealand	rtPA	0.9 mg/kg (maximum, 90 mg)	0–6	Blood pressure; computed tomographic evidence of early infarct; age

rtPA = recombinant tissue plasminogen activator.
*Mean time from onset to treatment.
†Median time from onset to treatment.

protocols did not. What remains most controvertible is whether the circumstances of the NINDS trial are externally valid and reproducible in broad clinical practice.

Critics correctly indicate that the NINDS study was performed by researchers with an interest and presumed expertise in the treatment of acute stroke. It is reasonable to question whether emergency physicians without such expertise and resources can reproduce the same results. Supporting this view are data demonstrating circumstances in which physicians have been unable to treat patients in a manner similar to the protocol used in the NINDS trial and data that patients treated in such systems did poorly.[18–20] Critics also rightly note the time from symptom onset to treatment is shorter in the NINDS trial than in current clinical practice (see Table 1) and believe this prevents extrapolation of the results to the community setting.

Advocates of the therapy point to data demonstrating that physicians in a variety of practice environments can treat patients in a manner similar to that used in the NINDS trial.[21–31] Proponents also believe that most patients with ischemic stroke are accurately identified for thrombolytic therapy.[32] They suggest that it is not surprising to find patients treated outside of recommended guidelines and that this is modifiable with training and experience. Indeed, in systems where initial experience with recombinant tPA in stroke was negative (even abysmal), further education and quality assurance measures have led to appropriate use.[21,33]

Ultimately, the successful reproducibility of the NINDS protocol in widespread clinical practice remains subject to judgment and interpretation. For the time being, individual health systems and their treating physicians together must determine if they are capable of providing care in a manner consistent with the set of conditions described in the NINDS protocol and should only treat stroke patients with tPA if they can meet these requirements.

THE UNCERTAIN

A greater uncertainty, however, lies beyond the interpretation of the existing data on this topic and within the realm of physician acceptance of new treatment recommendations. Physician behavior in adopting changes in clinical practice is clearly multifaceted and is poorly understood.[34] Translation of clinical trial data and associated guidelines into general clinical practice involves 1) physician awareness and familiarity with data and guidelines, 2) physician agreement with data, 3) the belief that one can deliver the therapy effectively, 4) the personal expectation of benefit for the patient, 5) overcoming inertia of previous practice patterns, and 6) modifying external barriers directly affecting physician behavior.[35]

Given these barriers to general acceptance, the controversy surrounding the use of tPA in stroke may represent more the result of a ''perfect (barrier) storm'' than disagreement over the larger concept of thrombolytic use in stroke. Specific barriers to acceptance of thrombolytic use include the previously noted controversies that have resulted in divergent recommendations from various professional organizations, perceived minimal cost–benefit impact, lack of confidence in the methods of guideline development, and issues regarding practical delivery of tPA. Acceptance has also been limited due to physician aversion to the rate of hemorrhagic complications. Because iatrogenic adverse outcomes carry a higher emotional burden than adverse outcomes associated with the natural history of a disease, some physicians may require greater certainty than usual to change their practice. Given the infrequency of treatment, both in the community setting and within emergency medicine training programs, it is understandable that physicians have concerns regarding effective fibrinolytic delivery in stroke. Furthermore, the historic nihilism regarding stroke care must also be overcome.

Even if the above issues have been surmounted, considerable external barriers remain. With increasing patient throughput pressure, lack of timely specialist availability or support (e.g., neurology and/or radiology), organizational constraints, patient consent issues, limited reimbursement, and perceived increased malpractice liability, it becomes clear that the barriers to broad acceptance are substantial.

THE FUTURE

Future research efforts are needed to resolve persistent controversies on the use of thrombolytics in acute stroke, but even more importantly, efforts should be directed toward what remains unknown. Can emergency physicians in the community diagnose and treat strokes in the manner performed in the NINDS trial? If not, what barriers keep them from doing so? How effective is the therapy when implemented in the community? Is the therapy effective when given to a population of patients with a longer mean time from onset of symptoms to treatment than the population treated in the NINDS trial? Why are patient outcomes sometimes poor in the early stages of implementing a system to treat stroke patients with tPA, and what can be done to minimize this start-up effect? How can the emotional, medicolegal, and educational components of physician decision making be addressed? Can hemorrhagic complications be reduced? Are medicolegal concerns based on facts or fears? Can continuing medical education improve emergency neurologic expertise? What is the impact of stroke teams and systems on effective delivery of thrombolytic therapy? Are there adjunctive therapies that may improve outcome or extend the treatment window when combined with thrombolytics?

In the larger perspective, stroke will always be a medical emergency. Future interventions for treating stroke will likely be more effective the earlier they are started. What can we do to encourage patients to seek care sooner? How can we respond to, transport, and triage patients with stroke most effectively? What do we do for the large proportion of stroke patients not recognized and treated early enough to be candidates for reperfusion?

The current controversy over the use of tPA in patients with acute stroke should not be allowed to mire emergency stroke care in a hopeless morass, but rather should be used as an opportunity to prove that we can learn what is needed to make this concept and future therapies work for our patients.—**Robert Silbergleit, MD** (robie@umich.edu), **Phillip A. Scott, MD,** *Department of Emergency Medicine, University of Michigan, Ann Arbor, MI*
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