



Emergency Medicine Treatment of Acute Stroke in the U.S.; Progress, Problems, and Politics Abstract

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The NINDS tPA stroke treatment trial was completed in December of 1995 and in 1996, the FDA approved t-PA for the treatment of acute stroke. Seven years later, only 2% of stroke patients in the United States are being treated with tPA for acute ischemic stroke. Despite evidence suggesting that outcome is significantly better after acute stroke with tPA treatment and that mortality is not affected, many emergency physicians in the U.S. feel uncomfortable using tPA for acute ischemic stroke. There are several issues contributing to this including knowledge gaps, team work issues, the potential for inducing harm by treatment with tPA and issues of patient selection. The American College of Emergency Physicians (ACEP), the American Academy of Emergency Medicine (AAEM), and the Canadian Association of Emergency Physicians (CAEP), have all come out with guidelines regarding the use of tPA for acute stroke. Most of these recommendations suggest that at a very minimum, there must be an institutional commitment to the treatment of acute stroke patients with thrombolytic agents which involves more than just the emergency department. The AAEM and CAEP statements go further in suggesting that thrombolytic treatment for acute stroke is not the standard of care. Efforts need to focus on further efforts to improve the safety of thrombolytic treatment, establish the time limits of efficacy, and investigating the role of other interventional treatments for patients with acute ischemic stroke. The NINDS symposium in 2002 developed a number of guidelines that should be helpful in guiding institutions in developing programs for acute stroke treatment.

Key Clinical Issues

What is the evidence suggesting that tPA is effective in treatment of acute ischemic stroke?

What are the problems preventing implementation of acute stroke treatment programs in most institutions?

What are important steps that we can take to address physicians' concerns about with thrombolytic therapy for acute stroke.

Key Learning Points

- The initial evaluation of the NINDS data as well as the repeat independent evaluation would suggest that tPA treatment for acute stroke within three hours has a significant benefit and that patients are more than twice as likely to end up neurologically normal if treated with IV tPA within three hours.
- Some of the problems, which have prevented implementation of acute stroke treatment programs in this country, are knowledge gaps among emergency physicians in the diagnosis of stroke and recognition of CT scans, lack of institutional support and lack of teamwork.
- There needs to be an institutional commitment and buy-in from emergency physicians, neurologists and radiologists before acute stroke treatment with thrombolytic agents should be undertaken at any hospital. Thrombolytic therapy in the absence of teamwork and institutional support is not likely to be beneficial or safe.

In December of 1995 the *New England Journal* reported a positive treatment effect for the use of IV tPA in the treatment of acute ischemic stroke patients within three hours of symptom onset. The NINDS tPA trial showed an 11% absolute and 30% relative improvement in the number of patients becoming neurologically normal after treatment with tPA for acute ischemic stroke (1). Despite an incidence of intracerebral hemorrhage that was ten times higher in the treatment group than the placebo group, the 90-day mortality was actually lower in the tPA treatment group although this was not statistically significant. The FDA approved the use of tPA for acute ischemic stroke in 1996. Despite a positive study and FDA approval, currently only about 2% to 3% of patients in the United States are being treated with tPA for acute stroke(2). Although many patients are ineligible for treatment because of time issues, many physicians are skeptical about the use of thrombolytic therapy for acute ischemic stroke. Part of this criticism stems from methodological and statistical questions about the original study in 1995. There was concern about imbalance of baseline NIH stroke scale between the tPA and placebo groups, whether the treatment effect was related to time from symptom onset to treatment and whether patients at risk for having an intracerebral hemorrhage related to tPA treatment can be identified. The NINDS appointed an independent committee in May 2002 to address the concern that eligible stroke patients may not benefit from tPA given according to the protocol used in the trials and whether the sub-group imbalance invalidated the entire trial. Six committee members were chosen and the results were presented at the SAEM meeting in 2003 by Dr. Michael O'Fallon, who was the committee chair. The conclusion of the committee was that despite sub-group imbalances, there was a statistically significant benefit of tPA treatment measured by an adjusted tPA to placebo global odds ratio of 2.1 for a favorable clinical outcome at three months. All adjusting variables were investigated as potential modifiers with the tPA treatment effect and none was found to have a statistically significant influence. The committee found no statistically significant evidence of the existence of a sub-group of patients who would either be harmed or be unlikely to respond favorably to the use of tPA in acute ischemic stroke.

While some of the controversy surrounding tPA treatment for acute ischemic stroke had focused on the validity of the NINDS tPA stroke trial results, there have been other issues raised as well.

Knowledge Gaps

Some emergency medicine physicians have argued that emergency medicine physicians have often had no formal neurological training in recognition of the subtleties of acute stroke. They also assert that there is a lack of familiarity with measurement tools. There have also been issues about inadequate training in CT interpretations and the question of how well emergency physicians can actually diagnose acute stroke. Regarding the emergency medicine physician's ability to diagnose acute stroke, there have been variable reports(3,4). Kothari in 1996 showed that emergency medicine physicians have 100% sensitivity and 98.6% specificity in diagnosing patients with acute stroke in the emergency department. Another article by Litman in 1996 states as many as 19% of patients diagnosed with acute stroke may actually be stroke "mimics". The only one of these studies actually performed in the emergency department in the U.S. was by Kothari.

Teamwork Issues

There has been a considerable amount of discussion surrounding issues of teamwork involved with the treatment of patients with acute ischemic stroke with thrombolytic agents. Despite the existing data, surveys have documented that less than 50% of neurologists in the U. S. are actually treating acute stroke patients with IV tPA and that a significant number of them are skeptical about the benefit and risks of thrombolytic treatment(5). At the 2002 NINDS symposium, issues were raised about the inadequate reimbursement for acute stroke treatment with thrombolytic agents(6). Teamwork issues are also involved in CT interpretations. Specifically the question has arisen about who should be interpreting CT's prior to treatment with tPA? There have also been issues about the ability of the physician or general radiologist who detect early hypodensity on CT scans(7). The European Cooperative Acute Stroke Study documented that a significant number of CT scans were improperly read in the emergent situation(8).

The NINDS study did not require detection of early hypodensity as a decision point in treating patients with acute stroke. The only prerequisite to treating with tPA with acute ischemic stroke was the absence of intracerebral hemorrhage or other significant intracranial pathology (such as subdural hematoma, brain tumor, etc.) The study in *JAMA* by Schriger cast doubt on the ability of emergency physicians and general radiologists to even detect blood on CT scans.

Institutional Support

Currently most hospitals will break even or even lose money on the stroke DRG payments if thrombolytic therapy is used. There is also no adequate reimbursement for physician time for acute stroke treatment. Because of this, many institutions are not willing to invest financially in support mechanisms for detection in treatment of patients with acute ischemic stroke. There have not been firm criteria to designate centers who either should or should not be treating with thrombolytic agents for acute stroke although proposals for certification of stroke centers has begun.

Potential for Harm

Despite the NINDS study statistics showing that there is an overall benefit with treatment with tPA for acute ischemic stroke, there is also the potential to harm the patient by producing an intracerebral hemorrhage. The incidence of symptomatic intracerebral hemorrhage was 10 times higher in the tPA treatment group than in the placebo group and many physicians are uneasy giving a treatment which has the potential to induce harm. There was also a concern that although the hemorrhage rate was only 6.4% in the NINDS study, that hemorrhage rates would be much higher when this treatment was used in the general community. A number of follow-up studies to the NINDS study have suggested that, with one exception, hemorrhage rates have not been significantly different from that shown in the NINDS trial(9).

Politics

Because the decision whether or not to treat an acute stroke patient with thrombolytics typically takes place in the emergency department, the emergency physicians are really in the hot seat on this issue. Patients have developed expectations based on news media and TV shows that they can be cured if they present with acute ischemic stroke and emergency physicians are the individuals at the point of treatment. Treating emergency physicians are concerned that without adequate support mechanisms from neurology, neuroradiology and institutions, acute stroke treatment with thrombolytic agents is not feasible. There have been an increasing number of lawsuits brought against emergency physicians and others for failure to treat patients with acute ischemic stroke with thrombolytic agents. Because of this, the emergency medicine organizations have developed physician statements on the use of tPA for acute ischemic stroke in an effort to protect practicing emergency physicians.

ACEP's position statement states that, "IV tPA may be an efficacious therapy but there is insufficient evidence to endorse the use of tPA when systems are not in place to insure that NINDS guidelines are followed". They suggest that the decision to use tPA should begin at the institutional level. The American Academy of Emergency Medicine (AAEM) goes further in commenting that the objective evidence is insufficient to warrant classification as a standard of care and that physicians are advised to use their discretion. The AAEM cites that the emergency physician at the bedside has not been convinced by those promoting this therapy and that there needs to be recognition that the circumstances and resources from the NINDS study cannot be easily duplicated by the average center. They also express efficacy concerns, safety concerns, and concerns about the ability to properly interpret CT scans. The Canadian Association of Emergency Physicians suggests that only radiologists or neurologists should provide interpretations of CT scans and further, that stroke thrombolysis should be limited to centers with appropriate resources. Emergency physicians should not in their opinion be primary decision-makers but neurologists should be directly involved. They go further in saying that the administration of thrombolytic agents should be carried out only in the setting of an approved research protocol or formal clinical practice protocol.

Where Do We Go From Here?

Hopefully, the validation study by the group of independent experts on the original NINDS data will put to rest some of the concerns about the validity of the findings. It is probably unlikely that another placebo-controlled trial evaluating the effects of thrombolytic treatment in acute stroke will be done in the future. With tPA being the FDA approved treatment for stroke, it would be difficult to justify a placebo group in future trials.

While future placebo-controlled trials are unlikely, further prospective studies evaluating the effectiveness and safety of tPA in community settings would be very helpful. Other types of studies which would be helpful at this point would investigate ways to make tPA treatment safer, either through alterations in treatment protocols or better patient selection.

Recognition that there needs to be an institutional commitment to the treatment of stroke patients is essential. The 2002 NINDS Symposium recommends that all hospitals develop plans for how they will deal with patients with acute stroke. It should not be an expectation that every hospital will deliver acute thrombolytic therapy to patients with stroke, but it is expected that all hospitals

should have a plan for either treating acute stroke patients or referring them elsewhere. If hospitals elect to deliver acute treatment for stroke, they should be prepared to develop the institutional commitment to do so with buy-in and cooperation from neurologists, emergency physicians and radiology as well as the institutional commitment to provide the resources necessary to enable this type of treatment. Emergency physicians should not be held accountable for the total amount of institutional commitment.

Further studies are also evaluating the use of interventional treatments for acute stroke. It is likely that percutaneous angioplasty and intra-arterial clot lysis will become more widespread in the future and perhaps change the face of acute stroke treatment, much as what has occurred in myocardial infarction.

It is clear from the data that early stroke treatment with thrombolytic agents is effective and that the earlier the treatment is delivered the better. It is imperative that institutions and emergency physicians evaluate ways to streamline the acute evaluation of stroke patients making life saving treatment possible in the future.

References

1. National Institute of Neurologic Disorders in Stroke rt-PA Stroke Study Group. "Tissue plasminogen activator for acute ischemic stroke," *N Engl J Med* 1995;333:1581-1587.
2. Barsan WG: NINDS – Proceedings from improving the chain of recovery for acute stroke. Dec 12-13, 2002.
3. Kothari R, et al: "Emergency physicians: Accuracy in the diagnosis of stroke,." *Stroke*. 1995, 26:2238-2241.
4. Libman R, et al: "Conditions that mimic stroke in the ED," *Arch. Neurol.* 1995, 52:1119-1122.
5. Katzan, et al: "Community use of IV t-PA for acute stroke," *Stroke*. 2001;32:861-865.
6. Incentives for enhancing stroke care, NINDS – Proceedings from improving the chain of recovery for acute stroke. Dec 12-13, 2002.
7. Schriger et al: "Crainial CT interpretation in acute stroke," *JAMA*. 1998. 279:1293-1297.
8. 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.
9. Albers GW, the STARS Investigators. Prospective, monitored, multicenter, post-approval experience with intravenous t-PA for treatment of acute stroke: the standard treatment with activase to reverse stroke (STARS) study [abstract]. *Stroke*. 1999;30:244.