Further Randomized Controlled Trials of Tissue Plasminogen Activator Within 3 Hours Are Required

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Although early (within 3 hours of onset) tissue plasminogen activator (tPA) has been approved as a treatment for stroke in several countries and endorsed by experts, it remains underused. Clinicians are still uncertain about whom to treat.

Why Are Stroke Physicians Uncertain of the Benefits of Early tPA?
An independent national survey of 1716 stroke physicians in the United Kingdom reported that 74% were uncertain of the benefits of thrombolytic therapies. A recent United States survey reported that less than half of the responding neurologists had administered tPA and only 30% believed the efficacy of intravenous tPA was "very convincing."

The Available Evidence
The randomized controlled trials (RCTs) of thrombolysis for acute ischemic stroke have been systematically reviewed with data from just over 5000 patients in 17 trials. The majority of the data derives from the 8 tPA trials (2955 patients). In the review it was noted that few older patients (aged ≥80 years) had been included. Unfortunately, there were too few data to perform many subgroup analyses, but overall 3 important conclusions were drawn: (1) there was a definite substantial risk of fatal intracranial hemorrhage; (2) there was a nonsignificant excess of deaths; and (3) these risks appeared to be balanced by an increase in independent survival, which appeared most beneficial for tPA given early (<3 hours after onset).

However, there were too few data to help determine the risk for individual patients. We do not have data on the effects of tPA subdivided by initial CT brain scan appearances, stroke severity, stroke subtype, patient age, or whether the benefits of tPA persist much beyond 6 months.

It is important to note that the NINDS trial was unusually positive and in general, has, been overemphasized. We cannot avoid the uncomfortable fact that no studies have been as positive. Was there something unique about the NINDS trial? Were they simply lucky? The use of block randomization ensured that 302 of the 624 patients in the NINDS trials were treated within 90 minutes. Patients had to recognize their symptoms, get to an appropriate hospital quickly, be assessed, be scanned, and provide consent, all within 90 minutes of the onset of symptoms—an astonishing achievement. Perhaps clinicians contemplating a tPA service feel unable to replicate this?

Ischemic stroke is such a heterogeneous entity that, given all the factors that could shift the risk/benefit equation (ie, age, time from stroke onset, severity, subtype, CT scan appearances, and comorbidity), it is far too simplistic to rely on just one of these to determine treatment eligibility (ie, time from onset). Does the fast-tracking change the case mix of those who present early (usually patients with severe stroke)? If so, this could change the risk-benefit equation of tPA used within 3 hours of stroke onset.

More Trials Are Needed
There is no doubt that tPA can be effective. However, clinicians now need more data to implement treatment. For whom is treatment most beneficial or risky? Case series and audit have not, and will not, be able to reliably answer these questions. We need more data from RCTs, including a wider range of patients. Uncertainty must still remain for many categories of patients with stroke seen within 3 hours; otherwise, why are these patients not currently being treated?

Ethically, which is better: To continue as we are, with few patients worldwide being treated, thus possibly failing to deliver an effective treatment, or randomizing hundreds more patients under 3 hours to provide convincing evidence?

What Makes Clinicians Change Their Practice?
By the mid-1980s, 33 thrombolytic therapy RCTs had been completed in acute myocardial infarction (MI), and a systematic review demonstrated a statistically significant benefit in survival. However, opinion did not change until convincing data emerged from the 17 187 patients randomized in the ISIS-2 trial. Eventually, some 60 000 patients were included in RCTs of thrombolysis for MI, and these robust results demonstrated that most major subgroups of patients could benefit from treatment. Really reliable and convincing data led to thrombolysis becoming a routine treatment for acute MI.
Some 16 years later we seem to be in a similar situation. We have positive results from one major study and a promising systematic review. However, unlike those with MI, many stroke patients do not have access to organized inpatient care, fast-tracking of stroke patients is limited to tertiary referral centers, the specialty of stroke medicine is only just emerging, and funding for stroke research is scandalously low. Our challenge is to ensure that stroke unit inpatient care, fast-tracking of stroke patients is limited to MI, many stroke patients do not have access to organized intervention trials. The most promising treatment to start with is tPA, but if we continue to argue among ourselves, nothing will happen.

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References


Further Randomized Controlled Trials of tPA Within 3 Hours Are Required—NOT!

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Intravenous thrombolysis is beneficial for patients with acute ischemic stroke: in 5 separate trials, treated patients improved more than placebo patients. The first 2 trials, the NINDS trials, were published in 1995 and led directly to the licensing of recombinant tissue plasminogen activator (rtPA) for acute ischemic stroke. In these trials, patients were treated within 90 or 180 minutes of stroke onset with 0.9 mg/kg rtPA after a careful selection procedure. Treated patients enjoyed a near-total resolution of deficit more often (30% to 50% relative benefit) compared with placebo. Symptomatic hemorrhage occurred in 6.4% of treated patients. It is not widely appreciated that in addition to the treated patients who totally cleared their symptoms, an additional 20% to 30% enjoyed a partial improvement. A similar trial utilized intravenous ancrod, a defibrinogenating agent that causes modest thrombolysis, hypofibrinogenemia, and mild anticoagulation. Benefits and risks were similar to those with rtPA. In the PROACT II study, patients thrombolysed within 6 hours of symptom onset did well, with an acceptable hemorrhage rate. Finally, a large European trial of rtPA showed a clear benefit for rtPA, using the analysis method devised for the NINDS trials.

The limitations on this therapy—the only proven stroke treatment—are legendary: patients must be treated promptly after stroke onset, must have no contraindications to thrombolysis, and must be treated by a team skilled in preventing potential complications. Much has been made of these limitations, to the point of considerable nihilism among neurologists. Yet, results similar to the NINDS data are obtained in communities with active stroke teams dedicated to proper use of intravenous thrombolysis. With only one exception, community experience with acute stroke therapy mirrors the NINDS trial results. Considerable prior experience is essential for appropriate case selection, but tutorials and basic texts are available.

A red herring occasionally thrown at thrombolysis is the issue of vascular imaging: thrombolytic therapy might be given needlessly to some patients unless an image of the occluded artery is obtained. Reassurance may be found by considering that very few patients were treated “needlessly”
in prior trials. For example, in the NINDS placebo group, only 2.6% of patients exhibited normal stroke scale scores 24 hours after stroke. This 2.6% included patients with transient ischemic attack and perhaps other nonstroke etiologies; it seems unlikely that vascular imaging prior to thrombolytic stroke therapy would add any benefit. Further, vascular imaging requires precious time: at least 60 minutes to mobilize and obtain the first images, even in the most dedicated centers. Further, it is apparently not harmful to administer tPA to patients in whom no blockage can be documented on angiogram: patients with lacunar syndromes responded to thrombolysis as well as or better than other subgroups. On the other hand, one important advantage of angiography is that intra-arterial therapy could be delivered directly into the clot. Recently, a large trial of intra-arterial prourokinase showed significant benefit with reasonable risk, even if treatment was delayed up to 6 hours following stroke onset.

Thrombolytic stroke therapy offers a real opportunity to eliminate stroke-related disability in some patients. Although the original trials met with appropriate skepticism, the results of these and subsequent stroke thrombolysis trials have been digested, criticized, confirmed, supplemented with additional data, and diffused widely. The therapy can be given to only a minority of patients, primarily those who present early enough, and only a minority enjoy a full response. So now, several questions must be answered: How can we increase the success rate? Will neuroprotectants add benefit or reduce risk when combined with thrombolytic therapy? Is the 3-hour time limit absolute, or is there some way to find patients in whom therapy could be given later? Most importantly, what can be done to educate more patients and potential stroke-witnesses about the signs of stroke and the need for immediate medical attention? Perhaps we will find a way to treat patients later than 3 hours, and further studies are needed to push the outer limit of the time window, but within the 3-hour window, no further trials are needed; the drug works. The dictum primum no nocere still applies: we must do no harm, either by actively committing an act or by withholding a proven therapy through inaction.

References

When Is Enough Enough?

We find it fascinating that the views expressed by the protagonists of our first controversy reflect the trans-Atlantic dichotomy of opinion concerning the use of tissue plasminogen activator (tPA). As most clinicians know, tPA is now licensed in North America (United States since 1996) and a number of South American countries. Licensing has been slower in Europe, Australasia, and Asia. Indeed, there is only restricted licensing in a limited number of countries outside North America.

Perhaps understandably, the use of tPA has been taken up more enthusiastically in the United States where the only unequivocally positive trial(s) of therapy was conducted and, importantly, under the auspices of their national funding body. The main difficulty is that an equivalent trial with a 3-hour time window has not been conducted elsewhere, although the cumulative meta-analysis supports the findings of the NINDS trial. Of importance, open phase IV studies with tPA indicate that the positive benefit/risk ratio of the NINDS trial may be replicated, provided that the therapy is administered in expert centers with strict adherence to the NINDS protocol.

Given our current dependence on evidence based medicine, investigators only wish to advocate a therapy when it is of proven value. Only a few thousand patients have been enrolled in tPA stroke trials. In contrast, tens of thousands of

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Stroke is available at http://www.strokeaha.org
patients were studied in the mega-trials of myocardial infarc-
tion before thrombolysis became accepted. This may be
because the single end point of mortality in myocardial
infarction necessitates larger sample sizes than stroke trials,
where a combined end point of death and disability increases
power. Some would say that unnecessary additional random-
ized trials of thrombolysis for myocardial infarction were
performed, well after the benefits were obvious by cumula-
tive meta-analysis (had it been used). Are we in the same
position with trials of thrombolysis for stroke?

In essence, it comes down to a view of when is enough
evidence enough. Clearly the view differs from physician to
physician, country to country, and continent to continent.

Our view is that tPA should now be used in expert centers,
according to NINDS guidelines, less than 3 hours after stroke
onset. However, there is still uncertainty about some sub-
groups within this time frame, such as those with very severe
neurological deficits or extensive early ischemic CT changes,
and randomization here may be appropriate. Perhaps more
importantly, there is a real need for randomized trials of
thrombolysis beyond the 3-hour time window and identifica-
tion of neuroimaging parameters, such as diffusion/perfusion
MRI, that may predict better outcome. Herein lies the real
challenge.

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