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

Richard Iain Lindley, MD, FRCP(Edin)

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\(^1\) of 1716 stroke physicians in the United Kingdom reported that 74% were uncertain of the benefits of thrombolytic therapies. A recent United States survey\(^2\) 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.\(^3\) 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\(^4\) 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)\(^5\)? 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.\(^6\) 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.\(^7\) However, opinion did not change until convincing data emerged from the 17 187 patients randomized in the ISIS-2 trial.\(^8\) 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.\(^9\) Really reliable and convincing data led to thrombolysis becoming a routine treatment for acute MI.
Further Randomized Controlled Trials of tPA Within 3 Hours Are Required—NOT!

Patrick D. Lyden, MD

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 anecrod, 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: thrombotic 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”...
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

References


Key Words: randomized controlled trials stroke, acute stroke, ischemic thrombolysis tissue plasminogen activator

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From the National Stroke Research Institute, Heidelberg West, Victoria, Australia.

Correspondence to Prof Geoffrey A. Donnan, National Stroke Research Institute, Level 1, Neurosciences Bldg, Banksia St. Heidelberg West, Victoria 3081, Australia.


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patients were studied in the mega-trials of myocardial infarction 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 randomized trials of thrombolysis for myocardial infarction were performed, well after the benefits were obvious by cumulative 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 subgroups 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 identification of neuroimaging parameters, such as diffusion/perfusion MRI, that may predict better outcome. Herein lies the real challenge.

Geoffrey A. Donnan, MD, FRACP
Stephen M. Davis, MD, FRACP

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Section Editors: Geoffrey A. Donnan MD, FRACP and Stephen M. Davis MD, FRACP and Richard Iain Lindley

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