Thrombolytic Therapy

Introduction

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The success of thrombolytic stroke therapy presents a novel situation for clinically active neurologists who must evaluate acute stroke patients for eligibility to receive a therapy that has a net benefit but also potential side effects. The first therapy for stroke is also the first therapy for which neurologists must urgently present difficult choices to patients and families for an immediate decision rather than decisions for treatments of chronic neurologic disorders that can be made over a much longer time period.

Over the past few years, the results of the stroke thrombolysis trials have been well-digested, criticized, confirmed, supplemented with additional data, and diffused widely. We now know that although treated patients do better than untreated patients, only a minority of treated patients gain a full recovery. Further enhancements of thrombolytic therapy are urgently needed. In this session of the Princeton conference, several new ideas were presented that could augment or replace intravenous thrombolytic therapy.

Yet as we develop new ideas, it is critical to simultaneously promote use of the currently approved standard, intravenous thrombolysis. In communities with active stroke teams, the frequency of intravenous thrombolysis can be improved from 2% to 3% to 10% or more of eligible patients with ischemic stroke. The novel ideas presented at this Princeton Conference should be studied and, if proven, added to a baseline of intravenous thrombolysis. Simultaneously with our commitment to new therapies, we must renew our resolve to increase the delivery intravenous thrombolysis in the standard fashion.

Intravenous thrombolysis is beneficial (safe and effective) for patients with acute ischemic stroke: in 5 separate trials, treated patients improved more than placebo patients. It is not widely appreciated that in addition to the treated patients who enjoyed near-total clearing of their symptoms, an additional 20% to 30% enjoy a partial improvement, moving from dependent on others to independent. The Ancrod trial showed similar benefits using an agent that causes modest thrombolysis, hypofibrinogenemia, and mild anticoagulation. Benefits and risks were similar to recombinant tissue plasminogen activator (rtPA). Recently, a pooled analysis of the large trials (NINDS, ATLANTIS, and both ECASS trials) confirmed the benefits of intravenous rtPA. The time window was longer in the pooled analysis because of the differing entry criteria, and benefit was seen when therapy was delivered as late as 5 hours after symptom onset. However, current prospective trials of this longer time window must be completed before intravenous thrombolysis can be recommended beyond 3 hours from symptom onset.

A “red herring” occasionally thrown at thrombolysis is the issue of vascular imaging: the precise location of the clot must be known before thrombolysis. It can be argued that because there were so few “transient ischemic attack-like” patients in the original NINDS placebo group—only 2.6% of patients exhibited no neurologic deficit (normal stroke scale score) when examined 24 hours after stroke—that it seems unlikely that vascular imaging before thrombolytic stroke therapy would add any benefit. Andropov presented data, however, that frequent transcranial ultrasound not only provided vascular imaging but also may have promoted clot dissolution. Confirmation of these promising results awaits a prospective, randomized trial. An advantage of direct arterial visualization is that therapy could be delivered directly into the clot. Barnwell presented data showing that direct clot removal with mechanical devices can be accomplished quickly in some cases with reasonable safety. It remains to be shown whether this technically demanding therapy can be deployed widely.

An alternative to direct imaging of vessels would be the labeling of the clot material itself. Lauffer presented intriguing pilot data showing that molecules can be engineered that not only will bind to fresh, intravascular thrombus but also can be imaged with computed tomography or magnetic resonance technology.

The risk of thrombolysis is small but finite—between 3% and 6% of treated patients have a symptomatic hemorrhage. Lo presented data that blood–brain barrier breakdown can be related to the activation of matrix metalloproteinases. In addition, rtPA may have a direct neurotoxic effect, although this point remains highly controversial. Further studies will examine whether less toxic thrombolytics can be developed. Matrix metallopro-
teinases inhibitors may hold promise for reducing the blood–brain barrier effects of rtPA.

References