Should physicians give tPA to patients with acute ischemic stroke?

Against: And just what is the emperor of stroke wearing? see also p 148

An intervention is *efficacious* if it produces more benefit than harm in the idealized setting of an expert-based study. It is *effective* if it is beneficial in daily clinical practice. Despite the enormous propaganda machine pushing the exciting new fashion of thrombolytic therapy for acute ischemic stroke, there is good reason to question the efficacy of such therapy and overwhelming reason to question its effectiveness.

With regard to efficacy, of 7 randomized controlled trials (RCTs) of thrombolysis to date,[1-7] only 1—the NINDS study—showed benefit in any primary clinical outcome measure.[1] The NINDS study, which made use of specialized expertise, included just over 300 patients who received tPA. The absolute benefit in the 3-month outcome (12%-13%) was modest, especially since 95% or more of stroke patients seen at study centers were not even eligible for inclusion. There was no mortality benefit from tPA in the trial, nor was there benefit in the other primary outcome of "substantial recovery" in the first 24 hours. On the basis of the NINDS study, thrombolysis could only help, at most, 1 of every 125 stroke patients.[8] Given that NINDS artificially inflated the number of patients seen early after the onset of symptoms—those seen in less than 90 minutes—even these estimates are conservative.

But there are many reasons to be skeptical about the NINDS trial, even though it is methodologically sound. Among innumerable examples of drugs for which a single trial suggests benefit, but subsequent and more substantial work ultimately proves that this is not the case, perhaps the most relevant to this discussion is the use of low-molecular-weight heparin for acute ischemic stroke. A study by Kay and colleagues, published as the next article in the very same issue of the *New England Journal of Medicine*,[9] had both a similar number of patients and a similar effect size as the NINDS trial. It did not receive a fraction of the publicity that the NINDS trial did, and alas, when the use of low-molecular-weight heparin was studied further in a far larger RCT, it proved to be without benefit. No similar follow-up RCT, to validate or challenge the NINDS trial findings, has been done, nor is one likely.

Furthermore, other RCTs of thrombolytic therapy in acute ischemic stroke have been done, the results of all of which have been either neutral or negative, and several found statistically and clinically important increases in mortality. This may be because the risk-benefit equation for thrombolysis is favorable only under the specific conditions (timing, dose, etc) of the NINDS trial. Without a single confirmatory RCT, however, an equally plausible explanation is that the disparity in results is due to chance. When similar trials are repeated many times, results will occasionally appear particularly good, particularly bad, or everywhere in between.

An even greater concern is that the effectiveness of thrombolysis in general community practice will be far less than any efficacy it achieved under the idealized circum-

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stances of the NINDS trial. Given the relatively small benefits found in the NINDS trial, even a small diminution of benefit, or increase in harm, could translate into overall harm to patients.

Patients misdiagnosed as having a stroke, who actually have a "stroke mimic"—such as Todd's paralysis, infection, or metabolic disorder—(none of which are identified by CT) can only be harmed by thrombolysis. Although stroke mimics were rare in the expert-based NINDS trial, they are far more common in community practice.[10] Thrombolysis will surely harm patients with an unrecognized hemorrhagic stroke, and few emergency physicians, neurologists, or general radiologists are able to identify all or even most subtle hemorrhages.[11] The use of thrombolysis more than 3 hours from the onset of symptoms is associated with worse outcomes and would also skew the risk-benefit ratio. Given the lesser resources in community practice and the pressure to treat patients at least occasionally, many patients with unrecognized hemorrhage are bound to be included, with predictable consequences.

Several groups that participated in various RCTs of tPA have published glowing reports about continued "success" outside an ongoing trial, which they note is statistically "consistent with" the NINDS results. Their claim that this is testimony to the effectiveness of thrombolysis is not appropriate, however, for many reasons. Such groups are not representative of standard community practice. Their results may reflect publication bias—only the groups with good results publish them. Their numbers are so small that virtually any outcomes are "consistent with" the results from the NINDS trial, as well as with terrible outcomes. Their outcomes are not measured by blinded observers and thus may reflect the enthusiasm, and bias, of the authors.

The only realistic effectiveness study published to date paints a very different picture of the effect of thrombolysis in community practice.[12] This trial included results from every stroke patient treated with tPA in essentially all the hospitals in Cleveland, Ohio, and thus was neither selective in its reporting nor reliant only on expert practitioners. It found, predictably, that many patients were treated inappropriately, that the rates of symptomatic and fatal intracranial hemorrhage were astronomic, and that the outcomes—including mortality—were far worse than would be predicted had these patients received only conservative therapy.

It would not be unreasonable to encourage widespread use of a new therapy, even in the absence of clear-cut evidence of benefit, for a condition in which the following conditions exist:

- outcome is virtually uniformly bad with standard therapy,
- the potential benefits of the new therapy are substantial,
- the proposed treatment is unlikely to cause harm, and
- there is no reason to suspect results will be substantially worse in general practice than they are in expert-based studies.

For thrombolysis in acute stroke, none of these conditions apply.

Although it is possible that individual patients with acute ischemic stroke may indeed benefit from thrombolysis, and such "saves" would be cause for celebration, creating fatal or devastating hemorrhage in other patients is equally tragic. Until there is better reason to think that the widespread use of thrombolytics would do more of the former than the latter, we should all ask why there's such a big parade and so many admirers of tPA's newest fancy clothes.

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