Clinical controversies

Thrombolysis for Stroke in Israel: Will We Step Up or Sit Out?

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Stroke is a terrible disease. It kills more humans in the western world than any disease except coronary atherosclerosis and cancer (1). It cripples more people than any other illness (2). Until recently there was little a physician could do for the patient but watch and hope as a life was shattered by a 'cerebral vascular accident.'

Most strokes are thromboembolic events, causing ischemia and infarction of brain tissue distal to the clot. The logic of quickly dissolving that clot, exactly analogous to the logic of treatment of myocardial infarction, is strong. Over several decades, different agents and dosages were attempted. Most turned out to be neither safe nor effective. In 1995 the National Institute for Stroke and Neurological Disorders (NINDS) published a paper which detailed two studies which seem to have the agent, dosage, and indications right (3). Mostly on the strength of these studies, in 1996 the FDA approved tPA for the treatment of stroke within three hours of onset. Later it was similarly approved in Canada and Europe. We have recently reported on our initial experience in the use of tPA in stroke in Israel at the annual meeting of the Israeli Association of Emergency Medicine (IAEM) (4).

The NINDS studies showed that, for patients treated with tPA within three hours of onset of stroke, it was more likely, across all subgroups, to have minimal or no neurological deficit at three months as opposed to those treated with placebo. The odds ratio was 1.7.

The percentage of patients with complete recovery on the NIH stroke scale was 31 percent with tPA and 20 percent with placebo (a 50% relative improvement). Using other scales the relative increase in neurologically intact patients was at least 30%, and the absolute increase in favorable outcome was 11-13%. These, clearly, were statistically and clinically significant results (3).

The main fear in giving tPA to patients with stroke is that of causing intracranial hemorrhage (ICH). Indeed in the NINDS trials about 6% of patients had symptomatic ICH versus 0.5 % of controls. There was no increase in overall mortality, and there was a significant decrease in chance of death or severe disability in the tPA group. So, according to NINDS, if you have a stroke of sufficient severity; you don't have a contraindication and are treated with tPA at the appropriate dosage within 3 hours; you are about 50% more likely to get back to your normal life than if you are not treated. You are more likely to have an intracranial bleed, it is true, but this notwithstanding, you are less likely to be severely crippled or dead. Since so much of the case for treatment with tPA is based on the NINDS trial, it has rightly been highly scrutinized. Concerns have been voiced regarding random imbalance of stroke severity between tPA and placebo groups, differential outcomes between those treated from 0-90 minutes versus 90-180 minutes, and whether certain subgroups are more likely to have intracerebral hemorrhage. Recently, an independent panel has reviewed the original data from the NINDS studies and found that that the odds ratio for benefit was actually higher than reported (2.1 as opposed to 1.7) These results have yet to be published but Dr Lewis Goldfrank of Bellvue Hospital discussed them recently at the annual meeting of the IAEM. It is clear from the NINDS trials that the earlier treatment is started the better, but it is also clear that the treatment benefited patients up to 3 hours after the onset of disease.

One problem is that not many people present to the ED in time to get treated. Other studies have attempted to expand the window of opportunity to 5-6 hours and were unable to show benefit (see ECASS and ATLANTIS trials) (5-7). The subgroup who were treated fortuitously with tPA within three hours in the ATLANTIS trial were more likely to have a favorable outcome at 90 days than those treated with placebo within three hours (60.9% vs 26.3% odds ratio 4.4; p=0.01) (8).

The above is convincing enough that the authorities in the USA, Canada and Europe have approved tPA for use in acute stroke. We believe that the evidence is convincing enough that Israeli patients also deserve to benefit. While there is good evidence that appropriate patients stand to gain from thrombolysis, we must be mindful of the risks involved if this therapy is applied without appropriate regard for treatment guidelines. In a study in Cleveland the authors report a 15.7 % rate of symptomatic ICH. However half of these occurred in patients whose treatment deviated from protocol (9). The relationship between deviation from guidelines and risk of ICH has been shown in other studies (10)

We need to be able to offer the best chance for our patients to get well. We cannot ignore the likelihood that we, by treating appropriate stroke patients with tPA, can prevent the ending of productive lives. In order to be able to treat these people, we need to educate the public and EMS so that they present in time. The stroke team in the Houston area reports treating 15% of acute ischemic stroke with tPA, as opposed to 1.8% in Cleveland. (9,11) We need to have dedicated teams of emergency physicians, neurologists and nurses who will efficiently develop and apply protocols so as to minimize violations and risk to patients from therapy.

As we become more aggressive in pursuing the timely diagnosis and treatment of stroke, we will find more patients who are amenable to other promising treatments besides IV tPA, such as intra-arterial thrombolysis (given up to six hours after onset). We will be able to enroll patients in studies of other time-dependant therapies.

The approach to acute stroke is no longer ‘diagnose and adios.’

References

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11. Grotta JC, Burgin WS, et al. Intravenous tissue-type plasminogen activator therapy for ischemic stroke: Houston experience 1996-2000. Arch Neurol 2001;58:2009-2013

Correction:

In the previous issue we mistakenly attributed the article "Acute coronary syndromes - low molecular weight heparins or unfractionated heparin" (page 25), to Dr. Magee, but indeed it was an article by Dr. Barry Diner, MD MSc (Candidate), Assistant Professor, Department of Emergency Medicine, Emory University, Atlanta, Georgia.

We sincerely regret the error.