Treatment of Acute Stroke

Past, Present, and Future

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INTRODUCTION

Progress in the treatment of acute stroke has been quite slow, marked by few successes and numerous failures. The prolonged transition from bench to bedside has focused on two critical areas: thrombolysis and neuroprotection. Both interventions are concerned with the restoration of normal neural activity in the ischemic penumbra – the area of brain tissue surrounding the core of the infarct that contains dysfunctional but not necrotic tissue. The restoration of blood flow into this zone can restore normal cellular and electrical activity, but only if timely use of neuroprotective agents can prevent apoptosis, excitotoxicicty, and oxidative damage. These considerations have a parallel in reperfusion therapy for acute myocardial infarction, where intervention to open an occluded coronary artery with thrombolytic agents, catheter interventions, or emergency coronary bypass, if uncontrolled and done too late, is much more likely to increase myocardial injury and electrical instability.

Clinical trials of agents to treat acute stroke predate computed tomography (CT) and showed little benefit, which is not surprising since there was wide variation in patient characteristics and the intervals between onset of symptoms and treatment. Additionally, it is likely that some patients enrolled in trials of thrombolysis actually had an unrecognized acute intracerebral hemorrhage. Over the last decade, however, protocols for acute treatment have become more selective, with the explosion in neuroimaging modalities, from rapid CT evaluation to diffusion/perfusion MRI imaging. Inclusion and exclusion criteria are now based on the results of neuroradiological evaluation as well as increasingly stringent clinical criteria.

This article will review notable prior efforts, current acute treatment modalities, and the results of some recent important trials of thrombolysis and neuroprotection.

INTRAVENOUS THROMBOLYTIC THERAPY

The only FDA approved agent for the treatment of acute ischemic stroke (AIS), is recombinant tissue plasminogen activator (rt-PA).[1]

Trials of other less successful thrombolytics helped to clarify the criteria for patients, dosage, and time intervals to treatment for subsequent studies. Three of the earliest major multicenter trials utilized the bacterial protein streptokinase. The Multicenter Acute Stroke Trial-Italy (MAST-I), Multicenter Acute Stroke Trial-Europe (MAST-E), and the Australian Streptokinase Trial differed principally in the time range from symptom onset to treatment: 6 hours in MAST-I and MAST-E, and 4 hours in the Australian trial. The trials were terminated prematurely due to increased rates of intracerebral hemorrhage (ICH) with no difference in death or disability. Despite treatment failured important lessons were learned from these trials: 1) dose may need to be adjusted for the patient's weight (all treated patients had received 1.5 million units of streptokinase); and 2) the interval from symptom onset to intervention may be very important. Patients treated within a three hour window *trended* towards a better outcome, though the sample size was very small.[2-5]

The next trials studied tissue plasminogen activator, and again Europe took the lead with the European Cooperative Acute Stroke Study, (ECASS). Though the window for treatment was again 6 hours, CT criteria were used to disqualify patients, and those with a large territorial infarct were not enrolled. The study also used weight-based dosing (1.1mg/kg), and excluded patients with mild symptoms. Functional outcome was measured at 90 days with the Barthel Index and the Modified Rankin Scale, the two standard tests of functional level and disability. Analyses of the data were done according to both intention-to-treat and target population. Intention-to-treat analysis uses all patients randomized to each group (including those who did not adhere to the protocol), while target population analysis excludes patients who violate the protocol and focuses on those who were correctly assigned. Target population analysis thus indicates a direct benefit of rt-PA, if one is present, while intention to treat provides an assessment of efficacy and outcome that is more "real world." In ECASS there was no difference in outcomes at 90 days in either

the target or intention-to-treat populations. Secondary analysis did show an effect in favor of rt-PA when the BI and the modified Rankin score were considered as a composite measure.[6-8]

Recognizing the strengths and weaknesses of the prior thrombolytic studies, the National Institute of Neurological Disorders and Stroke (NINDS) coordinated a stroke study that demonstrated a benefit when rt-PA was used in the treatment of acute ischemic stroke within 3 hours.[1] The study is not without its detractors. Some feel that the bleeding rate is too high to recommend its use in clinical practice, while others feel that the study was biased by stroke severity and etiological subtype and thus doesn't provide a basis for widespread application of its protocol. Most clinicians feel that subsequent analysis and review of the NINDS outcome data does not support these concerns.

In the NINDS trial, patients with acute ischemic stroke symptoms seen within 3 hours of onset were randomized to either placebo or rt-PA only if they met the study's rigid inclusion criteria.[1] The study was divided into two parts: one analyzed effectiveness within 24 hours, and the other looked at 90 day improvement in functional measures. A global test statistic was developed that combined the scores on the Barthel Index, the Modified Ranking Scale, the National Institutes of Health Stroke Scale (NIHSS), and the Glasgow Outcome Scale (GOS). A favorable outcome was indicated by a BI of 95-100 as well as an MRS and NIHSS of ≤1, and GOS of 1.

At 24 hours (part one), there was no significant difference in the NIHSS between the treatment and placebo groups, but there is more to the story. First is the possibility that a response to rt-PA within 24 hours reflects improvement that would have occurred spontaneously, but in a retrospective analysis, 18% of patients treated with rt-PA, and only 4% of controls, had an NIHSS ≤1 within 24 hours of symptom onset. Thus, unless almost 5 times as many TIA patients were enrolled in the treatment arm, there clearly was a trend to early treatment benefit.

At 90 days (part 2), the global test statistic described above indicated a 30% greater likelihood of an improved functional outcome with rt-PA. Of course the downside was a statistically significant increase of 6.4% (1/15) in the rate of symptomatic and fatal ICH in treated patients. Half of those with bleeding related to rt-PA died. Yet despite those sobering numbers, thrombolytic therapy with rt-PA produced a significant increase in the number of patients free from death or major disability. The drug was equally effective in strokes caused by cardiogenic embolism, small vessel disease, and large artery atherosclerosis. As a result of this study the Food and Drug Administration approved intravenous rt-PA for the treatment of acute ischemic stroke within 3 hours of symptom onset.

ENDOVASCULAR TREATMENT OF ACUTE STROKE

Endovascular therapy for stroke has several advantages over intravenous thrombolysis, including direct application of the agent to the clot, mechanical disruption, a lower dose of thrombolytic medication, and a longer therapeutic window. The Intra-arterial Prourokinase for Acute Ischemic Stroke Trial (PROACT II) tested the effect of Prourokinase (r-proUK) plus heparin, versus heparin alone, in the treatment of middle cerebral artery occlusions within 6 hours of symptom onset. At 90 days 40% of the r-proUK group demonstrated an improved functional outcome (defined as a modified Rankin scale of ≤ 2) compared with 25% of controls. The bleeding rate was 10% in the study population, reflecting the longer treatment window and the use of heparin. The FDA did not approve r-proUK for this indication, and r-proUK is not available in the United States. Despite that decision, many large stroke centers utilize intra-arterial thrombolysis with rt-PA off label for patients who fall between three and six hours, and have thrombus in proximal segments of intracranial arteries.[9]

Mechanical removal of the clot itself can be accomplished through the use of the Merci retrieval device (Concentric Medical), and was approved by the FDA for that purpose in 1995. The MERCI trial enrolled patients seen within 8 hours of symptom onset who had occlusion of a large artery. Effectiveness of the device in achieving recanalization was compared with the placebo arm of the PROACT trial, but unlike the PROACT protocol, which was restricted to middle cerebral artery strokes, in the MERCI trial the target vessel could be in the anterior or posterior circulation. In the MERCI trial recanalization was achieved in 53.5% of the population with a complication rate of only 7%, compared with PROACT, where recanalization occurred in 18% of subjects. However, in MERCI the mortality rate overall was almost 40%, and among those who failed to undergo successful

embolectomy the rate was a staggering 61%. 25% had a successful clinical outcome (i.e. modified ranking score ≤2), similar to the outcome of PROACT's control arm. So why with such bleak numbers would the FDA approve such a therapy? The FDA did not require that the device produce a specific clinical outcome, only that it achieve restoration of blood flow, which as a paraclinical marker *should* indicate an improvement in outcome.

It is apparent that we must be careful when determining the results of device trials in a broad clinical context as long as clinical outcome is considered a primary, rather than a secondary measure. Still, there are specific situations in which a mechanical approach may be superior to intravenous or other intra-arterial therapies, such as in an acute postoperative infarct, or in a pregnant women suffering an acute stroke.[10]

Other Thrombolytic Agents

There are many other thrombolytic agents available, though only a few have been tried in stroke patients. One which showed promise was *desmoteplase*, (r-DSPA α1), a recombinant protein derived from the saliva of a vampire bat. The purported advantages of r-DSPA α1 include increased fibrin selectivity as well as absence of neurotoxic effects. The Desmoteplase in Acute Ischemic Stroke Trial, (DIAS) used magnetic resonance technology to identity the ischemic penumbra by diffusion-perfusion mismatch. Therapeutic effects of r-DSPA α1 were assessed 3-9 hours after onset of symptoms. In this phase II dose escalation trial, the reperfusion rate was 70% in the highest dose group and 60% of these patients experiencing a favorable clinical outcome. The symptomatic ICH rate in the high weight-adjusted dose group was 2.2%. When non weight-based doses were used in Part 1 of the study the bleeding rate reached almost 26%. Though the study group was small it indicated that weight based dosing of r-DSPA α1 was safe and effective in the presence of a diffusion-perfusion mismatch and prompted the Dose Escalation of Desmoteplase for Acute Ischemic Stroke trial, (DEDAS). DEDAS enrolled 37 patients, randomized to 90μg/kg, 125μg/kg, or placebo. 12 patients were excluded due to a violation of the protocol's imaging criteria. This limited the intention-to-treat analysis which showed a trend towards statistical significance in the high dose group. In a target population analysis (excluding the protocol violators) the clinical outcome reached statistical significance compared to placebo. Based on DIAS and DEDAS it is uncertain whether or not r-DSPA α1 is an effective treatment outside of the classic therapeutic window and requires technology that isn't available in all hospitals.[11,12]

Sonothrombolysis

The CLOTBUST trial explored the use of high frequency sound waves to penetrate the skull and disrupt the clot, thus providing increased exposure of fibrin to plasmin. A standard transcranial Doppler ultrasound probe provided constant insonation to the suspect vessel, while patients received rt-PA intravenously. If reperfusion failed, intra-arterial rt-PA was optional. Investigators were blinded as to whether or not the patient was receiving active ultrasound or placebo. There was increased reperfusion in the ultrasound group, but only a trend toward a significant difference in clinical outcome.[13]

Neuroprotection

The brain's blood flow is tightly controlled by autoregulatory mechanisms which keep cerebral blood flow constant at around 50ml/100g brain tissue/min. An ischemic event has significant and immediate neurochemical consequences. The lack of blood glucose and oxygen causes depletion of energy reserves and ion pump failure. At 20ml/100g brain tissue/min electrical functions of the neuron cease, but are recoverable. When the value reaches 10ml blood/100g brain tissue/minute synaptic vesicles are released leading to unopposed actions of excitatory amino acid transmitters, especially glutamate. In addition mitochondrial aerobic respiratory mechanisms fail, intracellular calcium levels rise, free radicals are generated, and if this critical level of diminished blood flow is not reversed promptly, programmed cell death occurs.

Given the biochemical cascade which produces neural dysfunction in the penumbral tissue, neuroprotective agents have been developed in hopes of disrupting the cascade and sustaining neurons until blood flow is restored. A few examples of such agents include: glutamate receptor antagonists, calcium channel antagonists, GABA (gamma-amino-butyric-acid) antagonists, free radical scavengers, growth factors, leukocyte inhibitors, nitric oxide inhibitors. Though acute stroke patients have not shown significant clinical benefit from these agents in clinical trials, one promising agent was studied at Lancaster General Hospital and will be discussed.

NXY-059, (Cerovive) was studied in Europe in the SAINT I trial, which found a significant improvement

in disability at 90 days when measured by the modified Rankin scale (MRS). This result provided reason to hope that when given within 6 hours, this agent could improve neuronal survival as well as provide a meaningful reduction in disability. Unfortunately, the resulting SAINT II trial in the United States failed to show clinical benefit at 90 days. Subgroup analysis of time-to-treatment, NIHSS, and reduced ICH also failed to show benefit when used in concert with thrombolytic agents. No further studies of this compound are planned.

Why did NXY-059 fail in SAINT II when showing such promise in the SAINT I trial? The results of the SAINT I trial were controversial in that the statistical significance was in the *distribution* of modified Rankin scores (MRS), not in the percentage of patients who reached an MRS of 0 or 1. When the latter measure is considered, only a modest clinical benefit is noted: 30.98% of placebo and 33.41% of treated patients attained this MRS. For a study with such a small difference to have adequate statistical power, thousands of patients would be needed. It appears that SAINT II proceeded despite marginal data because of what Alan Greenspan would call "irrational exuberance."[14]

Is it all over for neuroprotective therapies? In the last 20 years numerous agents have been tried which showed considerable promise in animals, but no benefit and considerable side effects in humans. The controlled conditions of the laboratory, where the agent can be applied within minutes of occlusion, or even before the vessel is occluded, do not mirror real world scenarios. This difference may explain why there has been no transition from the bench to the bedside. In animal models occlusions are removed at a specific time point, whereas recanalization rates in humans are much smaller (See PROACT placebo data above). The agents also do not take into account the mechanistic heterogeneity of stroke in humans. While cortical protection may be expected to work on a large artery or cardioembolic stroke, it should have no effect on a purely subcortical ischemic lesion.[15-18]

Despite all of their potential limitations, the story of neuroprotection is unfinished. The use of newer thrombolytic agents with a longer therapeutic window may allow higher drug concentrations in the affected region. Phase III trials of such agents are currently underway. One must always remember the axiom that the "absence of proof is not proof of absence".

CONCLUSIONS

Trials of therapies for acute stroke have had few successes and numerous failures in humans, but the future is not bleak. Failures contribute to our knowledge and lead to the design of newer compounds and protocols. Currently, treatment of acute ischemic stroke is limited to intravenous or intra-arterial rt-PA. Mechanical retrieval of clot may be considered under certain circumstances in the hands of an experienced operator.

The stroke protocol at Lancaster General Hospital identifies patients with onset of symptoms within 6 hours. Those seen within 3 hours are candidates for intravenous rt-PA while those outside the 3 hour window may be candidates for clinical trials. In 2007 142 patients were identified with acute ischemic stroke and 7% received treatment with rt-PA. Other patients who were not candidates for thrombolysis were enrolled in clinical research studies. The 7% figure may not seem impressive, but the national average for rt-PA treatment is only 4%, with the highest rate of 15% at the University of Texas-Houston.[19,20] Thus the treatment rate at LGH is almost twice the national average!

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