CME CREDIT

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Advances in the treatment of hemorrhagic stroke: A possible new treatment

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ABSTRACT

Recombinant factor VIIa may be the first proven treatment for intracerebral hemorrhage (ICH); to be effective, it must be given soon after the onset of symptoms. Surgical removal of the hematoma by craniotomy at about 24 hours does not appear to offer much benefit compared with conservative therapy and delayed surgery, except possibly for superficial ICHs. Standardized management of medical complications remains important. New randomized treatment trials of recombinant factor VII and surgery are in progress or just beginning.

FOR THE FIRST TIME, solid evidence is emerging on how to manage strokes due to intracerebral hemorrhage (ICH), the second most common type of stroke and the most deadly. In the past few years:

- A large randomized clinical trial has found that giving recombinant factor VIIa (NovoSeven), a coagulant agent, early after the onset of symptoms offers some benefit in terms of limiting the volume of ICH and improving functional outcomes.[1]
- Another large randomized clinical trial found that surgical evacuation of the blood did not improve outcomes—although the results are open to interpretation (see below).[2]
- Guidelines for the management of ICH,[3] developed in 1999, will likely be updated soon.

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SECOND MOST COMMON CAUSE OF STROKE

ICH causes 15% to 30% of all strokes; most of the rest are ischemic, and subarachnoid hemorrhage causes much fewer.

Compared with the other types, ICH causes a higher mortality rate and worse functional outcomes. At 7 days, the mortality rate is more than 20%, rising to more than 40% at 1 month, and 53% at 1 year. Only 10% of patients are functionally independent at 1 month, and 20% at 6 months.

The location of the ICH varies. In a population-based study that included 1,041 patients with ICH, 50% of the hemorrhages were deep in the brain, 35% were lobar (ie, in the temporal, frontal, parietal, or occipital lobes), 10% were in the cerebellum, and 5% were in the brainstem (J. Broderick, personal communication, 2005). The survival rate is best for cerebellar hemorrhages and worst for brainstem hemorrhages.

However, survival and morbidity are most highly correlated with the volume of ICH as measured on the baseline computed tomographic (CT) scan. The average volume of ICH in an earlier study was 34 cm^3, about halfway between the volume of a ping-pong ball and a golf ball. Almost no one with a baseline volume greater than 30 cm^3 had a good functional outcome.[4]

HOW OFTEN DOES ICH GROW?

Before the 1990s, the accepted wisdom was that the bleeding in ICH occurred over min-

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utes and then remained stable. It was also thought that the region of low density surrounding the clot frequently seen on the baseline CT scan was due to a breakdown in the blood-brain barrier.

In the early 1990s, a prospective study funded by the National Institute of Neurologic Diseases and Stroke was performed in 103 patients in the greater Cincinnati area who underwent serial imaging.[5] A baseline CT scan was done within 3 hours after symptom onset, a second scan was done 1 hour later, and a third scan was done 20 hours after the first scan.

Surprisingly, the hematomas continued to grow significantly (an increase of > 33% in volume) after the first CT scan in 38% of patients: 26% within 1 hour, and 12% between 1 and 20 hours. This growth occurred in all locations and was associated with clinical deterioration on the National Institutes of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale during these same time intervals. This study demonstrated for the first time a potential window to stop or slow bleeding.

More than 1/3 of ICHs continue to grow

Subsequent clinical and animal studies also demonstrated conclusively that the low-density region surrounding the ICH was due to extruded serum from the blood as it clotted and that this serum was rich in thrombin.[6,7] This hypodensity also grew during the first 24 hours in parallel with the volume of ICH but was not independently associated with worse outcome.

TREATMENT OF ICH

Until recently, no therapies for ICH have shown benefit in randomized clinical trials, including surgical evacuation, osmotic diuretics, glucocorticoids, glycerol, and hemodilution.

In 1999 the American Heart Association published the first guidelines for managing ICH.[3] At that point no therapy had convincing level 1 evidence to support its use, although patients with ICH frequently need many interventions because of the severity of their illness.

The general management of ICH is similar to that of any acute focal brain injury and is aimed at complications such as increased intracranial pressure, mass effect, and secondary infections. Critical care of these conditions is important, and I urge readers to consult the guidelines. However, the rest of this paper will cover new data on the medical and surgical treatment of the ICH itself.

Potential new treatments for ICH include stopping or slowing the bleeding during the first several hours, removing the blood after the bleeding has stopped, and delivering agents that limit the effects of blood (not discussed here).

RECOMBINANT FACTOR VIIa

Recombinant factor VIIa (NovoSeven) is available and approved for treating bleeding related to hemophilia in patients who have antibodies to factor VIII or IX, Glanzmann's thrombasthenia (in the European Union only), and factor VII deficiency (in the European Union only). Could it also control bleeding in ICH?

How it works. Recombinant factor VIIa forms a complex with tissue factor that leads to thrombin generation. Recombinant factor VIIa also activates factor X to factor Xa on the surface of activated platelets, leading to an enhanced thrombin burst at the site of injury.[8]

The half-life of recombinant factor VIIa is about 2.6 hours, and the recommended dose is 90 μg/kg intravenously every 3 hours. It must be given acutely to stop bleeding within the first several hours, although it may be effective later in patients receiving warfarin.

Potential risks and adverse effects include ischemic stroke and other vascular events. Since patients with ICH may also have a prior history of ischemic stroke, the risks of ischemic adverse events are being closely monitored in clinical trials in ICH.

Pilot study

In phase 2 testing, doses of 10 to 160 μg/kg were given to 48 patients with ICH. No major safety concerns were detected.[9]

Major trial

The Recombinant Activated Factor VII Intracerebral Hemorrhage Trial compared recombinant factor VIIa in three different

doses (40, 80, 160 μg/kg in an intravenous infusion, given over 1 to 2 minutes) and placebo in their ability to stop bleeding in ICH.

Between 2002 and 2004, 400 patients were randomized (1 patient subsequently withdrew) at 73 medical centers around the world. Patients underwent a baseline CT scan within 3 hours of symptom onset and began treatment within 4 hours of symptom onset.

The mean interval from onset of symptoms to CT scanning was 114 minutes, the mean interval from CT scanning to needle insertion was 54 minutes, and the mean onset-to-needle interval was 167 ± 32 minutes.

Serious adverse events. The frequency of thromboembolic events such as myocardial infarctions and ischemic strokes ranged from 2% in placebo recipients to 10% in the highest-dose group; the difference was not statistically significant. Most of the events occurred early and were not severe.

Results. The estimated mean percent increase in ICH volume at 24 hours was 29% with placebo, 16% with recombinant factor VIIa 40 μg/kg, 14% with 80 μg/kg, and 11% with 160 μg/kg.

The mortality rate at 90 days was 29% with placebo compared with 18% to 19% in the active treatment groups. Functional outcomes were better with treatment: at 90 days, 69% of the placebo group had a modified Rankin score of 4 to 6 (on a scale of 0 [no deficit] to 6 [death]) compared with 55%, 49%, and 54% in the three active-treatment groups. The effect of recombinant factor VIIa appeared to be largely within the first 3 hours after onset.

We concluded that recombinant factor VIIa significantly reduces hematoma growth in a dose-dependent fashion, reduces mortality, and significantly improves global functional outcome at 90 days, and is associated with a small increase in the risk of acute thromboembolic events.

A subsequent phase 3 randomized trial of recombinant factor VIIa is scheduled to start in the summer of 2005. Other pilot studies in progress or under design will examine acute blood pressure control and hypothermia as treatments.

SURGICAL THERAPY: THE STICH TRIAL

The International Surgical Trial in Intracerebral Haemorrhage (STICH),[2] conducted from 1995 to 2003, compared early surgery to remove blood and initial conservative management of ICH.

Eligibility requirements:

- Patients had to have CT evidence of a spontaneous supratentorial ICH that had arisen within 72 hours.
- The responsible neurosurgeon had to be uncertain about the benefits of either treatment.
- The study guidelines recommended that patients have a minimum hematoma diameter of 2 cm and a Glasgow Coma Scale score of 5 or more.

Exclusion criteria. Patients were excluded if:

- The ICH was probably due to an aneurysm or an angiographically proven arteriovenous malformation, tumor, or trauma.
- The patient had a cerebellar hemorrhage or extension of a supratentorial hemorrhage into the brainstem.
- The patient had severe preexisting physical or mental disability (eg, Alzheimer disease) or severe comorbidity that might interfere with the assessment of outcome.
- Surgery could not be done within 24 hours of randomization.

Patients were randomized to undergo either surgery or initial conservative management, although patients receiving conservative management could cross over and undergo surgery if necessary in the judgment of the neurosurgeon.

Prognosis was assessed on the basis of Glasgow score, age, and ICH volume. A favorable outcome was defined differently for patients with a poor or good prognosis at baseline.

A total of 1,033 patients were randomized in 83 centers in 27 countries.

Results. There was no significant difference in outcome between the two treatment groups. The only subgroup that appeared to have a better outcome with surgery was the group in whom the hematoma was within 1 cm of the cortical surface.

Giving factor VIIa reduced ICH volume, disability, and mortality

Comments. This study does not entirely disprove the benefit of surgery for ICH, for several reasons.

The median time from onset to treatment for the early-surgery group was somewhat long: 30 hours (interquartile range 16–49 hours). Thus, this trial cannot speak to the effectiveness of surgery within the first 12 hours after onset.

Also, 26% of the conservative treatment group crossed over and had surgery at a mean of 60 hours (interquartile range 27–99 hours). Thus, the trial is better described as a trial of early surgical removal vs delayed surgical removal for those who required surgery in the judgment of the treating investigator.

Finally, 75% of the surgeries were done by craniotomy, and relatively few patients had minimally invasive surgery to remove clots. Other recent small randomized trials used stereotactic treatment.[10,11] A pilot study funded by the National Institute of Neurologic Disorders and Stroke is to begin in the spring of 2005: patients will undergo stereotactic instillation of tissue plasminogen activator to dissolve the clot, and then the hematoma will be aspirated.

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