Intracerebral Hemorrhage

Introduction

Steven M. Greenberg, MD, PhD

The starting point for any discussion of intracerebral hemorrhage (ICH) is that it is a bad disease. Despite improvements in neurological intensive care (and concerns that ICH outcome may be worsened by physician pessimism), the fact remains that fewer than one-third of ICH victims make a good functional recovery. Another study examining trends in ICH outcome found essentially no improvement between 1988 (1-year mortality of 59%) and 1998 to 2003 (1-year mortality 53%), likely reflecting the lack of proven treatments for acute ICH. The incidence of ICH should remain stable or rise, as ongoing improvements in blood pressure control are offset by other trends that favor ICH occurrence such as aging of the population, greater use of anticoagulants and thrombolytics, and the absence of preventive treatment for cerebral amyloid angiopathy.

There are grounds for optimism in the acute ICH field, however, as presented in the accompanying articles by Lo, Wagner, Xi, and Mayer. Hemostatic therapy with recombinant activated factor VII, the prospect of having other rational biological targets for potential therapies, including matrix metalloproteinases (MMPs), thrombin, iron, glutamate, inflammation, oxidative stress, and perihematoma hypoperfusion. As we await results from the phase III study of recombinant activated factor VII, the prospect of having other candidate approaches to acute ICH raises the question of what elements need to be in place before proceeding to further clinical trials. In considering this issue, it is worth studying the lessons learned from ischemic stroke trials, both positive and negative. Among key questions are:

1. Which animal models of ICH most faithfully reflect human ICH and are therefore likeliest to yield results that can be translated to clinical studies? Models using injection of autologous blood or collagenase, for example, do not involve an underlying vascular pathology and may therefore mimic only some aspects of clinical ICH. How do we account for these differences when moving from animal to human studies?
2. How do we identify the ICH victims likeliest to benefit from acute treatment? By analogy to ischemic stroke, this question translates to finding markers in ICH that identify brain tissue at risk for injury but still salvageable by protective therapy.
3. What are the appropriate end points for declaring a treatment effective? Should studies be judged by a dichotomous end point based on emerging with minimal deficits, or by the type of proportional-odds model used to demonstrate improvement across a full range of functional outcomes in the recent trial of NXY-059?

A final set of questions concerns the relationship between ICH treatment and ICH prevention. Do the studies of acute ICH described in the accompanying articles teach us anything about the chronic processes of vessel damage, degeneration, and eventual rupture? One possible example is the role of the MMPs. This class of enzymes is acutely activated in the brain after ischemic or hemorrhagic stroke, possibly initiating the chronic process of poststroke neurovascular remodeling. MMP activation provides an intriguing potential mechanism for the epidemiological observation that stroke begets stroke, ie, that history of ischemic stroke is a potent risk for future hemorrhagic stroke. A second possible connection between acute and chronic ICH is the process of hematoma expansion—a key determinant of acute ICH outcome that could also bear on why hemorrhages can occur either as asymptomatic microbleeding or large symptomatic ICH. If it is a truism that ICH is generally bad, it is equally evident that ICH generally begins with a diseased vessel. It is therefore worth looking at studies in the ICH field with one eye toward their relevance to the treatment of acute ICH and the other toward possible implications for prevention of the vascular processes that cause it. Although some perihematoma tissue may be salvageable, much of the damage associated with ICH likely occurs quickly and irreversibly with the explosion of local intracranial pressure at the site of arteriolar rupture. Thus, although acute treatment remains a central goal, prevention may ultimately prove the more effective strategy for reducing the burden of this devastating illness.

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From the Department of Neurology, Massachusetts General Hospital, Boston, Mass.
Correspondence to Steven M. Greenberg, MD, PhD, Massachusetts General Hospital, 175 Cambridge Street, Suite 300, Boston, MA 02114. E-mail sgreenberg@partners.org

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