Ultra-Early Hemostatic Therapy for Intracerebral Hemorrhage

Stephan A. Mayer, MD

Background—Intracerebral hemorrhage (ICH) causes higher morbidity and mortality than other forms of stroke and has no proven effective treatment. Hematoma volume is a powerful predictor of outcome after ICH.

Summary of Review—Historically, ICH bleeding was considered to be a monophasic event that stopped quickly as a result of clotting and tamponade by surrounding brain tissue. More recently, prospective and retrospective CT-based studies have demonstrated that hematoma growth occurs in up to 38% of patients initially scanned within 3 hours of onset and in 16% scanned between 3 and 6 hours, even in the absence of coagulopathy. Progressive bleeding of this type has been associated with contrast extravasation on CT angiography and poor outcome after early (<4 hours) surgical clot evacuation. On the basis of these observations, it is plausible that ultra-early hemostatic therapy given in the emergency setting might reduce ICH volume in some patients and improve outcome. Among candidate agents for this indication, the most promising is recombinant activated factor VIIa, which promotes local hemostasis at sites of vascular injury in both coagulopathic and normal patients.

Conclusions—Ultra-early hemostatic therapy, given within 3 to 4 hours of onset, may potentially arrest ongoing bleeding and minimize hematoma growth after ICH. Given the current lack of effective therapy for ICH, clinical trials testing this treatment approach are justified. (Stroke. 2003;34:224-229.)

Key Words: cerebral hemorrhage • factor VIIa • hemostasis • stroke management

Intracerebral hemorrhage (ICH), defined as spontaneous bleeding into the brain, is the deadliest, most disabling, and least treatable form of stroke. Compared with ischemic stroke and subarachnoid hemorrhage, victims of ICH suffer higher mortality and are left with more severe deficits. Of the nearly 40,000 Americans who experienced an ICH in 1997, 35% to 52% were dead within 1 month, and only 20% were living independently at 6 months. The hospital mortality rate of ICH victims who are comatose and mechanically ventilated is approximately 60%.3,4 ICH constitutes 15% of all strokes in the United States and Europe and 20% to 30% in Asian populations.1 Advancing age and hypertension are the most important risk factors for ICH. Degeneration and rupture of small arteries or arterioles due to sustained hypertension is the most common cause of ICH, accounting for more than 60% of cases.3,6 Cerebral amyloid angiopathy has become increasingly recognized as a cause of lobar ICH in the elderly, accounting for approximately 10% of cases.1,5

Current Therapy of ICH

In contrast to advances in the acute management of subarachnoid hemorrhage and ischemic stroke, effective therapies for ICH are not available, treatment is primarily supportive, and outcomes remain poor. Blood pressure reduction and osmotherapy are usually given in the acute setting, but the effect of these interventions is unclear.2,3 The impact of blood pressure reduction after ICH remains untested, and clinical trials of dexamethasone7,8 and glycerol9 therapy have failed to show a benefit. The role of surgical hematoma evacuation remains controversial as well. In the most comprehensive meta-analysis to date, 530 ICH patients randomly assigned in 7 trials to surgical or medical management showed a nonsignificant trend toward increased death or dependency after surgery.10 Recent studies have demonstrated the feasibility of CT-guided stereotactic thrombolysis and clot aspiration for small deep hematomas11 and intraventricular local thrombolytic therapy for hastening the removal of intraventricular hemorrhage,12,13 but definitive trials of these interventions have yet to be performed. According to a recent American Heart Association Scientific Statement, “treatment studies of ICH are urgently needed. . . . We hypothesize that ultra-early treatment will be critical for patients with ICH.”14

CT Studies of Early Hematoma Growth

In recent years, attention has shifted to early hematoma growth as an important cause of early neurological deterioration after ICH. Historically, bleeding in ICH was thought to be completed within minutes of onset, and neurological deterioration during the first day was attributed to cerebral edema and mass effect around the hemorrhage.14 In the 1980s, several case series described early growth of ICH on repeated CT scans in the absence of coagulopathy.15-18 More recent prospective and retrospective studies indicate that...
early hematoma growth occurs in 18% to 38% of ICH patients scanned within 3 hours of onset and is highly correlated with early neurological deterioration (Table 1).19–24

In the only prospective study of this phenomenon, Brott et al19 performed a baseline CT scan within 3 hours of onset in 103 patients with ICH and found a substantial increase in the volume of parenchymal hemorrhage (>33%) in 26% of patients when rescanned 1 hour later. An additional 12% of patients had hematoma growth between the 1- and 20-hour CT scans. Overall, ICH growth occurred in 38% of patients scanned within 3 hours of symptom onset, and this figure was believed to be an underestimate because several patients who were moribund or who went to surgery did not have a follow-up scan. Hemorrhage growth between the baseline and 1-hour CT scans was associated with concurrent neurological worsening, as measured by changes in Glasgow Coma Scale score and National Institutes of Health Stroke Scale scores. No baseline clinical or CT variables were predictive of hemorrhage growth, including blood pressure, baseline hematoma size, and admission Glasgow Coma Scale scores. Patients with hematoma growth had higher mortality (44% versus 34%) and worse disability scores 30 days after onset, but these differences did not reach significance.

Retrospective studies have confirmed that ICH growth is relatively common within 6 hours of onset and much less frequent thereafter (Table 1).21–23 These studies have also linked hematoma growth to early neurological deterioration and increased mortality. Kazui et al,23,24 for instance, reported an increased frequency of early clinical deterioration (66% versus 14%) as well as ICH-related mortality (29% versus 3%) in patients with hematoma growth compared with those without. The only consistently identified risk factor for early hematoma growth is the interval between symptom onset and the initial CT: the earlier the scan, the more likely it is that a follow-up CT will show enlargement.21,24 Other risk factors that have been identified include liver disease,24 a history of cerebral infarction,24 hypertension (systolic blood pressure >200 mm Hg) in the setting of hyperglycemia,24 irregular hematoma shape,24 depressed level of consciousness,21 alcohol use,21 and reduced fibrinogen levels,21 but these have yet to be confirmed. There appears to be no impact of ICH location on the frequency of hematoma growth (Table 2).

Supportive Evidence: CT Angiography and Ultra-Early Surgery
Further evidence that ongoing bleeding can occur for several hours after the onset of ICH comes from CT angiographic studies that have demonstrated contrast extravasation into the hematoma. In these studies contrast extravasation occurred in 30%–25 and 46%26 of patients scanned on average within 6 hours of onset, was more likely to occur with earlier scanning,25,26 and was associated with increased mortality26 and subsequent hematoma enlargement.25 The clinical significance of early rebleeding after ICH was emphasized in a pilot study of ultra-early surgical ICH evacuation performed within 4 hours of onset. This study was aborted after fatal postoperative rebleeding occurred in 3 of the first 11 patients (27%) treated in this fashion.27 In an earlier study of 100 ICH patients treated with surgical evacuation within 7 hours of onset, the investigators concluded that “the most common cause of a poor outcome . . . is incomplete hemostasis resulting in reaccumulation of the hematoma.”28

Pathophysiology of Early Hematoma Growth
The pathogenesis of early hematoma growth is poorly understood. There is no animal model for early hematoma growth, nor is it likely that one can be developed that can faithfully recreate the complex and dynamic nature of human ICH. The reasonable and conventional notion is that hematoma growth results from persistent bleeding or rebleeding from a single site of arterial or arteriolar rupture. Although this may be true in many cases, several lines of evidence suggest that early hematoma enlargement may also result from secondary bleeding into perilesional tissue in the periphery of the clot.

<table>
<thead>
<tr>
<th>TABLE 1. Frequency of Early Hematoma Growth</th>
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<tr>
<td>Interval from symptom onset to CT (h)</td>
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<tr>
<td>0–3</td>
</tr>
<tr>
<td>3.1–6.0</td>
</tr>
<tr>
<td>0–6</td>
</tr>
<tr>
<td>6.1–24.0</td>
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NA indicates data not available. Hematoma growth was defined as a >33% increase in volume by Brott et al, a >50% or 20-ml increase by Fujii et al, and a >40% or 12.5-ml increase in volume Kazui et al. A definition was not specified by Fujitsu et al.

<table>
<thead>
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<th>TABLE 2. Relationship of ICH Location to Frequency of Hematoma Enlargement</th>
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<tr>
<td>Initial CT time (h)</td>
</tr>
<tr>
<td>Putamen, %</td>
</tr>
<tr>
<td>Thalamus, %</td>
</tr>
<tr>
<td>Lobar, %</td>
</tr>
<tr>
<td>Cerebellar, %</td>
</tr>
<tr>
<td>Pons, %</td>
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<tr>
<td>Other, %</td>
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<td>Total, %</td>
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First, careful pathological studies of brain tissue in the periphery of fatal hemorrhages have revealed multiple microscopic and macroscopic hemorrhages believed to represent ruptured arterioles or venules. Second, simultaneous CT and single-photon emission CT studies have demonstrated instances in which ICH growth results from the addition of multiple confluent hemorrhages to the periphery of an existing clot in the perilesional low-flow zone (Figure 1). Third, a team of investigators found an association between early hematoma growth and irregular clot morphology, which is presumably the result of multifocal bleeding. Fourth, simultaneous bleeding from multiple lenticulostriate arteries has been demonstrated angiographically immediately after ICH.

These clinical data suggest that early hematoma growth may result in some cases from bleeding into a "penumbra" of damaged and congested brain tissue immediately surrounding a hematoma. Although human positron emission tomography and diffusion-weighted imaging studies have failed to demonstrate ischemia in the low-flow zone surrounding a hematoma beyond 5 hours of onset, pathological and experimental studies have shown that a thin rim of ischemic damage develops in the hyperacute stage of ICH. Secondary bleeding from arterioles and venules may initially result from increased intravascular hydrostatic pressure and may progress because of regional mechanical, ischemic, or plasma-mediated inflammatory tissue damage. As a clotted hematoma forms, plasma rich in thrombin, fibrin degradation products, and plasmin quickly seeps into the surrounding brain tissue. These coagulation end products may cause inflammation, local metalloprotease induction, changes in blood-brain barrier permeability, or a local coagulopathic environment. However, the time course and possible relevance of these processes to early hematoma growth remain unclear.

Figure 1. Early hematoma growth in a 71-year-old woman with left putaminal hemorrhage. The ICH volume increased by 80%, from 15 mL at 2.5 hours to 26 mL at 11.5 hours. Concurrent single-photon emission CT images indicate that the enlargement resulted from the addition of discrete hemorrhages within the no-flow zone around the existing clot (yellow arrows). Modified from Mayer et al, 1998, with permission.

Figure 2. Estimated effect of the interval between CT scan and treatment on the probability of interval hematoma expansion when the initial CT scan is performed on average 90 minutes after ICH onset. Data are extrapolated from Brott et al, 1997.

Rationale for Ultra-Early Hemostatic Therapy for ICH

The 3 most consistently identified predictors of poor outcome after ICH are hematoma volume, the presence of intraventricular hemorrhage, and depressed level of consciousness. Of these, hematoma volume has been identified as the single most powerful predictor of 30-day mortality after ICH. Given the evidence that ongoing bleeding can occur for several hours after onset, it is plausible that ultra-early hemostatic therapy might minimize hematoma volume and improve outcome. In this paradigm, ultra-early hemostatic therapy for ICH could be used as the counterpart to thrombolytic intervention for acute ischemic stroke. Although the challenges of stroke treatment within a narrow time window are well established, the feasibility of this approach is supported by the fact that ICH patients present to emergency departments earlier than ischemic stroke patients. Arrest of hematoma growth might reduce the frequency of neurological deterioration by preventing early worsening related to hematoma growth, as well as late deterioration (>12 hours after onset) related to perihematomal edema and mass effect, which is most often a problem once a large hemorrhage has been established. If effective, ultra-early hemostatic therapy might also make early surgical hematoma evacuation safe enough to become a feasible treatment option.

As is the case with all stroke treatments, hematostatic therapy must be given as soon as possible after the onset of ICH to be effective. By extrapolating the data that Brott et al collected on patients initially scanned within 3 hours of onset (mean, 89 minutes), if one assumes that early rebleeding occurs midway between a linear and exponential rate during the next 60 minutes, even if a hemostatic intervention is completely effective, hematoma enlargement would be expected in 10%, 17%, or 22% of patients after a 15-, 30-, or 45-minute treatment delay following the baseline scan (Figure 2).

Hemostatic Agents: Therapeutic Options

Replacement therapies such as fresh frozen plasma, prothrombin complex concentrate, and factor IX concentrate...
are used to treat bleeding in coagulopathic ICH patients, such as those treated with warfarin, but would not be expected to enhance hemostasis in patients with normal coagulation. Human and recombinant factors VIII and IX are used as replacement therapy for patients with hemophilia A or B, respectively, but, similarly, a strong procoagulant effect in patients with normal levels of these factors would not be expected. Cryoprecipitate is specifically used to enhance hemostasis in patients with hypofibrinogenemia, and desmopressin diacetate arginine vasopressin (DDAVP) is used in patients with primary or acquired platelet disorders. In patients with normal coagulation, the most feasible hemo-

static agents for ultra-early ICH therapy include the antifibrinolytic amino acids aminocaproic acid and tranexamic acid, aprotinin, and activated recombinant factor VII (rFVIIa). Our present understanding of the pathophysiology of early ICH growth suggests that rFVIIa may be well suited for limiting early hematoma growth in acute ICH. FVIIa is an important natural initiator of hemostasis and exerts its primary effects locally in regions of endothelial disruption and vascular injury. When vessel rupture occurs, tissue factor is exposed in the subendothelial layers of the vessel wall, and local platelet aggregation occurs. Factor VII, of which only 1% normally circulates in the active form, forms a complex with exposed tissue factor, activating the hemostatic mechanism locally to form a hemostatic plug. The FVIIa–tissue factor complex initiates the conversion of factor X to Xa, which in turn converts prothrombin to thrombin. Pharmacological doses of rFVIIa amplify this process and also catalyze the conversion of factor X to Xa on the surface of activated platelets in the absence of tissue factor. In 6 years of clinical use for the treatment of hemophilic patients with inhibitors, rFVIIa has been associated with a low risk of systemic coagulation or thromboembolic complications and has a good record for treating intracranial hemorrhage. Preliminary clinical trials indicate that rFVIIa also promotes hemostasis in patients with normal coagulation systems. It is rapidly acting and has a relatively short half-life of 2.5 hours, which corresponds well with the duration of high risk for continued bleeding in the acute stage of ICH.

Aminocaproic acid and tranexamic acid are synthetic derivatives of the amino acid lysine; they can enter the extravascular space and have antifibrinolytic activity in humans. Tranexamic acid has a longer half-life than aminocaproic acid and is much more potent. These acids are effective for treating primary menorrhagia, upper gastrointestinal bleeding, and mucosal bleeding in patients with coagulation disorders or thrombocytopenia. Because these drugs primarily inhibit fibrinolysis, they are more suitable for clot stabilization than for the promotion clot formation. Clinical trials and large observational studies indicate that these agents reduce the frequency of rebleeding after aneurysmal subarachnoid hemorrhage but increase the frequency of delayed cerebral ischemia and other thrombotic complications, resulting in no overall benefit on outcome.

Aprotinin is a polypeptide that inhibits the action of several serine proteases (including plasmin and kallikrein) by forming reversible enzyme-inhibitor complexes. By inhibiting kallikrein, aprotinin indirectly inhibits the formation of activated factor XII, which disrupts coagulation. Aprotinin primarily inhibits the initiation of both coagulation and fibrinolysis induced by contact of blood with a foreign surface, but it has no effect on platelet function. Its main indication is for reducing perioperative bleeding, including cardiac surgery and orthotopic liver transplantation rather than the treatment of spontaneous internal bleeding. Aprotinin can cause hypersensitivity reactions and arterial or venous thrombosis but has not been found to increase the frequency of thrombotic complications in controlled surgical trials.

**Future Directions**

At present, published clinical trials for ICH have been focused on surgical removal of the clot or treatment of cerebral edema with dexamethasone or glycerol. In the recent past, several investigators have explored the feasibility of ultra-early hemostatic therapy for ICH with aminocaproic acid (M. Diringer, MD, and J. Grotta, MD, oral personal communication). Two dose-escalation phase IIA studies are currently in progress to determine whether rFVIIa is a safe and feasible treatment for ICH patients scanned within 3 hours of onset. A larger phase IIB dose-ranging “proof-of-concept” study that will compare the efficacy of 3 different doses of rFVIIa for reducing the frequency of CT-documented early hematoma expansion is planned. This study will test the hypothesis that ultra-early hemostatic therapy can limit ongoing bleeding in acute ICH and, if positive, may provide justification for a definitive phase III trial.

**Acknowledgments**

Drs J.P. Mohr, Thomas Brott, Ulla Hedner, and Nicolai Brun provided important advice and support regarding this project.

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Stroke. 2003;34:224-229; originally published online December 12, 2002;
doi: 10.1161/01.STR.0000046458.67968.E4
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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World Wide Web at:
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