

## Advances in Intracerebral Hemorrhage Management

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Recent advances in the evaluation and management of intracerebral hemorrhage (ICH) include: the identification of molecular markers that correlate with events in its early course, complications, and outcome; the impact of previous treatment with antiplatelet or anticoagulant agents on the outcome after ICH; the analysis of the results of the large international STICH (Surgical Trial in Intracerebral Hemorrhage) study; and the publication of the results of the recombinant activated Factor VII trial in ICH.

### Molecular Markers of ICH Complications, Course, and Outcome

Recent research interest in ICH has attempted to produce a better understanding of the events that occur early in its course, including hematoma growth, development of perihematoma edema, and the resultant tissue injury, factors that can cause early neurological deterioration and can have impact on its long-term outcome.<sup>1-3</sup> These interrelated processes are accompanied by a cascade of events that correlate with elevation of certain molecular markers in serum.

The process of perihematoma edema formation starts early after ICH onset, generally within 3 hours,<sup>4</sup> and it increases gradually in severity for at least 72 hours.<sup>5</sup> Several mechanisms in sequence contribute to the formation of edema, including: a first phase of clot retraction with extrusion of serum; a second phase (for the first 2 days) of activation of the coagulation cascade with production of thrombin; and a final phase (after 3 days from onset) of red blood cell lysis with hemoglobin-induced neuronal damage.<sup>5</sup> The central role of thrombin in promoting perihematoma edema has been documented in both experimental<sup>6</sup> and human<sup>7</sup> ICH, with evidence of reduced edema formation after administration of thrombin inhibitors. The deleterious effects of thrombin in the perihematoma tissues are mediated by inflammation, cytotoxicity, and disruption of the blood-brain barrier.<sup>8-10</sup> The molecular correlates of perihematoma edema include elevated levels of glutamate, tumor necrosis factor- $\alpha$ , interleukin-1, and intercellular adhesion molecule-1, but only tumor necrosis factor- $\alpha$  levels are independently associated with volume of perihematoma edema. High levels of serum glutamate correlate with poor neurological outcome after ICH.<sup>11</sup>

Another set of markers that play an important role in the complications and outcome of ICH are the matrix metalloproteinases (MMPs). These are proteolytic, zinc-dependent enzymes that degrade the endothelial basal lamina.<sup>12</sup> Serum levels of the MMP-9 form of these enzymes are correlated with initial edema volume and subsequent enlargement after ICH onset.<sup>13</sup> The MMPs, especially MMP-9, have recently been shown to play a role in the hemorrhagic complications that may follow use of tissue plasminogen activator (tPA) for acute ischemic stroke. Baseline elevations of MMP-9 were an independent predictor of ICH in patients treated with intravenous tPA.<sup>14</sup> In addition, a documented correlation between serum glucose levels and MMP-9 titers<sup>15</sup> may possibly explain the observation that baseline hyperglycemia has been associated with an increased risk of symptomatic ICH after intravenous<sup>16,17</sup> and intra-arterial<sup>18</sup> thrombolysis. Another potential marker of increased hemorrhagic risk after thrombolysis is cellular fibronectin, a glycoprotein confined to the vascular endothelium. An elevated plasma level of cellular fibronectin may indicate endothelial damage as the potential mechanism for the observed increased risk of hemorrhagic complications after treatment with tPA.<sup>19</sup>

### Effect of Regular Previous-Use of Anticoagulants or Aspirin on Outcome After ICH

Incidence of ICH is higher than that of subarachnoid hemorrhage, increases exponentially with age, and is higher in men than in women.<sup>20</sup> Most spontaneous hematomas are attributed to chronic arterial hypertension.<sup>21</sup> Other independent risk factors for ICH are alcohol consumption and anticoagulant treatment, and the risk is increased also with aspirin-use, thrombolytic therapy, use of amphetamines or cocaine, cigarette smoking, and diabetes mellitus.<sup>20-24</sup> Coagulation disorders and bleeding tendency (eg, thrombocytopenia) are rare causes of ICH. These factors increase risk for ICH especially in young and middle-aged adult people, whereas amyloid angiopathy becomes a common mechanism with advanced age.

Case-fatality rate and functional outcome of survivors are determined independently by the severity of the bleeding as assessed by the initial level of consciousness, volume of hematoma, presence of intraventricular blood, and location of

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hematoma (subcortical and cerebellar hematomas are associated with a better prognosis than deep hemispheric ones).<sup>25</sup> Among the risk factors for ICH, patient age and possibly amount of alcohol consumed before ICH are independent risk factors for poor functional outcome. Anticoagulant treatment (warfarin) and, recently, use of antiplatelet treatment before ICH have been shown to increase the likelihood of death.<sup>26,27</sup>

In a population-based study, prior use of either warfarin or aspirin increased the risk of death after ICH, independently from the severity of bleeding.<sup>26</sup> Warfarin-use is associated with severe bleeding and large hematoma size already present at hospital admission.<sup>26</sup> Although intensity of anticoagulation may be associated with ICH risk, it does not independently predict death after ICH. Aspirin users with ICH do not have a more severe bleeding than nonusers at admission, but aspirin-use may lead to an increase in hematoma size after admission.<sup>26,27</sup> The relative risk of regular preictal aspirin-use for death after ICH was 2.5 (95% CI, 1.3 to 4.6) as compared with nonusers, after adjustment for confounding factors.<sup>26</sup> Similar findings were shown in a retrospective hospital-based study.<sup>27</sup> Use of antiplatelet therapy (mostly aspirin) before ICH was followed by acute deterioration (assessed as death or need for emergency surgical evacuation of hematoma) with an increase in hematoma volume (>40%) within 2 days after the onset of ICH. In this study, the authors did not determine whether antiplatelet therapy impaired outcome beyond 2 days from onset, thus remaining unknown how the initial increase in hematoma volume or antiplatelet therapy affected overall outcome. These 2 studies showed that aspirin/antiplatelet therapy increases risk of death after ICH likely through a high propensity to cause early increase in hematoma volume. Overviews of antiplatelet trials have previously shown that antiplatelet therapy increases the risk of fatal but not of nonfatal hemorrhagic stroke.<sup>24</sup> This risk, however, is smaller than the benefits obtained when this therapy is used for secondary prevention of ischemic cardiovascular and cerebrovascular disease. These new results, however, suggest that antiplatelet agents should not be used for primary prevention of cerebrovascular disease.

### **Surgical Management of ICH: the International STICH Trial Results**

Operative treatment with clot removal is used for <20% of all patients with spontaneous ICH.<sup>20,25,26</sup> Patients with a subcortical or cerebellar hematoma at least 3 cm in diameter and impaired consciousness are generally considered to benefit from surgical hematoma evacuation, which reduces both case-fatality and morbidity. Treatment of hematomas located in the basal ganglia, the most common site of ICH, has been controversial because of lack of evidence of benefit from surgical treatment. The first prospective randomized controlled trial of surgery for supratentorial spontaneous ICH was published in 1961,<sup>28</sup> and the next 2 studies, performed during the computed tomography era, were published in 1989.<sup>29,30</sup> None of these showed that surgical clot removal improved the outcome of patients with hematomas located in the basal ganglia. Endoscopic evacuation of hematomas in the subcortex, but not in the putamen or thalamus, improved the outcome of alert or somnolent patients; case-fatality was

reduced in large (volume >50 mL) hematoma cases and functional outcome was better in those with smaller hematomas.<sup>29</sup> Evacuation of hematomas in the basal ganglia in patients with Glasgow Coma Score (GCS) of 7 to 10 by craniotomy reduced case-fatality, but the quality of life remained poor in survivors.<sup>30</sup> After a few additional randomized studies with small sample sizes and generally negative results, the long-awaited results of the international STICH study were recently published.<sup>31</sup>

STICH included 1033 patients (503 in the early surgery group with median time from ICH onset to surgery of 30 hours [25th–75th percentile range, 16 to 49 hours], and 530 in the initial conservative group) from 83 centers in 27 countries. A method of prognosis-based outcome evaluation was used: patients were categorized at randomization into good and poor prognosis groups according to a prognostic score calculated from the GCS, hematoma volume, and patient age. Outcome of these groups was assessed by different outcome thresholds.

STICH did not show any definite beneficial effect from early surgery (within 24 hours of randomization) on outcome after supratentorial spontaneous ICH.<sup>31</sup> Of patients randomized to early surgery, 26% had favorable outcome compared with 24% randomized to initial conservative treatment. A pre-specified subgroup analysis suggested a possible advantage of surgical treatment for superficially located ( $\leq 1$  cm from the cortical surface) lobar hematomas. The overall results of STICH, however, do not mean that surgery for all ICH cases is useless. Included were only those patients for whom the responsible neurosurgeon was uncertain about the benefits of either treatment (ie, the clinical equipoise). Thus, STICH excluded all those patients who were considered to need early surgical clot evacuation by the responsible neurosurgeon.

Of patients randomized to initial conservative treatment, 140 patients (26%) were, however, operated on within a few days (median 60 hours, range of 27 to 99 hours) after ICH, mostly because of significant deterioration of their clinical condition. At randomization, these patients had significantly ( $P < 0.0001$ ) larger hematomas (>50 mL) and more likely ( $P < 0.0001$ ) had subcortical hematomas than those in the initial conservative group. If this group of patients had not been operated on, the overall benefits of surgery in the subgroup with large subcortical hematomas may have been more significant, particularly concerning mortality, as was also shown in a previous randomized trial.<sup>29</sup> It also remained open whether this group of patients would not have deteriorated if they had been operated on soon after bleeding. For the purpose of hematoma evacuation, craniotomy seemed to be a better method than others.

In conclusion, the STICH results do not significantly change current practice. Patients with a subcortical or cerebellar hematoma at least 3 cm in diameter and impaired consciousness should be operated on, whereas the benefits of surgery for patients with putaminal ICH in somnolent, stuporous or “semi-comatose” state (GCS 7 to 12) are still uncertain. In the future, treatment of these hematomas with minimally invasive methods may be useful if done early after ICH onset, but control of hemostasis may be difficult because the hematomas tend to continue to enlarge within the first 6

hours after onset. According to the results of STICH and other randomized studies, comatose patients (GCS  $\leq$ 8) with ICH in the basal ganglia or thalamus very unlikely benefit from clot removal.

### Medical Management: the Recombinant Activated Factor VIIa Experience

The nonsurgical approaches to the treatment of ICH have included a handful of trials that tested the value of steroids,<sup>32</sup> osmotic diuretics,<sup>33</sup> and hemodilution<sup>34</sup> in reducing mortality and disability. The negative results of these medical interventions determined that attention continued to be focused on the surgical option of drainage of the hematoma using a variety of techniques. The recent publication of neutral results in the large, prospective, and randomized international STICH study<sup>31</sup> coincided with the publication of the results of the phase IIB trial of recombinant activated factor VIIa (rFVIIa) in ICH.<sup>35</sup> The study assessed several doses of the hemostatic agent rFVIIa (NovoSeven, Novo Nordisk, Denmark) on their effect of decreasing the early enlargement of the hematoma (primary outcome); in addition, the effect of treatment on several clinical secondary outcomes was measured at 90 days. The results showed that each of the 3 doses of rFVIIa (40, 80, 160  $\mu$ g/kg) given within 4 hours of symptom onset were followed by a significant reduction in hematoma growth in comparison with placebo. The beneficial effect on early hematoma growth was accompanied by improved survival and favorable clinical outcomes in the treatment group. The clinical effect of rFVIIa translated into a number needed to treat of about 6 in order to prevent 1 unfavorable outcome.

The encouraging therapeutic benefit of rFVIIa has to be balanced with the potential thrombotic complications, as the frequency of predominantly arterial thromboembolic events in the rFVIIa-treated group (7%) exceeded that of the control group (2%). Because one-half of the 16 arterial events in the rFVIIa group occurred in the highest dose (160  $\mu$ g/kg) group, it is probable that the use of lower doses may lead to a reduced risk for this complication. This approach is part of the design of the on-going phase III FAST (rFVIIa in Acute Hemorrhagic Stroke Treatment) international trial, in which doses of 20 and 80  $\mu$ g/kg of rFVIIa are compared with placebo. The documentation of a net benefit of rFVIIa in the FAST trial will solidify the potential indication of rFVIIa in patients with spontaneous ICH, and may justify consideration of testing this agent in situations of high risk of ICH enlargement, such as in warfarin-related ICH.

Other issues to consider include the fact that the benefit of rFVIIa was highly significant when the treatment was initiated within 3 hours of symptom onset, but those patients treated more than 3 hours after onset had no difference in hematoma growth in comparison with the placebo group. This suggests that the time window available for intervention is limited to this short interval, and treatment may thus be beneficial for only a subset of patients with ICH. Another issue of potential importance is that in the analysis of clinical outcomes, there was no adjustment for blood pressure,<sup>36</sup> a factor known to affect the outcome of ICH.<sup>37</sup> Attention to this issue in future trials could identify interactions of rFVIIa with blood pressure that could modify the magnitude of the benefit

in patients with ICH. Finally, the known enhancing of thrombin generation on the surface of activated platelets by rFVIIa<sup>38</sup> raises a theoretical concern about thrombin-induced increase in perihematoma edema<sup>6</sup> in patients treated with this hemostatic agent. However, the mean volume of the combination of ICH, intraventricular hemorrhage, and perihematoma edema at 72 hours remained essentially stable (and significantly smaller than in the placebo group) across the 3 doses of rFVIIa, arguing against an edema-enhancing effect of this agent.

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