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Advances in the Treatment and Management of Intracerebral Hemorrhage

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Currently there are no "gold standards of care" in place for the treatment of intracerebral hemorrhage (ICH). Clinical trial data have indicated that the largest expansion of the hemorrhage volume occurs within the early hours after the onset of symptoms. This expansion of hematoma volume has been shown to be a critical factor in predicting mortality 30 days postictus. Thus, it is reasonable that minimizing hematoma growth, and any associated perihematomal edema, could potentially provide clinical benefit, reduce the degree of neurological damage, improve functional outcomes, and reduce mortality. Traditionally, surgical interventions were the only option for improving patient outcome or preventing mortality. There has been a great deal of debate surrounding the clinical benefit of surgery. The results of the International Surgical Trial in Intracerebral Hemorrhage conclusively demonstrated that there was no clear advantage gained by the early surgical evacuation of hematomas, as compared with conservative treatment. The results of a recently concluded clinical trial of ICH patients demonstrated that the early administration of the hemostatic agent, recombinant activated coagulation factor VIIa, within 4 hours of the onset of symptoms, reduced hematoma expansion as compared with placebo. In addition, the treatment of ICH patients with recombinant activated coagulation factor VIIa also demonstrated significant improvements in several neurological, functional, and disability scales. This review will summarize the current understanding, provide an overview of new treatment trends, and suggest potential strategies for future investigations into ICH.

KEYWORDS intracerebral hemorrhage, stroke, STICH, rFVIIa

Intracerebral hemorrhage (ICH), the most common type of nontraumatic intracranial hemorrhage,[1] is the deadliest, most disabling, and least treatable form of stroke and is estimated to affect approximately 60,000 people annually in the US.[2] This incidence corresponds to roughly 10% of all strokes annually (the rest being predominantly ischemic in origin).[3]

As compared with ischemic stroke where the spontaneous recovery rate is relatively high (50 to 70% of survivors regain functional independence),[3] the prognosis for ICH is very poor: 35 to 50% of ICH patients die within 1 month of the hemorrhage, and only 10 to 20% of the survivors regain functional independence.[4-6] In an analysis of 137 community hospitals performed by Reed and coworkers, mortality rates during hospitalization were 33% for ICH patients as compared with 29% for patients with subarachnoid hemorrhage (SAH) and 7% for those with ischemic stroke.[7]

The poor outcomes following ICH, namely high mortality and reduced functional independence, in addition to the paucity of successful therapeutic interventions, create an important and timely critical need for a systematic assessment of therapies to fulfill the unmet medical needs of this patient population.

Current Management of ICH Patients

Symptoms of ICH are similar to, but often more severe than, those of ischemic stroke. There is no specific proven medical therapy or surgical intervention available for the treatment of ICH.[4] Treatment guidelines on stroke published by the American Heart Association (AHA) Stroke Council, European Stroke Initiative (EUSI) Executive Committee, and the

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EUSI Writing Committee focus almost exclusively on strokes of ischemic origin.[8] In their guidelines for the treatment of ICH, the AHA Stroke Council emphasizes ICH as a "medical emergency of the highest degree,"[4] but these guidelines are in need of updating as they were developed in the late 1990s.

Medical intervention using steroids,[9,10] hemodilution,[11] and glycerol[12] showed no treatment benefit for ICH. Any recommendations for treatment are based on reports from clinical series and general best practice management of patients in neurointensive care units.[4] This "symptomatic" approach focuses primarily on active blood pressure and intracranial pressure (ICP) management, fluid management, prevention of seizures, and controlling body temperature.[4]

ICH as a Dynamic Process

The volume of the ICH has been shown to be a major factor determining functional outcome and mortality.[13,14] Immediately following small blood vessel rupture, a penumbra of functionally impaired (but potentially viable) tissue develops surrounding the hematoma.[15-17] Recent experimental evidence has described the role of thrombin, produced during clot formation, in the development of perilesional edema.[18,19] Heme oxygenase releases iron from hemoglobin,[20] inducing an influx of neutrophils,[21] and activating microglia[22] and the complement system.[23,24] In addition, iron-loaded transferrin (holotransferrin) interacts with thrombin resulting in edema, DNA damage, oxidative stress, and accumulation of iron.[25] Thus the added volume of the perilesional edema can lead to an area of brain dysfunction that extends beyond the area of the acute hematoma. The resultant elevated ICP and reduced cerebral perfusion pressure can in turn induce perihematomal ischemia and can also contribute to poor clinical outcomes.[26,27]

Treatment Strategies for Patients with ICH

Surgical Treatment

Surgical evacuation of the hematoma continues to be a common therapeutic intervention used in the management of ICH. Clot evacuation could potentially restore function and improve patient outcomes. Early clinical trials provided conflicting evidence on the benefits of surgical intervention for ICH.[16,28] Even with improvements in surgical techniques, neuroimaging, and peri- and postoperative care, a recent meta-analysis of seven clinical trials reported no clear evidence of benefit of surgical intervention.[29] The continued use of surgical interventions supported the need for an additional clinical trial to evaluate the role of surgery in the treatment of ICH. In 2005, Mendelow and colleagues published the results from the International Surgical Trial in Intracerebral Hemorrhage (STICH).[30] The goal of STICH was to evaluate the effectiveness of early surgery (within 24 hours of randomization) as compared with initial conservative medical treatment with later surgical intervention if deemed necessary. The study was designed to be multicenter and randomized, with controlled parallel groups in which 1033 patients with spontaneous ICH received either surgery or initial conservative treatment.

The trial included patients with CT-confirmed, spontaneous ICH that had occurred within the previous 72 hours and where the choice of therapeutic intervention was not obvious (ie, clinical equipoise between surgery and medical management). Patients were excluded from the trial if the hemorrhage appeared to be due to an aneurysm, arteriovenous malformation, trauma, or tumor. In addition, patients were excluded if cerebellar hemorrhage, extension of a supratentorial hemorrhage into the brainstem, severe preexisting physical, mental disability, or comorbidity were present.

Hematoma evacuation, supplemented with best medical treatment, occurred within 24 hours of randomization for the early surgery treatment group. Patients randomized to conservative treatment had the best medical treatment, with the option for subsequent surgical evacuation of the hematoma on evidence of neurological deterioration. The primary endpoint of the study was patient mortality and disability at 6 months using the extended Glasgow Outcome Scale (eGOS). Secondary outcomes included the Barthel Index (BI) and the modified Rankin Scale (mRS).

A total of 1033 patients from 83 centers in 27 countries was enrolled. The trial population ranged in age from 19 to 93 years (median age, 62 years) and comprised mostly males. Half of the patients were randomized within 20 hours of the onset of symptoms (range 2 to 72 hours). Hematoma volumes varied from 4 to 210 mL (median 38 mL) as determined by the ABC/2 method[31]; the median depth from the cortical surface was 1 cm, with the location of the hematomas (lobar, basal ganglia/thalamic) being equally distributed across the treatment groups. Craniotomies were the most commonly performed surgical procedure (465 patients, 77%). Endoscopic, stereotactic, and burr-hole approaches were some of the other procedures performed in the remaining patients. Statistical analysis indicated a trend toward significance ($P = 0.07$) between surgical method and outcome.

Of the 496 patients randomized to the early surgery treatment group, 94% (465 patients) actually received surgery. Of the 529 patients randomized to the initial conservative treatment group, 59% had marked deterioration in their Glasgow Coma Scale (GCS) values, with 26% (140 patients) eventually requiring surgery. The results indicated that, at 6 months posttreatment, 122 patients (26%) who received early surgical intervention had favorable outcomes compared with 118 patients (24%) who received initial conservative treatment (odds ratio 0.89 [95% CI 0.66 to 1.19], $P = 0.414$). Mortality during the first 6 months did not differ significantly between the two groups, as it was 36% in the early surgery treatment group compared with 37% for the initial conservative treatment group (odds ratio 0.95 [95% CI 0.73 to 1.23]). Results from planned subgroup analyses indicated that there was a significant treatment interaction between surgery and the depth of the hematoma from the cortical surface. That is, there was statistical significance for surgical evacuation of the hematoma if it was located at a depth of ≤ 1 cm from the cortical surface ($P = 0.02$). Therefore, STICH patients with