Intraventricular Hemorrhage
Severity Factor and Treatment Target in Spontaneous Intracerebral Hemorrhage

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Background and Purpose—This review focuses on the emerging principles of intracerebral hemorrhage (ICH) management, emphasizing the natural history and treatment of intraventricular hemorrhage. The translational and clinical findings from recent randomized clinical trials are defined and discussed.

Summary of Review—Brain hemorrhage is the most severe of the major stroke subtypes. Extension of the hemorrhage into the ventricles (a 40% occurrence) can happen early or late in the sequence of events. Epidemiological data demonstrate the amount of blood in the ventricles relates directly to the degree of injury and likelihood of survival. Secondary tissue injury processes related to intraventricular bleeding can be reversed by removal of clot in animals. Specific benefits of removal include limitation of inflammation, edema, and cell death, as well as restoration of cerebral spinal fluid flow, intracranial pressure homeostasis, improved consciousness, and shortening of intensive care unit stay. Limited clinical knowledge exists about the benefits of intraventricular hemorrhage (IVH) removal in humans, because organized attempts to remove blood have not been undertaken in large clinical trials on a generalized scale. New tools to evaluate the volume and location of IVH and to test the benefits/risks of removal have been used in the clinical domain. Initial efforts are encouraging that increased survival and functional improvement can be achieved. Little controversy exists regarding the need to scientifically investigate treatment of this severity factor.

Conclusions—Animal models demonstrate clot removal can improve the acute and long-term consequences of intraventricular extension from intracerebral hemorrhage by using minimally invasive techniques coupled to recombinant tissue plasminogen activator-mediated clot lysis. The most recent human clinical trials show that severity of initial injury and the long-term consequences of blood extending into the ventricles are clearly related to the amount of bleeding into the ventricular system. The failure of the last 2 pivotal brain hemorrhage randomized control trials may well relate to the consequences of intraventricular bleeding. Small proof of concept studies, meta-analyses, and preliminary pharmacokinetics studies support the idea of positive shifts in mortality and morbidity, if this 1 critical disease severity factor, IVH, is properly addressed. Understanding clinical methods for the removal of IVH is required if survival and long-term functional outcome of brain hemorrhage is to improve worldwide. (Stroke. 2009;40:1533-1538.)

Key Words: functional outcome ■ intracerebral hemorrhage ■ intraventricular hemorrhage ■ recombinant tissue plasminogen activator ■ thrombolysis

Although mortality and functional outcomes for intracerebral hemorrhage (ICH) have not changed in the past 20 to 30 years,1-3 the results of recent animal4 and human investigations5,6 radically alter the likelihood of changing poor outcome in this disease. It is now plausible to reverse the course of blood clot-mediated injury of brain tissues and convert this reversal into gains in human function after a bleeding event. The clinical procedures needed to identify and treat this disease (computed tomography around the clock, extraventricular drainage use, and image guidance) have proliferated worldwide at primary stroke centers, as has the knowledge of the specific disease processes in humans. Organized, multicomponent intensive care, including acute blood pressure control and support for impaired cardiorespiratory functions, has improved and become widely available.7-9 Furthermore, several key treatment capabilities have been tested prospectively in clinical trials over the past decade. Specifically, practical experience with intracranial pressure (ICP) control, routine utilization of neurocritical care,7 experience with thrombolysis,10 knowledge of intracra-
nial drug delivery, and image-based decision making are now widespread. Applied together as a coordinated treatment program, these tools offer the unique opportunity to reverse the effects of ICH. The scientific challenge that remains is to produce a definitive demonstration that the organized use of a specific combination of treatments and treatment goals leads to a predictable set of good outcomes. This review discusses the role of intraventricular extension of bleeding after spontaneous hypertensive brain hemorrhage as a critical, treatable event in the ICH disease process.

Cerebral Ventricular System

The cerebral ventricular system provides a low-pressure pathway for the movement of cerebrospinal fluid. This system is frequently broken into when blood at near-systolic pressures passes through a defect in the arterial wall, forming a spontaneous ICH as it dissects brain tissue. Brain hemorrhage can occur from defects in the vessel wall, such as aneurysms, arteriovenous malformations, or small vessel microaneurysms, coagulation profile, or just increased blood pressure creating bleeding sites. Thus, multiple different diseases, including trauma, tumors, and blood pressure elevation, are capable of producing collections of blood that may occlude or obstruct the intraventricular space. Bleeding at deep intracranial sites near the ventricles leads to early intraventricular rupture and compromise of the normal pressure regulation of the cranial vault, whereas bleeding sites further away from the ventricles may accumulate clotting blood before mechanical pressure and hemorrhage size produces a rupture into the ventricles. The actual rupture is often associated with a decreased consciousness that can be recognized clinically and is frequently associated with subsequent death. Thus, the seriousness of rupture rapidly becomes evident.

CT and ICP monitoring rapidly moved intraventricular hemorrhage (IVH) out of the pathological and epidemiological domain and into the clinical domain permitting qualitative and quantitative measurement of intraventricular bleeding and its effects on ICP. The utilization of serial brain imaging has gradually altered the diagnosis, management, and clinical response to the occurrence of intraventricular hemorrhage in the past 3 decades. The academically accepted approach of emergent ICP management and blood clot drainage until ventricular reopening remains a pragmatic approach, the generalizability and value of which have not been rigorously tested in a large randomized control trial. However, this approach is supported by translational models.

Validating Therapy: Reversibility of Injury Mechanisms in Animals

Multiple animal models support the biological rationale that IVH is one of the necessary disease factors to manage to make human recovery a reality for diseases like ICH. It appears that both mechanical and biochemical factors are responsible for brain tissue injury. In both canine and porcine IVH models, the greater the volume of blood clot injected into the ventricles, the greater the likelihood of animal death. Similarly, prolonged exposure of the ventricles to blood leads to altered consciousness and, at the tissue level, inflammation, fibrosis, and hydrocephalus. The removal of blood clot improves level of consciousness and prevents tissue inflammation in animal treatment simulations, even when there is substantial delay in initiating and accomplishing the removal. Histological assessments demonstrate that hydrocephalus and inflammation are prevented with thrombolytic-mediated removal of clot. Specific models have indicated reversal/prevention of ventricular enlargement, herniation, and coma, white cell infiltrations, periventricular edema, and generalized edema. Two important characteristics of these successful models are early control of ICP and significant removal of significant volumes of clot from tissue. The ability of clot removal to inhibit blood clot-mediated progressive tissue injury and reverse prolonged neurological dysfunction provides the underlying biological principle for the translation of the animal models of IVH to the human situation.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of Study</th>
<th>No. of Subjects</th>
<th>IVH %</th>
<th>Mortality With IVH %</th>
<th>Mortality Without IVH %</th>
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<tr>
<td>Draper et al (1991)</td>
<td>Retrospective</td>
<td>n=374</td>
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<td>31</td>
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<td>41.79</td>
<td>56.36</td>
<td>20.30</td>
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Epidemiological Observation Demonstrates IVH as a Severity Factor in ICH

Observations from retrospective clinical series and prospective clinical trials have confirmed the importance of IVH as a clinical factor associated with poor outcomes including coma, mortality, and long-term functional impairment. The presence of intraventricular blood has been strongly associated with impaired consciousness at presentation. Simple comparison between ICH subjects with and without IVH extension suggests that mortality is substantially increased if IVH is present (Table). Tuhrim was the first to consistently demonstrate a powerful relationship between the presence of IVH in a brain hemorrhage patient and the likelihood of death. This relationship was prospectively demonstrated in several subsequent studies and noted to be continuously related to the complete range of incremental increases in the volume of intraventricular blood. Multivariate regression analysis performed on other convenience samples almost always defines the presence of IVH as an independent risk factor for mortality and poor functional outcome. Randomized controlled studies in the past decade have confirmed this point by demonstrating a similar relationship between poor outcomes and the extent of IVH. These post hoc evaluations of carefully collected clinical trial data from >2000 subjects are consistent with animal model findings. These evaluations demonstrate that presence of IVH is associated with <20% good functional outcomes, as measured by the 90- to 180-day modified Rankin scale. For example, a separate analysis of the CT images from the Surgical Trial in ICH (STICH) trial demonstrated that although 31% of the entire set of study subjects had good functional outcomes as defined by Glasgow Outcome Scale (normal, good, or moderate recovery), only 15% of the 377 STICH subjects with IVH experienced this same level of recovery. If radiographically confirmed hydrocephalus occurs, then the frequency of a favorable recovery decreases to 11.5%. This same finding is repeated in the NovoSeven in ICH trial in which 140 of 374 subjects had IVH at presentation and 169 subjects had IVH at 24 hours. Only 20% of those subjects having IVH at presentation experienced good outcomes (modified Rankin score, 0–3) vs 43% of those subjects with no IVH at presentation. When expansion of IVH occurred in the first 24 hours, only 7% of subjects were noted to have good 90-day outcomes by these same modified Rankin score criteria. Thus, in a recent multivariate analysis of the NovoSeven trial, the effect of IVH and IVH expansion (>2 cm^2) on functional outcome ranges from an OR of 2.53 to 4.21, providing substantial support that IVH removal is an excellent therapeutic target. Most importantly, no organized effort to remove IVH was undertaken in either trial.

IVH and Poor Outcomes

Early attempts to treat IVH focused on ICP elevation as the critical abnormality. This focus was reasonable, because severe ICP elevations are associated with herniation and ischemia—2 common sequelae in IVH. However, detailed intensive care unit assessments of the benefit of ICP management have not produced any biological indication of improved consciousness, functional improvement, or improved mortality. It is noted that ICP management reverses symptoms of herniation and leads to improved outcomes in a case series. Thus, European and North American guidelines define as clinically appropriate interventions a “gradual or graded” approach to the identification of mass effect and management to promote ICP control to “normal” levels. However, utilization of ICP treatments in IVH or ICH remains low, most likely because of the absence of overall clinical benefit demonstrated in randomized trials. Recent trials of surgery (STICH) and recombinant factor VIIa (FVIIa; novoSeven) therefore did not specify IVH removal or ICP treatment goals.

The STICH tested the hypothesis that a policy of ICH removal would improve functional outcome. No attempt to stabilize clot enlargement was undertaken, nor was there any provision in the protocol to remove the ventricular blood that occurred in 42% of subjects. A post hoc evaluation of the STICH trial segregated 221 subjects with lobar ICH and no IVH. The removal of ICH from these subjects who did not have IVH was more effective and produced a 12% absolute improvement in functional outcome compared to the medically treated subjects. This is a substantial improvement over all surgery treated STICH subjects (ie, those in whom 41% did have IVH); this group had only a 4% improvement in Glasgow Outcome Scale outcome vs medically treated control subjects. STICH II is now actively investigating the hypothesis that removal of isolated lobar ICH (no IVH) is beneficial. Similarly, FVIIa has been evaluated for its ability to stop early clot expansion and produce improved functional outcome in ICH patients presenting in the first 4 hours after initial symptoms. There was no standard plan for removal of IVH despite a 49% rate of IVH occurrence in this trial. In fact, the frequency of ICP monitoring to manage IVH was 7%, suggesting limited attempts to treat ventricular expansion. The pivotal Factor VII for Acute Hemorrhagic Stroke Treatment (FAST) trial used the same design and protocol as the previous successful NovoSeven in ICH trial, but demonstrated no effect of factor VIIa on functional outcome, in large part because of higher occurrence of IVH in the active arm of the study cohort. The decision to avoid systematic attempts to remove IVH may have further masked the benefits of clot stabilization (a physiological benefit that did occur). Taken together, recent trials demonstrate a consistent picture of 3 major independent severity factors, each strongly associated with poor outcome: ICH volume, early deterioration, and IVH size. Importantly, these well-organized but unsuccessful trials chose to mitigate only 1 ICH severity factor (ie, STICH, ICH size; novoSeven, early deterioration/hematoma enlargement). The neutral findings in STICH and NovoSeven–FAST further support the likely independence of each factor’s effect on outcome. These trial findings suggest the hypothesis that for a treatment program to be sufficient to alter ICH outcome, a program must incorporate treatment of all 3 factors. In summary, recent clinical trial experiences suggest that an effective therapy for intracerebral hemorrhage must include: (1) stability of the initial bleed; (2) removal of the IVH; and (3) minimization of the volume/mass effect of the ICH.
Proof of Treatment Concepts in Humans

The CLEAR IVH trial tested removing IVH with catheter-delivered recombinant tissue plasminogen activator. This catheter-based treatment of IVH is consistent with the rationale that amelioration of intraventricular clot decreases the severity of the disease by decreasing mortality.17 Lower rates of mortality have been consistently observed when the treatment policy involves: (1) the use of an intraventricular catheter to maintain ICP within the normal range and (2) efforts to remove clot by injecting low doses of thrombolytic.10,11,17,20,46 Treatment that solely maintains ICP is insufficient to alter mortality or morbidity10 and inconsistent with the critical therapeutic goal of blood clot removal after emergent control of ICP is achieved with the intraventricular catheter.47 The initial results of the CLEAR IVH trial are consistent with the proposition that a protocol for removal of intraventricular clot from ICH subjects with small, stable parenchymal clots (ie, ICH size <30 cm³) can produce close to 50% good functional outcomes as defined by modified Rankin score at 180 days,48 despite the presence of, on average, 45 mL of intraventricular blood at the start of treatment (Figure 1). Detailed analysis of the final results of this trial will be necessary to understand if a relationship exists between the amount of blood removed and the degree of benefit achieved in the treated group of subjects. Should such a relationship exist, it would be a link between therapeutic intent and therapeutic efficacy. Several expert groups have suggested that a trial testing the efficacy of IVH clot removal is an important goal for advancing our knowledge of ICH treatments.10,20,49 Plans for such a trial are now well-described and await peer review.50

Refining Removal Therapy

Efforts to improve clot removal as a treatment are now underway. Animal models continue to improve our understanding of the sequence of inflammatory events that occur after hemorrhage and clot stabilization. Multiple biological mechanisms could be tapped to minimize the negative effects of clot on tissue, particularly if substantial physical removal of blood clot volume can occur via a minimally traumatic mechanism before initiation of such a “biological” clean-up. These biological points of attack include blockade of thrombin-induced activation of inflammatory and cell death signals,51 scavenging of residual free iron,30 and enhanced phagocytosis of clot red blood cells.52 Progress with enhanced, minimally invasive surgical manipulations that lead to rapid atraumatic catheter-based clot removal appears possible.53 Each of these avenues can potentially improve the amount and qualities of clot removal from the ventricle. Post hoc analyses of best available data suggest a 10% to 15% absolute benefit might be achieved in selected populations of IVH and ICH subjects, if blood clot can be removed from the brain.48,53 It is now time to test the viability of clot removal from the ventricle as the critically untested yet needed treatment in ICH.

Limitations of Our Knowledge

Despite the progress described, limitations of our knowledge regarding IVH are significant. We do not fully understand the
role of coagulation events and vessel wall injury/repair in the sequence of bleeding events. Improvements leading to a safe and more rapid termination of bleeding could further limit the injury to tissue. Similarly, identifying the critical steps from clotting to inflammation to cell death, while identified in animals, have only recently been initiated in human ICH. Additional knowledge regarding the mechanical and anatomic relationships that occur with spontaneous ICH is needed. Finally, our ability to prognosticate while improving is still of limited value, because current diagnostic techniques provide anatomic rather than physiological information. Additional methods that establish, with precise sensitivity, irreversible injury to vital brain tissues will be necessary, if prognostication can become sensitive enough to be used routinely in clinical judgments regarding treatment. Rigorous scientific investigation in clinical trials should bring additional information to clinical use within the next decade.

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Disclosures

The Johns Hopkins University uses patent application #10/509,694 (Dr Hanley has disavowed interest in this patent).

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