Despite major advances in early diagnosis, improvements in neurosurgical critical care, and refinements in microsurgical techniques, the efficacy of surgical treatment for primary ICH is still controversial, as shown in the most recent prospective, randomized, multicenter clinical trial. The major goal of surgical treatment in patients with ICH is safe and thorough clot evacuation, with maximal preservation of neurological function. Note, however, that even less invasive approaches for hematoma puncture by using stereotactic procedures or endoscopy to minimize trauma to overlying normal brain tissue do not provide a better functional outcome.

Edema Formation

One of the major challenges after a primary ICH is the formation of perihematomal edema, which forms rapidly after the ICH, contributing to a documented increase in perihematomal volume by approximately 75%. The formation of edema after ICH follows three distinct temporal phases: in the first hours after ICH, retraction of the clot begins. Intact red blood cells within the hematoma area have not been found to contribute to edema formation. As the coagulation cascade becomes activated over the following 24 to 48 hours, however, thrombin becomes activated and promotes edema formation and further disruption of the integrity of the blood–brain barrier. The third phase of edema formation starts when red blood cells in the hematoma begin to lyse, and hemoglobin and its degradation products are deposited into the brain parenchyma, thus initiating a potent inflammatory reaction.

Information regarding the nature of this edema derives mostly from experimental models of ICH in animals. Two models of experimentally induced ICH are used most often: one involves the injection of bacterial collagenase; and the other, injection or infusion of autologous blood into the brain parenchyma. Neither of these protocols entirely mimics the pathophysiology of primary ICH, but each does provide adequate information to study the involved molecular mechanisms and sequences of events that take place. The collagenase injection into the caudate putamen results in degradation of the basal lamina of surrounding vasculature and leakage of blood into the surrounding parenchyma. The method of basal lamina degradation in this model is different from what occurs in primary ICH, and the timing of the potential infiltration of systemic inflammatory cells can be accelerated. The model reproduces the slow leakage of blood into the brain as it occurs after a ruptured blood vessel. The second widely used model of injection of autologous blood into the brain provides the benefit of mimicking a space-occupying hematoma but lacks the timing and events of the slower progression of a primary hematoma.

Abbreviations used in this paper: CBF = cerebral blood flow; CPP = cerebral perfusion pressure; ICH = intracerebral hemorrhage; ICP = intracranial pressure; IL = interleukin; tPA = tissue-type plasminogen activator.
Extensive study data from various groups have shown that in both models of ICH induction, there is a large peri-hematomatous area that undergoes neuronal death. Increased water content and inflammatory infiltrates characterize the area. The causes of this peri-hematomatous area of edema and cell death are not decisively known. Experimental data indicate that the presence of whole blood, but not intact red blood cells, induces edema formation. As red blood cells lyse, however, edema is observed, and the volume of edema correlates with the volume of lysed red blood cells. Hemoglobin and its degradation products induce edema formation and accumulation of reactive glia cells at the site of delivery. One presumed function of hemoglobin degradation products is the generation of reactive oxygen and nitrogen species that would lead to lipid peroxidation, carboxylation, and tyrosine nitrosylation of proteins as well as eventual uncoupling of mitochondria.

An additional contributor to neuronal death is the increased presence of cytokines. Elevated levels of IL-6 and IL-1β have been associated with ICH and edema formation. Administration of IL-1β resulted in neuronal death and vasogenic edema, whereas the overexpression of IL-1 receptor antagonist reduced the extent of edema, indicating that proinflammatory cytokines play causative roles in the adverse outcomes of ICH.

Components of the complement system have also been found in the peri-hematomatous area. Using immunohistochemistry and Western blot analysis, the presence of C3d and C9 have been documented in the parenchyma, and depletion of the complement reduced the volume of edema after ICH. The cause of complement activation is not entirely known; diffusion of thrombin and the release of hemoglobin are among the factors that result in complement activation and the formation of membrane attack complexes. The intracerebral administration of both a plasminogen activator (tPA) and urokinase-type plasminogen activator; used experimentally for the liquefaction of hematomas) and thrombin resulted in extensive edema, an outcome that agrees with the extensive edema observed in a pig model of ICH in which the hematoma was evacuated after tPA administration. It is worth noting that tPA mice exhibited a significantly smaller region of edema compared with their wild-type counterparts early after ICH induction, although clot liquefaction using exogenous tPA produced late edema in the animals, regardless of their genotype.

Different approaches have been taken experimentally to reduce the volume of edema after ICH. Based on findings from animal models, these approaches have included inhibitors of thrombin early after the onset of ICH and thrombin preconditioning; inhibitors of monocyte/microglial cell activation, which would lead to a decrease in the levels of released cytokines; inhibitors of complement activation; glutamate receptor antagonists such as N-methyl-D-aspartate receptors, which have been shown to be involved in ICH edema; antioxidants and erythropoietin; and albumin, which has been shown to exert protective effects against both ICH and ischemic stroke. For clinical use, however, the current approaches are limited.

**Current Treatment Options**

As mentioned previously, one of the current protocols for treating a deep-seated ICH is its evacuation after liquefaction using tPA. Such local instillation of a fibrinolytic agent to facilitate the dissolution of a clot, and thus to increase the volumetric yield of aspirated liquefied blood, has been shown in animal models to aggravate secondary tissue injury in terms of edema formation and inflammatory reactions.

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indirectly from hyperacute bleeding into the perilesional region or herniation related to brain swelling.

Imaging abnormalities within the perihematomal region have been reported previously, but the extent and mechanisms of cellular injury are incompletely understood. It has been hypothesized that the perihematomal region is hypoperfused, primarily due to microvascular compression, resulting in ischemia and cytotoxic edema. Previous studies of blood flow in acute ICH have yielded conflicting results, and no clear markers of ischemia have been demonstrated. Mayer and colleagues have shown that perilesional blood flow tended to normalize from initially depressed levels as edema formed during the first 3 days after ICH, and the eventual extent of edema correlated with the size of the initial perfusion deficit and the volume of reperfused tissue. Perihematomal hypoperfusion has also been interpreted as a consequence of reduced metabolic demands (diachisis) rather than a sign of ischemic penumbra. Edema has also been postulated to be vascular in origin, resulting from the swelling effects of intrahematomal blood clotting. Rational medical therapies require a better understanding of perihematomal edema origins, especially acute blood pressure management because the proposed mechanisms of edema formation support opposing treatment strategies. Specifically, acute blood pressure reduction can theoretically inhibit hematoma expansion. Conversely, hypotension can exacerbate or even invoke cerebral ischemia. Clinical trials on the early use of antihypertension drugs in ICH are therefore underway.

Although the results of the International Surgical Trial in Intracerebral Haemorrhage did not help formulate evidence-based recommendations regarding the role of surgery in spontaneous ICH, surgery is generally consid-

**Fig. 2.** Non–contrast-enhanced computed tomography scans demonstrating hemorrhages before (a and c) and after (b and d) surgery. A left-sided lobar hemorrhage (a) was evacuated via a craniotomy (b). A right-sided cerebellar hemorrhage (c) compressing the brainstem was surgically removed, relieving pressure in the posterior fossa. The formerly compressed fourth ventricle became patent again (d).
ered in patients with moderate to large lobar (Fig. 2) or basal ganglia hemorrhages and in those suffering progressive neurological deterioration. Elderly patients whose Glasgow Coma Scale score is less than 5, those with brainstem hemorrhages (Fig. 3), and those with small hemorrhages do not typically benefit from surgery. Patients with cerebellar hemorrhages larger than 3 cm (Fig. 2), those with brainstem compression and hydrocephalus, and those exhibiting neurological deterioration should undergo surgical evacuation of the clot.

Nonsurgical treatment is used in patients whose hemorrhages are not space-occupying or who lack focal neurological deficits (Fig. 4a). In contrast, patients with hemorrhages at locations not surgically accessible are subjected to medical treatment (Fig. 4b). Patients also require elaborative medical treatment after surgical removal of the blood clot to prevent secondary tissue injury. The goal of medical treatment is to prevent secondary insults, reduce brain edema (Fig. 5) and ICP, maintain blood supply and oxygen delivery, and optimize cerebral metabolism in a neurointensive care setting. Protocols have been developed to provide a stepwise approach to the control of brain swelling and increased ICP. although these guidelines address traumatic brain injury, they have been applied to patients with ICH and brain edema for their supportive value. If relatively simple therapeutic maneuvers, such as sedation, ventilation, and a head-up position, fail to control brain swelling, more advanced medical treatment can be applied, including inotropes, hypertonic saline, mannitol, and hypothermia. Cerebral perfusion pressure and ICP have become therapeutic targets in preventing potentially life-threatening cerebral hyperfusion. Recent guidelines recommend target levels of ICP less than 25 mm Hg and CPP greater than or equal to 60 to 70 mm Hg. The various protocols for intensive care management, such as controlled CPP, controlled ICP, or Lund therapy, differ substantially. Nonetheless, results of a recent retrospective study in which authors compared the CPP- and ICP-oriented protocols have indicated better outcomes when the former protocol is applied during active pressure regulation of CBF, and the latter protocol is more appropriate when pressure regulation of CBF is impaired. In unresponsive patients and those with a Glasgow Coma Scale score less than 8 on admission, an ICP monitoring device is implanted to allow the physician to react quickly to increased pressure in an attempt to prevent secondary tissue injury from pressure-induced ischemia. A ventricular catheter allows venting of cerebrospinal fluid and is the quickest method of lowering ICP. Situations in which a very rapid reduction in ICP is needed are also indications for therapy with osmotic agents such as mannitol. Rapid infusion of hypertonic solutions of mannitol quickly reduces brain water by creating an osmotic gradient between the brain and plasma. When mannitol (1 g/kg) is given over 10 to 15 minutes (for example, 250 ml of a 20% solution in an average adult), a reduction in ICP of 30 to 60% can be expected for 2 to 4 hours. Massive osmotic diuresis will follow mannitol therapy and can be forced by giving furosemide in concert with mannitol. Mannitol appears to enhance circulation by decreasing ICP as well as by creating a direct

Fig. 3. Photographs illustrating the gross pathophysiology in two cases of ICHs unsuitable for surgical evacuation. A deep left basal ganglia hemorrhage (a) with massive intraventricular bleeding and mass effect, and a pontine hemorrhage (b). (Photograph provided courtesy of J. Weis, Department of Neuropathology, RWTH Aachen, University Hospital Aachen, Germany.)

Fig. 4. Non–contrast-enhanced computed tomography scans revealing a small, deep-seated left basal ganglia hemorrhage (a) that caused no impaired level of consciousness and only minor right-sided motor deficits on clinical examination of the patient (medically treated) and a pontine hemorrhage (b) that was inaccessible to surgical intervention in a comatose patient (also treated medically).
effect on cerebral perfusion in the microcirculation. It reduces blood viscosity with increases in CBF and oxygen delivery via immediate plasma expansion. Amino-caproid acid, and aprotinin. Data from a Phase IIB trial in which investigators used recombinant activated factor VII (NovoSeven) have shown less hematoma expansion and improved clinical outcome in terms of functional independence and neurological impairment on Day 15 after hemorrhage. The Phase III trial focused on mortality rate and severe disability at Day 90 is still in progress.

Conclusions

In summary, the treatment options for brain edema complicating ICH are mostly supportive. A better understanding of perihematodal edema origins might offer more specific treatment options for secondary injury to perihematodal brain tissue, thereby potentially improving the outcome of ICH.

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