

Advances in the Management of Spontaneous Intracerebral Hemorrhage

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Spontaneous intracerebral hemorrhage (ICH) is associated with the highest mortality of all cerebrovascular events, and most survivors never regain functional independence. Many clinicians believe that effective therapies are lacking for patients who have ICH; however, this perception is changing in light of new data on the pathophysiology and treatment of this disorder, in particular, research establishing the role of medical therapies to promote hematoma stabilization. This article discusses the basic principles of management of ICH, including initial stabilization, the prevention of hematoma growth, treatment of complications, and identification of the underlying etiology. In addition, minimally invasive surgery (MIS) to reduce clot size is discussed, with the goal of preserving neurologic function through reduction in parenchymal damage from edema formation.

Initial stabilization

As in other medical emergencies, initial resuscitative measures should be directed to establishing adequacy of airway, breathing, and circulation. Indications for endotracheal intubation include the lack of adequate airway protection, herniation syndrome, uncontrolled seizures, and respiratory failure. Hyperventilation might be necessary in the event of acute herniation, but, extrapolating from brain trauma literature, its prophylactic use is unlikely to be of benefit. If an intracranial pressure (ICP) monitor is

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available, it seems reasonable to maintain a physiologic cerebral perfusion pressure (> 60 mm Hg), or in the absence of an ICP monitor, a systolic blood pressure of greater than 90 mm Hg to maintain adequate cerebral blood flow [1].

Control of blood pressure

Because hypertension is the most common cause of spontaneous ICH, its treatment in this setting is of considerable importance, but the therapeutic goals are controversial. The debate on blood pressure control has involved two key points. The first is the possibility that there is a perihematoma “penumbra” of brain tissue that is vulnerable to ischemia if blood pressure is reduced acutely, which results in increased injury in the zone surrounding the hemorrhage. Recent studies using positron emission tomography and MRI do not support the hypothesis of an ischemic perihematoma penumbra; thus, judicious blood pressure control seems to be safe [2].

The second issue is the possibility that hematoma growth may be accelerated by hypertension in the setting of acute ICH. The occurrence of ICH is strongly related to premorbid blood pressure; however, the relationship between the growth of hematoma and uncontrolled blood pressure remains to be clarified. Recently, Jauch and colleagues [3] demonstrated that there was no definitive correlation between hemodynamic parameters, such as blood pressure, and hematoma growth. Current consensus guidelines emphasize a blood pressure control to be less than systolic blood pressure of 185 mm Hg and diastolic blood pressure of 105 mm Hg [1]. The question of whether blood pressure control influences survival needs to be evaluated in prospective trials. A multicenter phase I clinical trial is underway to assess the feasibility and safety of antihypertensive treatment (with intravenous nicardipine) for patients who have acute hypertension in the setting of ICH. A detailed discussion on blood pressure management in acute cerebrovascular disease by Urrutia and Wityk can be found elsewhere in issue.

Coagulopathy

The presence of coagulopathy, in particular warfarin-related, has been noted to worsen the prognosis of ICH by increasing the rate and time window for hematoma expansion [4]. Early administration of fresh frozen plasma and vitamin K to reverse this coagulopathy is recommended, although recent data suggest that practical issues causing delays in the administration of fresh frozen plasma might lead to continued expansion of hematoma, despite normalization of international normalization ratio [5]. This argues for alternative or additional treatment options to reverse coagulopathy in the setting of ICH.

Treatment of complications

Elevated intracranial pressure

Intracranial hypertension has been associated with worse outcomes following ICH, which suggests that ICP monitoring may be of benefit in selected high-risk patients [6]. In the setting of increased ICP or a herniation syndrome, controlled hyperventilation to a PaCO₂ of 27 to 30 mm Hg decreases ICP rapidly by causing cerebral vasoconstriction with an almost immediate reduction in cerebral blood flow. Osmotherapy should be instituted using mannitol with a serum osmolality goal of more than 300 mOsm/kg or hypertonic saline with a Na⁺ goal of 145 to 155 mmol/L [6,7]. For refractory elevations in ICP, additional options include pharmacologically induced coma or decompressive hemicraniectomy [8–10]. Steroids have no role in the management of cerebral edema or increased ICP [11]. Rangel-Castillo and Robertson provide a detailed discussion on the management of ICP elevation elsewhere in this issue.

Seizures

Seizures were believed to occur in 10% to 15% of patients after ICH [12,13], but more recent data suggest a higher prevalence when these patients are monitored with continuous electroencephalography, especially patients in a comatose state [14,15]. In its guidelines, the Stroke Council of the American Heart Association recommended uniform seizure prophylaxis in the acute period after intracerebral and subarachnoid hemorrhage [1], but it did not define the duration nor classify the patients by location of hemorrhage. Given the possible risk for neuronal damage and elevated ICP secondary to seizures, it seems reasonable to administer phenytoin prophylactically in patients who have cortically located, lobar hemorrhages, and in the absence of seizures, to discontinue prophylaxis 2 to 4 weeks after the ICH [16,17].

Identification of underlying etiology

In patients who are older than 45 years with a history of hypertension and an ICH located in the basal ganglia, thalamus, and posterior fossa, further investigations to confirm the etiology of hemorrhage are unnecessary [18]. In younger nonhypertensive individuals, further investigations, such as angiography to rule out aneurysms and arteriovenous malformations, are warranted. Because older patients are at higher risk for tumors and metastasis, MRI might be the first imaging modality used. Amyloid angiopathy is a common etiologic factor in older patients, especially those older than 65 years who have multiple lobar hemorrhages. In hemorrhages in patients who are on anticoagulation, a risk benefit ratio needs to be established before restarting anticoagulation.

New therapeutic approaches

The medical management of acute ICH revolves around the concept of hematoma stabilization. Brott and colleagues [19] clarified the idea that hematoma size is an important determinant of mortality in the setting of acute ICH, and demonstrated that early hematoma growth does occur. Davis and colleagues [20] clarified that early hematoma growth is the most strongly predictive variable for poor outcome. Other investigators demonstrated that acute edema formation also is predictive of bad outcome [21]. These observations suggest that reduction in the progression of ICH growth is key to improving survival of these patients in the setting of the ICU.

Activated factor VII

A new therapy offers the promise of reducing hematoma growth. In a recent phase II study, recombinant activated factor VII given within the first 4 hours of acute ICH improved survival and reduced hematoma expansion. The relative risk for mortality was reduced by 30% for all doses of activated factor VII included in the study [22]. A large randomized controlled study is underway to substantiate these results.

Intraventricular thrombolysis

Existing data indicate that in patients who have smaller ICHs (<30 mL) and intraventricular hemorrhage (IVH), outcomes are related, in large part, to IVH [23]. Therapies that limit the consequences of IVH and reduce the length of stay in the ICU may improve survival significantly. An example of such a therapy is intraventricular thrombolysis of clots in IVH. Several small case series present evidence that support intraventricular lysis of clot as a safe intervention, yet provide no conclusive evidence about its efficacy. These data were summarized in a Cochrane systematic review [24]. An ongoing clinical trial, Clot Lysis Evaluating Accelerated Resolution of Intra-Ventricular Hemorrhage, is designed to determine the optimum dose and timing of intraventricular recombinant tissue plasminogen activator (rt-PA) in patients who have IVH.

Minimally invasive surgery

The role of MIS in the treatment of ICH has gained importance over the past decade. Surgical therapies have been unable to improve the neurologic outcome of these patients, as evidenced by the results of the International Study of the Treatment of Intracranial Hemorrhage. It failed to demonstrate a significant benefit of aggressive surgical treatment over conservative medical treatment for the acute care of ICH. Prospective research testing novel therapies to improve the clinical outcome of patients who have ICH is lacking.

Additionally, fundamental questions regarding the pathophysiology of secondary injury following ICH remain to be investigated. Nevertheless, recent studies suggest that reduction of clot burden is an important factor in limiting brain edema and additional neuronal injury, and in reducing the severity of neurologic deficits following ICH. If MIS with or without thrombolytic therapy were capable of achieving safe and efficient clot reduction, it might modify patient outcomes positively.

Therapeutic targets

Thirty-day mortality after ICH approaches 50%. Among surviving patients, only 20% achieve a meaningful level of functional recovery at 6 months [23,25]. Case-control cohort studies have consistently identified hematoma volume and admission Glasgow Coma Scale as the main prognostic factors affecting the survival and neurologic outcome of these patients [26]. Reduction of hematoma volume could lead to improved neurologic outcome by several mechanisms. Reduction of clot size directly reduces local mass effect, which decreases the risk for fatal complications, such as brainstem compression. In addition, minimizing hematoma volume also could lead to a decreased risk for elevated ICP that is due to obstructive hydrocephalus ("trapped ventricles"). Conceivably, hematoma evacuation also could minimize the process of secondary neuronal injury, which leads to perihematoma tissue swelling that is caused by a variety of biochemical mechanisms that are triggered by the interaction between blood and viable brain parenchyma [27].

The relationship between blood, blood degradation products, and perihematoma edema following ICH continues to be unraveled. Hemoglobin and its derivatives (methemoglobin, deoxyhemoglobin, hemosiderin) have potent molecular and physiologic effects on adjacent brain parenchyma. Hemoglobin with its prosthetic iron group is a nitric oxide absorber with long-lasting physiologic effects [28]. In addition, thrombin was shown to induce blood-brain barrier disruption and vasogenic cerebral edema.

To minimize brain tissue trauma that is induced by surgical manipulation, and in view of the failure of craniotomy/hematoma evacuation to improve survival and neurologic outcome after ICH, new modalities (eg, stereotactic-guided aspiration) have emerged as treatment alternatives that are amenable to testing.

Approaches to hematoma evacuation

Studies that tested the safety and efficacy of MIS techniques in the treatment of ICH have centered on two different procedures: endoscopic aspiration of the hematoma, and stereotactic placement of a flexible catheter in the core of the hematoma followed by the administration of thrombolytic agents. In the late 1980s, Auer and colleagues [29] performed a randomized study that compared hematoma endoscopic aspiration with medical management in the treatment of patients who had ICH. The main inclusion

criterion in this study was the presence of a supratentorial hematoma with a volume greater than 10 mL. All hemorrhages that occurred because of identifiable brain lesions (eg, tumor, arteriovenous malformation, aneurysms) were excluded. At 6 months, the mortality was 42% in the group that was treated with MIS, which compared favorably with the mortality (70%) in the group that was treated medically. Nevertheless, there were no significant differences between the two cohorts in the quality of life of patients who had large (> 50 mL) hematomas. In patients who had smaller hematomas (< 50 mL), quality of life was improved with MIS, without a noticeable impact on mortality. Critics of this study suggested that lack of blinding could have led to differences in the medical management of the two treatment groups. Furthermore, the benefits of this technique seemed restricted to lobar hemorrhages and to patients who were younger than 60 years old.

A study by Marquardt and colleagues [30] focused on a novel, multiple-target aspiration technique in 64 patients to aspirate a “sufficient proportion” of the hematoma with minimal risk for the patient. More than 80% of the hematoma volume was aspirated successfully in 73.4% of the patients, with only one episode of rebleeding. Enthusiasm for endoscopic aspiration has decreased in recent years in light of data showing favorable outcomes with the local instillation of fibrinolytic agents into the core of the hematoma.

Fibrinolysis with clot aspiration

Stereotactic clot aspiration is similar to endoscopic aspiration, but clot resolution is enhanced by thrombolytic agents, such as streptokinase [31], urokinase, or rt-PA. Clot evacuation combining the use of fibrinolysis with clot aspiration has emerged as a promising surgical modality in the acute care of ICH. Clinical trials testing this technique are generating increased interest particularly in light of the failure of open evacuation to achieve outcomes superior to medical management [32]. Studies with animal models of ICH and IVH have demonstrated the efficacy of thrombolysis in reducing clot volume. Furthermore, the increase in perihematomal edema observed when ICH develops a complication of rt-PA for ischemic stroke has not been observed in trials of spontaneous ICH [33–36]. This observation suggests that rt-PA may be used safely to accelerate hematoma volume resolution. The testing of rt-PA in the treatment of ICH has moved into clinical trials.

Clot lysis using urokinase as a thrombolytic agent, combined with stereotactic aspiration, was compared with best medical treatment alone in the Stereotactic Treatment of Intracerebral Hematoma by Means of a Plasminogen Activator trial [37]. Thirty-six of the 71 patients who were enrolled in this multicenter trial were randomized to the surgical group within 72 hours of symptom onset. Inclusion criteria were age older than 45 years,

spontaneous supratentorial ICH greater than 10 mL, and summed Glasgow Eye and Motor scores between 2 and 10. There was a statistically significant reduction in the volume of the hematoma in the group that was treated surgically, but no significant reduction in the 6-month mortality (56% and 59% with surgery and medical treatment, respectively). The rebleed rate with surgery (22%) was deemed crucial in negating any benefit of reduced lesion mass. The role of other confounding factors on the study results, such as significantly larger hematoma volumes at baseline in the group that was treated surgically, is unclear.

Smaller nonrandomized studies in the United States and Europe have shown promising results [38–46]. Montes and colleagues [38] demonstrated that clot lysis combined with stereotactic aspiration is safe and accelerates clot volume reduction. This study was completed in 12 patients. There was a mean reduction in hematoma volume of 57%, and an increase in clot size in only 1 patient. A mean reduction in clot size of 84% was achieved in another small case series by Lippitz and colleagues [39]. Rohde and colleagues [40] showed a decrease in clot burden following frameless stereotactically guided catheter placement and clot lysis.

The optimal dosing of rt-PA for the treatment of ICH remains unknown. Different groups of investigators have empirically used different regimens. Dose escalation studies from thrombolytic therapy in the treatment of IVH that aimed to clarify this subject are close to completion. Schaller and colleagues [45] used a novel method to calculate the initial rt-PA dose. The amount of rt-PA was directly proportional to the maximal diameter of the initial hematoma volume. The dosage was recalculated daily based on clot diameter as measured by daily CT scans. A recent report by Barrett and colleagues [46] used rt-PA, 2 mg every 12 hours, for hemorrhages larger than 35 mL in diameter until the hematoma volume was reduced to less than 10 mL, or the catheter fenestrations were no longer in continuity with the clot. This dosage was based on safety data obtained from previously published studies in ICH and IVH [40,47].

Most of the reported clinical experience in the field of stereotactic surgery for ICH comes from Japan [48–54]. Matsumoto and Hondo [48] described the use of a 3.5-mm diameter silicone tube that was inserted into the center of the hematoma following three-dimensional CT images or biplane CT images taken to determine the coordinates of the target point in 51 patients (34 basal ganglionic, 11 subcortical, 3 thalamic, 3 cerebellar hematomas). Following placement of the catheter through a burr-hole under local anesthesia, aspiration of the hematoma was attempted with a syringe. Immediately after the first trial of hematoma aspiration, urokinase (6000 IU/5 mL saline) was administered through this silicone tube, and the drain was clipped. Subsequently, aspiration and infusion of urokinase were repeated every 6 or 12 hours until the hematoma was evacuated completely. The silicone tube was removed when repeat CT scans revealed no residual hematoma. These investigators reported more than 400 stereotactic aspiration

procedures in patients who had hypertensive ICH. A favorable outcome at 6 months was seen in stereotactically treated patients who had a basal ganglionic ICH, compared with patients who underwent conventional surgery or best medical treatment alone [49,50]. Niizuma and colleagues [51] reported significant rebleeding in only 4 of 97 patients who had a hypertensive ICH that was treated with CT-guided stereotactic aspiration. The investigators used urokinase for clot liquefaction, followed by aspiration through a drainage catheter. In 70% of the cases, at least 80% of the clot was evacuated.

Studies that investigated long-term clinical outcomes in stereotactic clot lysis and removal have been completed. A retrospective review of 85 patients indicated favorable long-term clinical outcomes in patients who received local urokinase following stereotactic hematoma evacuation [52]. Conversely, another review of 126 patients who had frame-based or frameless stereotactic hematoma puncture followed by clot irrigation with rt-PA did not demonstrate improved clinical outcomes, despite the observed decrement in hematoma size. In this study, there was an associated increase in poor outcomes in patients who were older than 65 years [53].

A recently published study by Vespa and colleagues [43] using frameless stereotactic aspiration of deep ICHs, followed by local rt-PA, suggested that this procedure was safe and linked to improved neurologic outcomes that correlated well with the degree of hematoma removal. This study demonstrated an improvement in the level of consciousness, and an improvement in the motor scores. No increase in the perihematomal edema was reported by these investigators.

Similar beneficial effects have been observed with the use of thrombolysis in IVH. Based on early data showing a trend toward improved 30-day outcomes in patients who received intraventricular urokinase [47], a randomized double-blinded pilot trial by Naff and colleagues [55] showed accelerated clot resolution with intraventricular urokinase. These results reinforce the multifactorial nature of the proposed therapeutic effect of rapid clot removal in different paradigms of intracranial hemorrhage.

In a recent Cochrane database review, it was concluded that endoscopic evacuation has not been shown to significantly decrease the odds of death and dependency among patients who have ICH [56]. Reports of treatment benefits in patients who were treated with endoscopic aspiration of ICH in Japan have led to the routine use of this modality as an alternative to craniotomy in that country. In the United States, this treatment modality has been restricted to research protocols in academic stroke centers, and it is not advocated widely as an option for the treatment of ICH.

Thrombolytic therapy is an attractive therapeutic option that has the potential to modify the natural history of ICH. Large randomized trials that prove the relative benefit of intracranial thrombolytic treatment over conservative medical management or craniotomy alone do not exist; however, interest in this treatment modality is increasing in light of the data summarized in this article. Several methodological issues surrounding this

form of treatment remain to be resolved, including comparison of the relative efficacies of various mechanisms of clot aspiration and drainage. A dose escalation trial also is needed to identify the fibrinolytic dose that has the optimal risk/benefit ratio. Clinically meaningful study end points should include global outcome measures that emphasize improvements in function and mortality [57–59]. Additionally, emphasis should be placed on the timing of the initiation and the cessation of therapy that are required to establish optimal clinical efficacy.

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