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REVIEW

Treatment Targets in Intracerebral Hemorrhage

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Abstract Intracerebral hemorrhage (ICH) imparts a higher mortality and morbidity than ischemic stroke. The therapeutic interventions that are currently available focus mainly on supportive care and secondary prevention. There is a paucity of evidence to support any one acute intervention that improves functional outcome. This chapter highlights current treatment targets for ICH based on the pathophysiology of the disease.

Keywords Intracerebral hemorrhage · Pathophysiology · Treatment · Clinical trials · Stroke

Introduction

Intracerebral hemorrhage (ICH) accounts for approximately 10 to 15% of all strokes that occur in the United States, Europe, and Australia, as well as 20 to 30% of all strokes that occur in Asian countries [1, 2]. ICH is more common in men than in women [3] and varies according to ethnic background. Individuals of African, Japanese, and Hispanic descent have a higher risk of ICH [4–6]. Blacks and Hispanics have been found to have double the risk of ICH compared to Caucasians [4, 6]. ICH continues to impart a considerable degree of morbidity and mortality, with 30-day mortality ranging from 44 to 50% [1, 7, 8]. ICH remains a devastating disease and current treatment options lag far behind those for ischemic stroke.

There is evidence that advancements in specialized care, such as neurological intensive care units [9], and neurointensivists [10] impact outcomes in patients with ICH; however, there are no approved therapies that improve outcome, and treatment remains mainly supportive. Despite the lack of available acute treatment options for ICH, the last decade of clinical and preclinical research has identified important concepts in its pathophysiology, and how this information might be used in developing treatment. Recent clinical trials in ICH have identified important considerations in patient selection, which have provided information for current and future trials in evaluating treatment for ICH, and preclinical work in ICH has identified new treatment targets.

It is intuitive that an understanding of the pathophysiology of the disease provides a starting point for identification of treatment targets. The pathophysiology of ICH begins with the predisposition of developing the disease. This includes genetics and risk factors that conspire to generate the ictus. Once present, ICH causes both primary and secondary injury. The primary insult is due to disruption of adjacent tissue and mass effect [11]. Secondary injury occurs with the development of edema, free radical formation, inflammation, and direct cellular toxicity due to the deposited hematoma and subsequent degradation byproducts. Each of these phases of disease provides a potential treatment target. The multiple steps along the path of disease also highlight the fact that successful treatment for ICH will most likely be multifaceted with different treatments at different time points.

ICH Genetics

The most common causes of spontaneous ICH include hypertension and cerebral amyloid angiopathy. However, anticoagulation associated ICH is increasing in incidence [12]. Warfarin use increases the risk of ICH 2 to 5 times,

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depending on the intensity of anticoagulation [13, 14]. The risk of ICH with anticoagulation may also depend on an individual's race. Asians have a 6 times higher risk on warfarin compared to whites and are twice as likely to have an ICH when compared to blacks and Hispanics [15].

The genetics of ICH is complicated as there are multiple environmental risk factors that interact with complex traits, such as hypertension, to increase the risk of ICH; however, there are also other well-defined genetic associations, which are risk factors for ICH with characteristic patterns. Although a complete discussion regarding the current status of ICH genetics is beyond the scope of this chapter, in this section we will discuss areas in which genetic data has or will provide information for future treatment efforts.

Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA) is a major risk factor for ICH with a recurrence rate of 10.5% per year [16]. CAA is age dependent, uncommonly occurring in individuals <60 years of age [17]. The most common locations of hemorrhage due to CAA are the cerebral and cerebellar cortices, in contrast to the deeper locations associated with hypertension. The deposition of protein consisting of amyloid in the tunica media and adventitia of the capillaries and arteries of the brain is the primary pathological feature of CAA. These amyloid deposits are similar to those seen in Alzheimer's disease. The amyloid-beta fragment is the primary component of the plaques [18, 19].

The pathogenesis behind the deposition of the beta amyloid peptide into cerebral blood vessels and its increasing incidence with age has not been clearly defined. There is, however, a relationship between apolipoprotein E (APOE) and CAA. APOE is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. Individuals carrying the APOE epsilon 2 (ε2) or epsilon 4 (ε4) alleles seem to be at greater risk for CAA-related hemorrhage than those with only the APOE epsilon 3 (ε3) allele, which is more common in the population [20, 21]. This connection has been clearly defined in Caucasian populations, but is not necessarily as clear in other ethnicities due to lack of evidence or a poor association as seen in the Japanese population [22]. Studies comparing normal controls against those with pathology positive CAA reveal that both APOE ε2 and ε4 are present in two-thirds of patients with CAA compared to one-fourth of those without. Individuals who have both alleles have an earlier onset of disease and an increased risk of recurrence [16, 21, 23]. Both APOE ε2 and ε4 are independent risk factors for lobar ICH, however, in the same large-scale genetic association study, APOE ε4 was also found to be associated with deep ICH [24]. Finally, there is now evidence that APOE ε2 may be associated with increased hematoma volumes at presentation, as well as subsequent hematoma expansion, which has important prognostic implications [25].

The pathogenesis of the hemorrhage associated with CAA begins with the deposition of amyloid beta-peptide into the wall of capillaries and arterioles. This deposition initiates changes of the blood vessel resulting in decreased integrity of the vasculature. There may be a synergistic effect of APOE in carriers of both the ε2 and ε4 alleles. The presence of the ε4 and ε2 genes may result in increased vulnerability of amyloid laden blood vessels. The ε4 allele has been demonstrated to increase the amyloid deposition [26], whereas the ε2 allele can induce necrosis of blood vessels with amyloid deposits [23].

The management of CAA lies mainly in supportive measures, and there is no evidence to support one specific therapy to help reduce the risk of recurrent hemorrhage. However, the use of proteoglycans and compounds that mimic the glycosaminoglycan moieties of proteoglycans have been observed to associate with amyloid fibril deposits *in vitro* [27]. These deposits have been implicated in the polymerization of amyloid proteins and the propagation of the deposition process. Recently a phase II study, Cerebril™ in Patients With Lobar Hemorrhage Related to Cerebral Amyloid Angiopathy, evaluating the safety of a glycosaminoglycan mimic moiety was completed [28]. The results of this study are pending, and if they are positive, they may lead to a larger phase III efficacy study in patients with CAA.

COL4A1

COL4A1 is located on chromosome 13q34 and encodes the α1 chain of type IV collagen, which is a basement membrane protein. Mutations in COL4A1 disrupt the basement membrane and weaken the blood vessel [29]. This mutation has been linked to a spectrum of cerebral small-vessel disease in humans, including perinatal ICH with consequent porencephaly [30], adult-onset ICH, microbleeds, lacunar strokes, and leukoaraiosis, and follows an autosomal dominant pattern of inheritance [31]. Mice with the COL4A1 mutation have hemorrhage associated with birth trauma, as well as clinically asymptomatic cerebral hemorrhage. The clinical phenotype in a family with this mutation was variable, demonstrating retinal arterial tortuosity, migraine with aura, infantile hemiparesis, leukoencephalopathy, and microbleeds [29, 32]. These findings suggest that a genetic predisposition combined with environmental stress (i.e., trauma, oral anticoagulant use, hypertension) may increase the risk of ICH [29]. This information may be important in determining ICH etiology in those patients without traditional ICH risk factors and it could have important preventive implications [33].

Technological advancements in the genetic evaluation of disease have transformed the scope and nature of genetic data that can now be obtained to understand a complex disease such as ICH. Researchers are now able to conduct accurate and efficient analyses across the entire genome of a study subject. Specifically, the genome-wide association study (GWAS) represents an experimental framework that can rapidly and efficiently identify novel pathogenic mechanisms, and can confirm a role for previously known mechanisms [34].

At present, GWAS studies of ICH among whites are ongoing. In the largest GWAS of ICH reported to date, no association with ICH was identified after multiple comparisons. This is consistent with ICH having a complex etiology with multiple risk factors [35]. Despite these advances, there is a critical lack of ICH cases among minorities with DNA available for genotyping, which limits our understanding of the epidemiology of ICH among minorities. Given the numerous risk factors to be examined and the potential for interactions, a large sample size is required, and no single center would be able to efficiently recruit sufficient numbers of cases and controls. The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study aims to address this gap in the literature. This multicenter study will enroll 1000 cases of ICH among whites, 1000 cases of ICH among blacks, and 1000 cases of ICH among Hispanics. In addition, 3000 controls will be matched to cases by race/ethnicity, age, gender, and geographic location. The study began in 2010 and is expected to be complete in 2015 [36].

Primary Injury

Primary ICH or spontaneous ICH is often believed to either be due to hypertension or CAA. Other risk factors for primary ICH include older age, alcohol consumption, and smoking [37]. The subsequent section will focus on hypertensive ICH because CAA was previously discussed.

Chronic hypertension is the most common modifiable risk factor for ICH. Hypertension pre-dating the hemorrhage has been found to be present in 45 to 56% of individuals, depending on the definition applied in the study. As one ages, the risk for ICH increases as an independent factor [38]. However, older age in conjunction with hypertension further increases an individual's risk [39]. Additional evidence supporting hypertension as an etiological factor is seen with improved control of hypertension leading to a decreased incidence of ICH [37].

Hypertensive hemorrhages are most commonly located in the putamen, thalamus, pons, and cerebellum; however, lobar hemorrhages are also frequently caused by hypertension [40, 41]. The most common belief regarding the etiopathogenesis of hypertensive-associated hemorrhages is due to the rupture of microaneurysms formed by chronic hypertension, which was supported by postmortem studies [42, 43]. The alternative explanation suggested that the pathology of the vascular change was due to true dilatations of the arterial wall; however, evidence emerged in the early 20th century that the pathological changes may actually be due to a dissection in the arterial wall leading to a pseudoaneurysmal dilatation [44]. This dissection may be due to chronic hypertensive induced intimal hyperplasia with vessel-wall hyalinosis leading to focal fibrinoid necrosis. The subsequent endothelial damage is also associated with subadventitial hemorrhages and extravascular clots. Continuous leaking of small amounts of blood from the pseudoaneurysm has been documented. The final step in the cascade leading to the actual ICH may be due to the breakdown in the balance between the clotting system and the rate of bleeding from the pseudoaneurysm [45, 46].

Ultimately, the intervention most likely to impact disease is the prevention of complications of hypertension; however, an understanding of the pathology related to hypertensive ICH may play a role in the downstream events that will influence hematoma size, expansion, and resolution.

Clinical Studies Targeting Hematoma Expansion

The evolution of the hematoma after initial hemorrhage has been well-described. The majority of the initial neurological deficit is due to the hematoma. Previously, early neurological decline was attributed to the development of edema; however, several authors have shown that early decline in neurological status can also be attributed to hematoma expansion (HE) [47–51]. One study enrolled 103 patients with ICH and performed computed tomographic (CT) scans 3 hours after symptom onset and follow-up computed tomographic scans after 1 h and 20 h. There was a 33% enlargement in 26% of patients at the 1-hour follow-up scan and an additional 12% had larger hemorrhages at the 20-h scan. The change in hematoma volume was associated with clinical deterioration [49]. HE has also been demonstrated in smaller series for as many as 5 and 6 days [52]. Even though early HE and its associated neurological worsening have been clearly demonstrated, the risk factors associated with HE have not been defined in large population studies [47, 49–51]. Current efforts are focused on identification of patients who will develop hematoma expansion with clinical, radiographic, or molecular markers. Certain biomarkers have been seen to be elevated in ICH, such as interleukin-6 and cellular fibronectin [53]. As previously mentioned, APOE ε2 may also be associated with subsequent hematoma expansion [25]. In addition, treatment efforts are directed at halting hematoma expansion. Because HE occurs in approximately a third of ICH patients, and because it is independently associated with worsening of

clinical status and outcome [54], HE represents a promising acute treatment target.

Hemostatic Agent

Recombinant factor VIIa (rFVIIa) has been studied to limit HE. After initial safety studies, a proof-of-concept trial was performed to observe the effect of rFVIIa on HE [55]. This study randomized patients who presented within 3 hours of symptom onset to either a single dose of 40 μg/kg, 80 μg/kg, or 160 μg/kg rFVIIa, or placebo within 1 h of baseline CT. Mean percent increase and mean absolute change in ICH volume was significantly lower in the 160 μg/kg group than in the placebo group. Thromboembolic events occurred in 2.1% in the placebo group and 6.9% in the treated group. The results of this proof of concept trial lead to a confirmatory efficacy study with similar enrollment criteria, except the exclusion for a history of thromboembolic disease was removed. The results were disappointingly neutral. There was no difference in the primary outcome measure of death or severe disability (modified Rankin Scale score (mRS), 5 or 6) in patients who received placebo compared with those who received rFVIIa. There was, however, a dose-related decrease in HE accompanied by a dose-related increase in adverse events in patients who received rFVIIa. The percent of change in ICH volume at 24 h was 28% in those receiving placebo, and 18% and 11% in the 20 μg/kg and 80 μg/kg groups, respectively. The percent of arterial thromboembolic events was 10% in the 80 μg/kg group and 5% in the placebo group, without any difference in venous thromboembolism [56].

Several explanations have been postulated as to why the clear radiographic benefit of rFVIIa did not translate to improved clinical outcome (e.g., time to treatment, older age, better-than-expected outcomes in the placebo group, and an increase in arterial thromboembolic events) [56]. However, the most salient explanation has to do with patient selection. Because there are only approximately one-third of patients who are expected to have acute HE, the treatment effect of rFVIIa may have been dampened by the enrollment of patients who would not have had significant enlargement, and thus would not be expected to benefit from this treatment. One way to improve patient selection for hemostatic treatment is to predict which patients are more likely to have significant HE and target that group for treatment. A radiographic marker of HE, the spot sign, has been retrospectively evaluated, and its presence has been found to be correlated with the risk for HE [57–59]. The spot sign represents a small focus or larger area of contrast extravasation within the hematoma on CT angiography, most often seen on source images [57]. In addition, contrast extravasation, seen on routine head CT after CT angiography, as pooling of contrast within the hematoma, may be a more sensitive predictor of ICH growth with a better negative predictive value than the spot sign [60]. A new study, Spot Sign for Predicting and Treating ICH Growth (STOP-IT) [61], is planned to evaluate the usefulness of rFVIIa in individuals with an ICH spot sign.

Blood Pressure

One of the most common clinical presentations in the acute setting of ICH is elevated blood pressure. In the acute period of ICH, elevated blood pressure has been correlated with a poor outcome in several studies. A meta-analysis performed by Willmot et al. [62] included 32 studies involving 10,892 ischemic and hemorrhagic stroke patients, which found that death was significantly associated with an elevated mean arterial blood pressure (odds ratio [OR], 1.61; 95% confidence interval [CI] 1.12-2.31) and high diastolic blood pressure (OR, 1.71; 95% CI 1.33-2.48). Combined death or dependency was associated with high systolic blood pressure (OR, 2.69; 95% CI 1.13-6.40) and diastolic blood pressure (OR, 4.68; 95% CI 1.87-11.70) in ICH. In another large recent Chinese trial that included a total of 1760 hemorrhagic stroke patients, it was found that the diastolic blood pressures were significantly and positively associated with odds of death or disability in acute hemorrhagic stroke. Compared to those with a systolic blood pressure less than 140 mmHg, multiple-adjusted odds ratio (95% confidence interval) of death/disability was 1.38 (0.96, 1.99), 1.42 (1.00, 2.03), 1.84 (1.28, 2.64), and 1.91 (1.35, 2.70) among participants with systolic blood pressure of 140 to 159, 160 to 179, 180 to 199, and at least 200 mmHg, respectively ($p<0.0001$ for linear trend) [63]. One interpretation of this data would be that rapid reduction in blood pressure might decrease the chances of poor outcome; however, this evidence does not demonstrate causality or reveal whether or not the aggressive management of elevated blood pressure in the acute setting will improve clinical outcome.

The association between elevated blood pressure and increased risk for HE is not clear, as some studies have not been able to define a relationship between the 2 [47, 49], and others have shown that there may be an associated risk for HE [64]. Controversy exists regarding the acute treatment of hypertension in ICH because of the possible expansion of what was once believed to be ischemic penumbra surrounding the hematoma. However, more recent positron emission tomographic evidence has shown that the area surrounding the hematoma is more likely to be due to metabolic suppression and not ischemia, and it is not affected by blood pressure reduction [65].

The results of 2 pilot trials designed to assess the feasibility and safety of rapid blood pressure reduction in the acute setting of an ICH have been reported. The Intensive Blood Pressure Reduction in Acute Cerebral

Hemorrhage Trial (INTERACT) randomized patients with acute spontaneous ICH within 6 hours of symptom onset, elevated systolic blood pressure (150–220 mmHg), and no definite indication or contraindication to treatment to early intensive lowering of blood pressure (target systolic blood pressure, 140 mmHg; n=203) or standard guideline-based management of blood pressure (target systolic blood pressure, 180 mmHg; n=201). The authors concluded that early intensive blood pressure lowering treatment is clinically feasible, well tolerated, and seems to reduce hematoma growth in ICH [66]. The second phase of INTERACT, known as The Second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT 2) [67], is now underway and plans to enroll 2800 patients who will be randomized to reducing their systolic blood pressure to less than 140 mmHg within 1 h or less than 180 mmHg. The primary outcome measure of this study is death and dependency at 3 months. One drawback of INTERACT is the majority of patients are of Chinese descent, which raises the question as to whether or not the results are generalizable.

The Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) trial was a nonrandomized, open-label study, which also assessed the feasibility and safety of acute blood pressure reduction in ICH. This pilot study differed from INTERACT in that there were 3 different groups of blood pressure goals and all patients were treated with nicardipine unlike INTERACT, which allowed the use of any available local intravenous anti-hypertensive agent. The ATACH trial consisted of 3 cohorts with systolic blood pressure ranging from 170 to 200 mmHg in the first cohort of patients; 140 to 170 mmHg in the second cohort; and 110 to 140 mmHg in the third cohort. Cohorts 2 and 3 had a trend toward worse outcome and more numerical deaths than cohort 1; however, the study was not powered to show an effect on death and disability. Consistent with findings from INTERACT, the study demonstrated that rapid blood pressure reduction was safe and feasible [68]. The ATACH-II trial, which is the next phase of ATACH, is a phase 3, randomized efficacy study designed to evaluate the therapeutic benefit of intensive acute blood pressure treatment (systolic blood pressure ≤140 mmHg) with intravenous nicardipine within 3 h of symptom onset compared with standard care (systolic blood pressure ≤180 mmHg). The primary outcome measure is death or disability (mRS, 4–6) at day 90. The study began in 2010 and plans to enroll 1280 patients [69].

Secondary Processes

The secondary pathophysiological processes have been implicated as causes of ongoing, injury including ischemia surrounding the hematoma, the development of cerebral edema [70], activation of apoptotic processes [71], toxic effects of components of the hematoma [72], and intraventricular extension of the primary hemorrhage [73]. The pathogenesis of symptoms and their subsequent recovery are also associated with hematoma size and location. Smaller hemorrhages may dissect along white matter tracts, which actually splits the fibers from each other instead of destroying them. If the hematoma takes this path, then there may be a higher likelihood of restoration of neurological function once the blood is resorbed. However, large clots, especially those with a cortical location involving the grey matter may result in a more sustained deficit. Hematomas greater than 5 cm in diameter have a larger risk of expansion associated with local irritation and tearing of tissue at its edge [74].

In addition to the hematoma, the associated edema may also contribute to the initial neurological deficit, subsequent decline, or death. The edema related to ICH has been cited as a reason for neurological deterioration after the first 24 to 48 h from the onset of symptoms [70], and it has, to a lesser degree, also been implicated with deterioration as late as 3 weeks [65]. The edema has been demonstrated to be predominately vasogenic with a cytotoxic component. The vasogenic edema is a consequence of blood brain barrier (BBB) breakdown. In the normal brain, the BBB prevents the flow of water into the brain due to hydrostatic pressure gradients. However, when the BBB is disrupted as occurs in ICH, the imbalance in hydrostatic forces result in the entry of an exudative proteinaceous fluid onto the brain parenchyma [74]. The disruption in the BBB is likely a consequence of an inflammatory cascade with resultant expression of specific cytokines and other markers of inflammation. The presence of red blood cells and their subsequent lysis and release of oxyhemoglobin may contribute to the leakage of the BBB [75]. The hemorrhage itself also induces the production of thrombin and the overexpression of matrix metalloproteinases. Thrombin has been demonstrated to be an important factor in the modulation of BBB breakdown [76]. Thrombin may be a major mediator of ICH-induced tumor necrosis factor-α production and an increase of perihematomal tumor necrosis factor-α levels contributes to brain edema formation after ICH [76]. Matrix metalloproteinases also promote BBB disruption [77, 78] and have been associated with increased edema volume [78] via extracellular matrix proteolysis, basal lamina destruction, and the degradation of c-fibronectin [79].

Cellular necrosis likely occurs at the core of the hemorrhage; however, apoptosis has been observed in the perihematomal region [71]. The apoptotic pathway in ICH may involve nuclear factor-kappa B (NF-κB), which is a ubiquitous transcription factor that, when activated, translocates to the nucleus and binds to DNA. NF-κB is associated with apoptotic cell death and has been reported

in the role of cell death after experimental ICH in rats [80]. In experimental models, peak apoptosis levels in the perihematomal area have been observed to occur on day 3 [81]. In addition to NF-κB, the activation of caspase 3 and the role of thrombin have also been demonstrated in perihematomal apoptosis [81].

The secondary injury caused by ICH is complex, but it offers multiple treatment targets. Currently, researchers are still elucidating the sequence of events of downstream processes and how each interacts. Each of these targets requires important preclinical data to inform clinical trials with respect to the optimal time frame for treatment, treatment duration, dose, and so forth. Without this important foundation, cytoprotective trials in ICH run the risk of falling into the same situation that has plagued ischemic stroke (i.e, namely, difficulty in translation of improved clinical outcomes from bench to bedside).

Clinical Trials Targeting Secondary Injury

Surgical Hematoma Clearance

Supratentorial surgical evacuation of an ICH has been a strongly debated topic in regards to its efficacy in producing good clinical outcomes. The current available evidence of surgical evacuation is largely based on the randomized prospective International Surgical Treatment of Intracerebral Hemorrhage (STICH) study [82]. Other available evidence includes a meta-analysis of 3 previously reported trials and case series [83]. The broad conclusion from these studies was that there was no difference in mortality or outcome between the groups randomized to surgical evacuation of the hematoma compared to medical management. Criticisms for STICH are that there was often crossover from the medical arm to the surgical arm and that many patients were taken to surgery beyond the predefined 24 h, which makes the results difficult to interpret. Interestingly, a subgroup analysis of patients with hematomas extending within 1 cm from the cortical surface and patients with a Glasgow coma scale (GCS) of 9 to 12 showed a trend toward a favorable outcome in patients who were randomized to surgery within 96 hours compared to medical management. However, neither of these results reached statistical significance [82]. This information has been used to form a follow-up trial called the Surgical Trial in Lobar ICH (STICH-II) [84], which is studying the possible benefit of surgical evacuation of cortical hemorrhages.

Other less invasive approaches to evacuation of the ICH are also being investigated. A small phase 2 study conducted by Vespa et al. [85] has shown that hematoma aspiration via a catheter is safe in conjunction with the use of thrombolytics to remove unclotted blood. This data has led to the development of the Minimally Invasive Stereotactic Surgery+[recombinant tissue plasminogen activator] rt-PA for ICH Evacuation (MISTIE) trial [86], which is comparing standard medical management to hematoma evacuation using a stereotactic catheter plus a thrombolytic-based approach.

Intraventricular Hemorrhage

One-third of patients with spontaneous ICH due to chronic arterial hypertension or small arteriolar degeneration and rupture have an associated intraventricular hemorrhage (IVH). The most common locations of an ICH associated with an IVH are thalamic, putaminal head, or caudate, resulting in spread to the lateral or third ventricles [74]. There is an established relationship between IVH with larger ICHs, midline shift, and increased morbidity and mortality [73]. An important consequence of IVH is hydrocephalus, which can develop acutely or gradually with time due to scarring of the arachnoid granulations from blood products. The clearance of the ventricular blood from the cerebrospinal fluid (CSF) occurs via several mechanisms. First, hemolysis occurs and begins within hours, reaching a plateau at 2 to 10 days after the IVH, depending on the size of the hemorrhage. Next is phagocytosis by macrophages, which occurs both in the leptomeninges irritated by blood and in the arachnoid granulations engorged with erythrocytes [87]. The breakdown of the actual clot within the ventricles is mediated by plasmin in the CSF. Plasmin is present in the CSF similar to serum in its precursor form plasminogen. As with serum, plasmin in the CSF is converted to its active form by tissue-plasminogen activator, which is released from the endothelium of the ependyma. The level of fibrinolytic activity is lower than plasma, but it is proportional to the clot burden in the ventricles and balanced by inhibitors released by irritated leptomeninges [87, 88]. Currently the only available treatment for IVH with hydrocephalus is the placement of an external ventricular drain; however, the external ventricular drain can become difficult to manage because of frequent obstruction from a thrombus resulting in interrupted drainage and increased intracranial pressure (ICP). An ongoing, multicenter study is attempting to evaluate a solution to this problem. The Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR IVH) trial is evaluating the safety and efficacy of intraventricular recombinant tissue plasminogen activator in clearing intraventricular blood and facilitating its drainage to help improve outcome in patients with IVH [89].

Pharmacologic Hematoma Clearance

The deposited blood causes local tissue deformation and elicits an inflammatory response after ICH. Although the inflammation involves most of the brain's cell types, the

brain's resident phagocytes, microglia, are the most prominent, and become activated within minutes after ICH [90, 91]. The activated microglia release chemotactic factors, which then recruit hematogenous phagocytes to the hemorrhagic area. These activated phagocytes engulf the deposited blood, damaged and dead tissue, and then provide a nurturing environment for local tissue reconstruction. It has been proposed that phagocytosis not only removes debris from the tissue, but also provides protection from local damage resulting from the release of toxic or proinflammatory contents [92, 93]. Microglia may also play a role in establishing trophic support involved in neuronal sprouting [94] and forming new vessels, which could then be used for removal of brain tissue debris after injury [95]. Ultimately, it is the inflammation (phagocytosis) that leads to the restoration of tissue structure and function [96, 97]. Although inflammation is triggered primarily to remove the blood and other debris left by the hemorrhage, the byproducts of this response are cytotoxic and lead to further tissue damage, blood brain barrier disruption, and edema [72, 97, 98].

One way to reduce the production of blood degradation products is hematoma evacuation. This has been the impetus for trials of hematoma evacuation, which, unfortunately, have not demonstrated benefit. However, few studies have focused on the natural history of hematoma absorption [75, 99–101]. With current clinical efforts focused on ICH treatment in the acute setting, a treatment that could enhance hematoma resolution, thus limiting secondary injury, would be a natural adjunctive treatment to acute therapy for this disease.

Another way to decrease the clot burden is to take advantage of the body's own mechanism of clot removal (i.e., phagocytosis). Pre-clinical work in our laboratory demonstrates that peroxisome proliferators-activated receptor-gamma (PPAR-γ) agonists promote hematoma resolution, decrease neuronal damage, and improve functional recovery in a mouse model of ICH [102]. We have also demonstrated that PPAR-γ agonists *in vitro* reduce production of proinflammatory mediators and free radicals produced during phagocytosis. Finally, PPAR-γ agonists *in vivo* demonstrate the ability to protect other brain cells from the secondary injury induced in a mouse model of ICH [102]. These data suggest that PPAR-γ in macrophages acts as an important factor in promoting hematoma absorption and protecting other brain cells from ICH-induced damage and may represent a promising therapeutic target in the management of ICH [103]. Clinically relevant PPAR-γ agonists include rosiglitazone and pioglitazone, which are approved by the Food and Drug Administration for glycemic control in type 2 diabetes mellitus.

The Safety of Pioglitazone for Hematoma Resolution In ICH (SHRINC) study is a prospective, randomized, placebo-controlled, dose-escalation safety trial in which patients with spontaneous ICH are randomly allocated to placebo or to treatment with escalating doses of pioglitazone followed by a maintenance dose for the duration of treatment. Functional outcomes are evaluated at 3 and 6 months. There is a planned sample size of 80 patients and enrollment is 50% complete [104].

Edema: Celecoxib

In the collagenase model of ICH, celecoxib demonstrated a time-dependent improvement in sensorimotor function that was persistent for as much as 4 weeks after the injury. In addition, celecoxib reduced infiltration of inflammatory cells, brain edema, and subsequent perihematomal cell death [105]. The authors postulate that this effect may be due to a decrease in prostaglandin E2, because prostaglandin E2 was markedly reduced in the celecoxib-treated animals.

A small, retrospective study investigated the efficacy and safety of celecoxib treatment in patients with ICH compared to a similar control group. Initial and follow-up hematoma and edema volumes of 17 patients with ICH who received celecoxib for ≥7 days were compared with a control group. Celecoxib treatment was significantly associated with a reduction in the volumes of edema on follow-up brain imaging compared with the volumes in the control group (30.2±17.7 *vs* 55.5±40.6 mL; p=0.027). There was no difference in the number of adverse events between the 2 groups. These results suggested that celecoxib may be safe and efficacious in patients with primary ICH [106].

To further evaluate these promising findings, a multicenter trial, named the Prospective, Randomized, Comparative Open with Blinded Endpoints (PROBE) trial, was developed to assess the safety and efficacy of administration of celecoxib in patients with ICH. The Administration of Celecoxib for Treatment of ICH: A Pilot Study (ACE-ICH) began enrollment in 2007 and was completed in 2009. The primary outcome measure was the change in perihematomal edema for a period of time. Patients were randomized to receive either celecoxib (400 mg twice daily) for a duration of 14 days or a placebo within 24 h of symptom onset. The primary outcome measure was change in volume of perihematomal edema for a period of time. Secondary outcome measures included neurologic function and the incidence of adverse events. The study was recently completed and the results will be available soon (personal communication, Dr. Roh).

Blood, Brain, Barrier Disruption: Albumin

It is difficult to ignore the similarities in mechanism of injury between acute ischemic stroke and ICH, namely, blood brain barrier disruption [107], edema, oxidative injury, inflammation, excitotoxicity, and apoptosis [108]. Thus, it

seems intuitive that treatments that provide neuroprotection in ischemic stroke might also do the same in ICH. Albumin has demonstrated neuroprotection in preclinical models of cerebral ischemia and researchers have attempted to extend the application of albumin to ICH as well.

In preclinical studies, albumin therapy administered 60 minutes after ICH improved neurological function as early as 2 h after treatment and was maintained through day 3 in a cortical model of ICH. Albumin also improved BBB integrity [107]. This group demonstrated similar findings in a subcortical model of ICH with albumin administered 90 minutes after ICH. In both studies, neither hematoma volume nor brain swelling were affected by albumin [109].

The Albumin for ICH Intervention (ACHIEVE) study is a phase 2, placebo-controlled trial evaluating the effects of albumin in patients with ICH within 24 h of symptom onset. The primary outcome measure is the frequency and severity of blood brain barrier disruption based on a magnetic resonance image with and without contrast. Secondary outcome measures included safety endpoints. The study began in 2009 with a planned enrollment of 40 patients and an estimated completion in 2012 [110].

Red Blood Cell Breakdown and Toxic Breakdown Products: Free Radical Scavengers

Several nitrone free radical-trapping agents (i.e., spin-trap agents) have demonstrated neuroprotection in rodent models of both transient and permanent focal ischemia [111, 112]. *NXY-059* (disodium 4-[(*tert*-butylimino) methyl] benzene-1,3-disulfonate *N*-oxide) is a novel nitrone-based compound that has free radical-trapping properties.

The Cerebral Hemorrhage and NXY Treatment (CHANT) study was a randomized, placebo-controlled trial that evaluated the safety and tolerability of NXY-059 (a free radical trapping agent) in patients with ICH within 6 h of symptom onset. At the time, NXY-059 was also being evaluated for potential treatment in patients with acute ischemic stroke. The intent of CHANT in ICH patients was to facilitate prompt administration of the treatment, potentially before neuroimaging. A total of 607 patients were randomized within 6 h of acute ICH (300 with NXY-059 *vs* 303 with a placebo). Mortality was similar in both groups: 20.3% for NXY-059 and 19.8% for placebo-treated patients. The proportion of patients who experienced an adverse event was the same for both groups, whereas for serious adverse events the proportion was slightly higher in the NXY-059 group; however, no pattern emerged to indicate a safety concern. There were no differences in 3-month function, disability, or neurological deficit scores. Based on this study, the authors concluded that NXY-059 given within 6 hours of acute ICH has a good safety and tolerability profile, with no adverse effect on important clinical outcomes [113]. It is unclear if there are plans to further evaluate this treatment.

Chelating Agent: Deferoxamine

At this time, deferoxamine (DFO) is probably the most thoroughly evaluated treatment in animal models of ICH, in terms of informing potential translational clinical efforts. Currently, DFO is further along in complying with the updated Stroke Therapy Academic Industry Roundtable (STAIR) recommendations [114] than most other treatments being evaluated in the preclinical setting. DFO has been studied in both the collagenase [115] and autologous whole blood models of ICH, as well as in both rodent and pig models [116] of ICH. DFO has been studied in both young and aged rodents [117] and has been shown to cross the BBB. The most recent studies evaluating DFO have addressed optimal doses and time windows for treatment [118]. The preclinical work with DFO consistently demonstrates decreased iron accumulation and improved neurologic function [115, 118, 119].

The Dose Finding and Safety Study of Deferoxamine in Patients with ICH (DFO in ICH) Study was a phase I open label study evaluating the safety and tolerability of varying doses of DFO to determine a maximum tolerated dose to be adopted in an efficacy trial in patients with ICH [120]. The study began in 2008 and was recently completed. The results were recently reported and demonstrated that repeated daily infusions of DFO in doses up to 62 mg/kg/day in patients with acute spontaneous ICH are feasible, well tolerated, and are not associated with an increase in serious adverse effects or mortality. Phase 2 evaluation of DFO is currently in the planning stages [121].

Anti-Inflammatory Agents: Statins

Despite the association of low cholesterol levels [122, 123] and the use of a statin with ICH [124], there is a growing interest in the pleiotropic effects of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (i.e., statins). The promising neuroprotective benefit of the statins in acute ischemic stroke [125–127] has led to a similar evaluation in ICH models. In the autologous whole blood model, atorvastatin at 2 mg/kg was beneficial, and higher doses did not improve outcome or reduce the extent of injury [128]. Atorvastatin reduced perihematoma cell death via an anti-inflammatory mechanism and this was also associated with sensorimotor recovery [129].

Both simvastatin and atorvastatin treatment for 1 week after ICH significantly improved neurological outcome and reduced hematoma volume and tissue loss at 4 weeks. The neurological improvement became apparent at 1 week and was consistent throughout 4 weeks. In addition, the statins increased cell proliferation and differentiation suggesting that enhanced neuroplasticity may be the mechanism for improved function [128, 130].

In the collagenase ICH model, atorvastatin exerted protection against ICH via modulation of inflammation. Taken together, these results suggest that statins may shift the balance of inflammation, such that the general milieu favors enhanced neuroplasticity, and thus the potential for improved recovery. The possible mechanisms of neuroprotection may include improved endothelial function, increased endothelial nitric oxide synthase expression [129], antioxidant effects, conferred resistance to N-methyl-D-aspartate excitotoxicity [131], promotion of neovascularization, and anti-inflammatory properties.

Although encouraging, the amount of preclinical data on the effect of statins in ICH is limited and some findings are not consistent. For example, 2 groups have demonstrated an effect of statins on hematoma volume [128, 130], whereas another group has not [129]. Thus far, preclinical studies demonstrate an effect on hematoma volume, brain atrophy, hemispheric water content, and neurologic function; however, clinical evaluation of the statins has been limited to a demonstration of associations between statin use and mortality, and perihematomal edema. Retrospective evaluation in a cohort of ICH patients demonstrated that prior statin use was found to be associated with decreased mortality with a greater than 12-fold odds of survival (p=0.05). The same patient population also demonstrated an association between statin use prior to ICH and decreased absolute and relative perihematomal edema at presentation [132]. There is a report of 1 small, prospective cohort of 18 patients treated with rosuvastatin compared to 57 historical controls [133]. The mortality rate during hospitalization was 5.6% in the statin group and 15.8% in the control group with an adjusted hazard ratio of 0.20 (95% CI 0.02-1.67), also suggesting that the use of statins during the acute phase of ICH may be associated with improved mortality.

The Simvastatin for ICH Study is a phase 2, randomized, blinded, placebo-controlled, efficacy study evaluating treatment with 80 mg of simvastatin or a placebo for 14 days on perihematomal edema. Secondary outcome measures include mortality at 30 days and functional outcome at 90 days. There is a planned sample size of 90 patients. The study began in 2008 and completion is expected in 2011 [134].

Other Treatment Considerations

Management of ICH in Patients on Concurrent Antithrombotic Therapy

The outcomes in individuals on antiplatelet therapy with an ICH are variable according to the available literature [135–139]. The best evidence includes a post-hoc analysis of the placebo arm of the CHANT study, which included 70 patients who were on antiplatelet therapy at onset of their ICH. The authors found that antiplatelet medications at ICH onset had no association with the volume of ICH at presentation, growth of ICH at 72 h, initial edema volume, or edema growth [139]. However, a meta-analysis by Thomson et al. [140] found that the use of antiplatelets at the time of ICH compared to no use was independently associated with increased mortality, but not with poor functional outcome. A retrospective analysis of patients who were on antiplatelet therapy prior to their ICH revealed they had an increased rate of death, and platelet transfusion did not prevent death or improve outcome [141]. Based on this limited information, some clinicians favor the use of platelet transfusion when patients present with an ICH and are on antiplatelet agents. There is data that reports an association with increased mortality when ICH patients receive blood products [142] and more information is needed to determine whether platelet transfusion should be a consideration for patients on antiplatelet therapy who present with ICH.

The Platelet Transfusion in Acute Intracerebral Hemorrhage trial was designed to help address this issue. This is an open-label study that will evaluate whether the use of antiplatelet agents results in an increased risk of hematoma enlargement after acute ICH. In addition, the study will evaluate the safety and efficacy of platelet transfusion for prevention of hematoma growth in patients who develop acute ICH while taking an antiplatelet agent. The primary outcome measure is hematoma growth within 24 h. Secondary outcome measures include Glasgow outcome, cardiovascular death occurring within the treatment period, death due to any cause occurring within the treatment, acute myocardial infarction, and venous thromboembolism at 90 days [143]. In addition, the Improving Platelet Activity for Cerebral Hemorrhage Treatment - DDAVP Proof of Concept (IMPACT) study is a phase 2, open label study in which patients who have spontaneous ICH are on aspirin or have a laboratory marker indicating the use of antiplatelet medication will receive a DDAVP injection (desmopressin acetate, 0.4 mcg/kg) to determine whether DDAVP improves platelet activity from baseline to 60 minutes after treatment start. The primary outcome measure is change in platelet activity, measured in seconds on platelet function assay, from pre to post-treatment [144]. Both of these studies will begin to fill a gap in the existing literature regarding the use of antiplatelets and blood products in the setting of ICH.

ICH associated with anticoagulation due to vitamin K antagonists is increasing in incidence [12]. Recent new anticoagulants, such as oral direct thrombin inhibitors, will likely contribute to the challenges of anticoagulation-related hemorrhages with more widespread use [145].

Individuals on warfarin with an international normalized ratio >3 have an increased risk for having larger hematomas [146]. To be able to potentially curtail the hematoma growth of different agents, including vitamin K (either with or without fresh frozen plasma), factor VII, and prothrombin complex concentrates have been used. There is no randomized controlled data to suggest that 1 agent is better than the other; however, the most recent guidelines for the management of ICH recommend against routine use of rFVIIa for warfarin reversal [147]. The dilemma of which agent to use is increased with oral direct thrombin inhibitors, such as dabigatran, and factor Xa inhibitors, such as rivaroxaban, as there are no proven therapies to reverse their anticoagulant effect.

Other Treatment Modalities Additional treatments that are being evaluated for ICH treatment include hypothermia [148, 149], stem cells, minocycline [98, 150], and rehabilitation interventions [151–153]. The latter treatment modalities are currently in the early stages of preclinical development. Regarding hypothermia, there is a planned clinical trial to evaluate the efficacy of hypothermia as acute treatment of patients with primary ICH. As of now, the trial is not yet open for enrollment. The primary outcome measures are neurologic function at 3 and 6 months. The trial will include patients with primary ICH who present with GCS≤8 and an ICH score of 2 to 4. Induction of hypothermia will begin within 6 h of symptom onset. Patients will be cooled to a core temperature of 34°C during 24 h with surface cooling [154].

Conclusions

Current challenges in developing treatment for ICH are the same challenges that are faced with acute ischemic stroke; these include having a solid preclinical foundation to inform clinical trials, choosing the appropriate clinical and surrogate outcome measures, and identifying the appropriate patient population. Given the challenges in addressing the heterogeneity of the patient population and the history of clinical trials in ischemic stroke, it may be necessary to consider changes in clinical trial design, such as adaptive designs for randomization, dose escalation, and outcome analyses.

To have an impact on this devastating disease, multiple treatment targets must be identified. The history of clinical trials in acute ischemic stroke tells us that the future of stroke treatment, both ischemic and hemorrhagic, will be multi-faceted with combined therapies aimed at both the primary and secondary injuries caused by disruption of the vasculature. In ICH, the most promising clinical trial was with the hemostatic agent, rFVIIa, which had a 4-h treatment window. Because a large number of patients with ICH may not be eligible for acute treatment options, given the well-known limitations in presentation to the emergency department, adjunctive therapy to more acute treatments are also being targeted. In addition, clinical and radiographic data are being used to identify the patient population most likely to respond to specific therapies. This multifaceted approach to the treatment of ICH lends hope for a treatment to be developed soon. The ideal treatment strategy will be one that is practical and applicable for both specialized stroke centers and community hospitals.

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