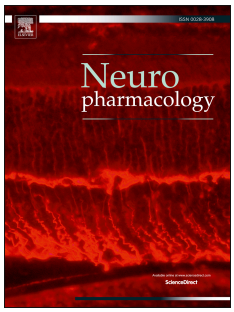
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Injury Mechanisms in Acute Intracerebral Hemorrhage

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Abstract

Intracerebral hemorrhage (ICH) is the most common hemorrhagic stroke subtype, and rates are increasing with an aging population. Despite an increase in research and trials of therapies for ICH, mortality remains high and no interventional therapy has been demonstrated to improve outcomes. We review known mechanisms of injury, recent clinical trial results, and newly discovered signaling pathways involved in hematoma clearance. Enthusiasm remains high for methods of minimally invasive clot removal as well as pharmacologic strategies to improve recovery after ICH, both of which are currently being evaluated in clinical trials.

Keywords: intracerebral hemorrhage; thrombin; iron; brain edema; hypertension; hematoma

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Injury Mechanisms in Acute Intracerebral Hemorrhage

1. Background

Intracerebral hemorrhage (ICH) is the most common hemorrhagic stroke subtype, with an estimated annual incidence of 16 per 100,000 worldwide, and an incidence over double that in the developed world (Sacco et al., 2009). The incidence of asymptomatic, clinically silent ICH is even higher, estimated at over 2 million cases per year in the U.S. (Greenberg et al., 2009; Leary and Saver, 2003). Both short-term and long-term outcomes for symptomatic hemorrhages are poor, with 1-month survival estimated at 60% (van Asch et al., 2010), and 5-year survival estimated at 29% (Poon et al., 2014). Outcomes are even worse when ICH extends to involve the ventricular system (Hanley, 2009). The association of ICH with advanced age means the number of new cases will likely increase with an aging population (Lovelock et al., 2007; Qureshi et al., 2009).

Spontaneous, non-traumatic ICH can be due to an underlying lesion such as a tumor, vascular lesion, or angiopathy, though the majority of cases in the adult population are not attributable to an underlying lesion. Hypertension is the most common systemic risk factor, present in up to 70% of ICH patients and associated with increased morbidity and mortality in all age groups (Mendelow et al., 2005; Ruíz-Sandoval et al., 1999). An increasing number of cases are associated with use of anticoagulant or antiplatelet medications. Cases associated with vitamin K antagonists have increased hematoma volume, rates of expansion, and ventricular extension, all of which portend worse prognosis (Biffi et al., 2011; Cervera et al., 2012; Flaherty et al., 2008; Kuwashiro et al.,

2010). Amyloid angiopathy is a significant etiology of bleeding in elderly patients, with certain apolipoprotein E alleles (e2, e4) leading to beta-amyloid deposition and weakening of the arterial walls (O'Donnell et al., 2000). Amyloid-associated ICH is more often in lobar areas of the brain, while hypertensive hemorrhages are more common in deep locations (Mehndiratta et al., 2012).

Most class I evidence for treatment of ICH is for supportive care, specifically care in a facility with neuroscience expertise, blood pressure control, and normalization of coagulation parameters or platelet counts (Hemphill et al., 2015). No interventional surgical or pharmacologic therapy has been shown effective in decreasing mortality or morbidity from ICH in trials in the U.S., though decompression of posterior fossa hemorrhage is widely accepted as decreasing mortality.

There has been a growing interest however in new therapies for ICH, both pharmacologic and interventional. This review examines injury mechanisms, results of recent trials for treatment and therapy, and new discoveries in the pathogenesis and repair after ICH.

2. Injury mechanisms

2.1. Primary brain injury

Mass effect and mechanical disruption from extravasated blood—either with initial hemorrhage or with continued hemorrhage and hematoma expansion—causes immediate primary brain injury due to both global increased pressure (increased intracranial

pressure or ICP) and mechanical compression of local structures (Fig. 1). The latter can be particularly deadly when bleeds occur in the posterior fossa, where local compression of the aqueduct of Sylvius can lead to obstructive hydrocephalus, or local compression of the brainstem may lead to cardiorespiratory dysfunction. Hematoma expansion is common, and in one study was noted to occur in over one-third of patients in the first 24 hours after ictus (Brott et al., 1997). Evidence of a 'spot sign' on computerized tomography (CT) angiography is highly sensitive and specific for predicting hematoma expansion when noted within 3 hours of symptom onset (Wada et al., 2007).

Global increases in ICP may lead to herniation syndromes causing arterial compression and resulting ischemia. In non-herniation syndromes though, both animal and clinical studies suggest that the reduced perihematoma blood flow seen with ICH is not low enough to cause a local ischemic penumbra or core (Orakcioglu et al., 2005; Schellinger et al., 2003), and may be due to reduced metabolic demand in the surrounding tissue, as evidenced by stable or decreased oxygen extraction fractions (Herweh et al., 2007; Qureshi et al., 1999; Zazulia et al., 2001). Strategies for mitigation of primary brain injury generally involve measures to prevent hematoma expansion with blood pressure control or correction of coagulopathy, or to physically remove or lyse the clot (sometimes accompanied by cerebrospinal fluid diversion), either through open surgical or minimally invasive approaches. It should be noted, however, that the benefit of surgical removal has, so far, not been proven in clinical trials in the U.S. (see below).

2.2. Secondary brain injury

Secondary brain injury is caused by the physiologic response to the hematoma (primarily edema and inflammation) as well as the toxic biochemical and metabolic effects of clot components. Strategies for prevention of secondary brain injury include not only clot removal but also pharmacologic strategies.

2.2.1. Edema

The formation of perihematomal edema can occur within hours of ICH and persist for days to weeks (Zazulia et al., 1999), with an average 75% increase in perihematomal edema within the first 24 hours after ICH (Gebel et al., 2002). A portion of edema develops due to clot retraction and serum protein accumulation around the clot with an initially intact blood-brain barrier (Wagner et al., 1996). Thrombin, an activated component of the final common pathway in the coagulation cascade that plays a prominent role in hemostasis after ICH, also plays a role in disruption of endothelial cells and the blood-brain barrier. Thrombin is implicated in the formation of vasogenic edema in experimental models (Lee et al., 1997), and its inhibition has been proposed as a way to reduce perihematomal edema after adequate hemostasis of the clot (Hamada and Matsuoka, 2000). Additionally, erythrocyte components, including hemoglobin and its degradation products (heme and iron), as well as carbonic anhydrase have been shown to contribute to brain edema in experimental models (Guo et al., 2012; Huang et al., 2002). Edema likely contributes to disruptions in cell wall ion processing, including that of K^+, Cl^-, and Na^+, though these disruptions may persist despite resolution of edema (Patel et al., 1999).

2.2.2. Inflammation

Previous studies have described the role of inflammation in both injury and recovery from ICH (Wang, 2010). Inflammatory responses both in the local perihematomal area as well as systemically are noted after experimental ICH (Illanes et al., 2011; Xue and Del Bigio, 2000), and both can have deleterious effects. Locally, diapadesis of neutrophils occurs within days and subsequently, microglia are activated. Their inhibition reduces brain damage in animal models (Wang et al., 2003). Experimental models have shown this brain inflammation is not restricted to the local area, as a receptor highly specific for leukocytes, intracellular adhesion molecule 1 (ICAM-1), has been noted in the contralateral hemisphere after experimental ICH (Gong et al., 2000). Aside from inflammatory cells themselves, other inflammatory mediators are upregulated with ICH, including tumor necrosis factor, adhesion molecules, and matrix metalloproteinases, and they appear to be involved in inflammation-related local brain injury (Hua et al., 2006; Ma et al., 2011; Masada et al., 2001). Hematoma size is predictive of the degree of systemic inflammatory modulation, and animals with larger hematomas are more prone to infection (Illanes et al., 2011). Clinically, systemic infection rates are high with ICH, with 31% of patients in one study having an infection following hemorrhage (Lord et al., 2014).

2.2.3. Blood product toxicity

The toxic effects of hemoglobin, iron, and other blood components on surrounding brain are thought to be another driver of secondary brain injury. The injection of lysed blood cells in an experimental ICH model caused marked edema, an effect not found acutely with injection of packed erythrocytes (Xi et al., 1998), suggesting the lysed products themselves are primary contributors to brain injury. Hemoglobin plays a role in injury, as it

inhibits the sodium-potassium pump and can cause neuronal depolarization and neuronal cell death in experimental models (Regan and Panter, 1993; Sadrzadeh et al., 1987; Yang et al., 1994). Iron is also implicated in ICH, and its chelation with deferoxamine reduced brain injury in animal models (Gu et al., 2009; Okauchi et al., 2010) (Fig. 2). The efficacy of iron chelation in patients is being studied in a clinical trial (Selim et al., 2011; Yeatts et al., 2013) (NCT02175225). Free-radical generation is one means by which iron may contribute to brain injury (Chen et al., 2011; Nakamura et al., 2005), though other sources also generate free radicals (Tang et al., 2005). Targeting free radicals with scavengers has been shown to reduce ICH-associated injury in experimental models (Hanley and Syed, 2007; Nakamura et al., 2008).

3. Therapeutic options—Results of recent clinical trials

An increase in the number of both preclinical and clinical studies over the past 2 decades have culminated in an increasing number of recently completed and ongoing trials (Keep et al., 2012). To summarize significant trial results from the past 4 years, a review of all clinical trials from clinicaltrials.gov was performed using the following terms: ICH, intracerebral hemorrhage, IPH, intraparanchymal hemorrhage, intracranial hemorrhage, IVH, intraventricular hemorrhage. All studies with results posted from 2013-2017 are contained in Table 1 and are summarized below.

3.1. Blood pressure control

Three recently completed trials examined the safety and efficacy of rapid lowering of blood pressure after ICH. ICH-ADAPT examined the effect of tight blood pressure control

(SBP <150) versus a higher threshold (SBP <180), finding no difference in the effect on perihematoma cerebral blood flow (Butcher et al., 2013), though it should be noted these were primarily small to mid-size hematomas, having an overall average volume of just over 25 cm^3. The finding of a lack of association between rapid lowering of blood pressure and ischemia established the safety (at least in the short term) of aggressive treatment of blood pressure, an issue being examined by larger trials already underway comparing aggressive versus less stringent control of blood pressure. The INTERACT2 trial examined the effect of intensive blood pressure control (<140 systolic) within 6 hours after ictus in patients presenting with elevated systolic pressure (>180 systolic). Although barely not reaching significance in finding a difference in the primary outcome of death or disability between intensive and less strict blood pressure control, the trial did show a modest increase in functional outcome on ordinal analysis of modified Rankin Scale (mRS) scores (Anderson et al., 2013). INTERACT2 and the earlier ICH-ADAPT study contributed the basis for the current guideline recommendations concerning blood pressure, namely that acute lowering to SBP <140 is safe (class I, level A) and may be effective for improving functional outcome (Hemphill et al., 2015). The ATACH-2 trial, however, did not support the conclusion that acute blood pressure lowering improved outcomes. It examined rapid (<4.5 hours), intensive blood pressure control (<140 systolic) in patients presenting with ICH and found no difference in death or disability compared with the standard treatment group (SBP <180). It also found a higher rate of adverse renal events seen in the intensive blood pressure control group (Qureshi et al., 2016). Despite two trials showing no significant benefit to the primary outcome of acute blood pressure lowering, the possibility of a mixed benefit/harm effect is possible, such that hematoma expansion is reduced but there can be

simultaneous hypoperfusion causing local ischemia in some patients (Butcher and Selim, 2016). Additional trials are ongoing that use magnetic resonance imaging (MRI) to assess for local ischemic changes with intensive blood pressure lowering (Gioia et al., 2017).

3.2. Therapy for ICH associated with antiplatelet agents

Current recommendations are to transfuse platelets for ICH with severe thrombocytopenia, but the utility of transfused platelets in patients with a history of antiplatelet agent use is uncertain. The PATCH study showed new findings however, demonstrating that patients taking antiplatelet therapy for at least 1 week prior to ICH did worse when randomized to early platelet transfusion after diagnosis of ICH compared to those managed without platelet transfusion. Its applicability to patients taking all antiplatelet agents is limited however, as over 70% of enrolled patients were taking only aspirin, with less than 20% taking dipyridamole and less than 5% using more potent adenosine phosphate (ADP) inhibitors (Baharoglu et al., 2016a).

3.3. Open surgery

Following the original STICH trial, which found no benefit to evacuation of supratentorial hematomas but a suggestion of differences in outcome when stratified by deep bleeds or those with intraventricular extension (Mendelow et al., 2005), the STICH II trial compared conscious patients with superficial supratentorial hematomas without intraventricular hemorrhage who were randomized to early open surgical hematoma evacuation versus medical management, finding no significant difference in the primary outcome of death or disability (Mendelow et al., 2013). There was a trend towards a

clinically significant survival benefit with surgery, and 21% of patients in the initial conservative treatment arm did go on to receive surgery. The current class I guidelines recommend surgery only for infratentorial hemorrhage, while stating that for most patients with supratentorial hemorrhage, the usefulness of surgery is unestablished (Hemphill et al., 2015).

3.4. Minimally invasive thrombolysis and clot removal

More recent trials have focused on minimally invasive efforts at thrombolysis, clot removal, or both. The MISTIE phase II trial, a small study designed to demonstrate safety and that minimally invasive removal with thrombolysis reduces ICH, showed equivalent outcomes between patients randomly allocated to minimally invasive surgery with alteplase thrombolysis compared with those randomized to best medical management. Asymptomatic bleeding was higher in the minimally invasive surgery plus alteplase group (Hanley et al., 2016), and a phase 3 trial is ongoing (NCT01827046). In a related study, stereotactic CT-guided endoscopic removal of hematoma without alteplase was safe and effective in a small number of patients, with a trend towards improvement in neurologic outcome (Vespa et al., 2016). Minimally invasive clot removal using a distinct endoscopic system (MISPACE) is being studied and compared with medical management, with a phase I study showing a high rate of clot removal with minimal adverse events (Labib et al., 2017), and an ongoing trial comparing with medical management (NCT02880878). Some minimally invasive strategies are already used extensively in Asia (Zhou et al., 2012). Two large clinical trials in Asia restricted to a small subset of ICH patients showed promise. A large, multicenter Chinese trial demonstrated improved functional outcomes after

minimally invasive removal of a narrow group of moderately sized basal ganglia ICH (Wang et al., 2009). A second from Korea likewise found better 1-month and 3-month mRS scores after minimally invasive treatment of basal ganglia ICH with size >30cm^3 compared to medical management (Kim and Kim, 2009). Additional trials in the U.S. are ongoing (NCT02654015).

Examining just the subgroup of ICH with intraventricular extension, the CLEAR III trial compared intraventricular injection of alteplase versus saline control in patients presenting with non-severe intraventricular hemorrhage and obstructive hydrocephalus, finding no difference in the primary outcome of death or disability. Mortality was higher in the saline (control) injection group, however this was tempered by a higher proportion of mRS 5 outcomes in the control group, indicating a shift from "death" to severe disability. Alteplase injection did not result in a higher rate of symptomatic bleeding (Hanley et al., 2017).

4. New pre-clinical discoveries in pathologic mechanisms of ICH

Pre-clinical studies have recently improved our understanding of the molecular basis of damage and repair in ICH and are increasingly being used to inform clinical trials (Keep et al., 2012). In this section we focus on some recent findings and particularly a developing concept that the hematoma may be a pharmacological target as well as more conventional targeting of the perihematomal tissue to induce neuroprotection. An overall schematic suggesting potential treatment modalities is outlined in Figure 3.

That hematoma resolution could be a pharmacological target was first suggested by the pioneering work of Zhao, Aronowski and colleagues, who found that peroxisome

proliferator-activated receptor (PPAR)-γ agonists could enhance the rate of resolution (Zhao et al., 2009). This has led to the current clinical trial of pioglitazone in ICH (Gonzales et al., 2013) (NCT00827892). Recent preclinical studies have also given insight on the regulation of hematoma phagocytosis. Cluster of differentiation 47 (CD47), an integrin-associated protein expressed on erythrocytes, plays a key role as a "don't eat me" signal and decreases with time in the hematoma (Fig. 4) (Cao et al., 2016). Its absence may result in more expression of pro-clearance M2 differentiated microglia/macrophages, with an ultimate result of faster clot resolution, with less brain swelling and less neurologic deficits in mice (Ni et al., 2016). Inhibition of CD47 is already under investigation in clinical trials to enhance phagocytosis in advanced cancers (NCT02367196) (Willingham et al., 2012) and is a candidate for future study as a therapy for ICH.

If erythrocytes within the hematoma are not phagocytosed, they may undergo lysis releasing potentially harmful hemoglobin and iron into the extracellular space. Cluster of differentiation 163 (CD163) is a known hemoglobin receptor involved in clearance of hemoglobin through microglia and differentiated macrophages, primarily through the CD163-heme oxygenase-1 (HO-1) pathway. CD163 was long known as a receptor mediating the intracellular uptake of hemoglobin into macrophages (Madsen et al., 2001). Recent studies have shown that CD163 is also expressed and involved in blood product clearance not only in glia, but also in neurons where it is upregulated in ICH (Chen-Roetling and Regan, 2016; Liu et al., 2017). The involvement of neurons themselves in hemoglobin clearance may be a proximate cause of neuronal damage after ICH. Treatment with iron chelators can reduce the upregulation of CD163 and decrease cell death (Liu et al., 2017).

The relative contributions of erythrolysis versus phagocytosis in blood clearance is an area of interest, though the time course of erythrolysis in hematomas is not well understood. Recently, erythrolysis was identified occurring earlier than previously suspected, within 24 hours of ICH (Dang et al., 2017). Early erythrolysis was correlated with upregulation of perihematomal CD163, and the degree of early erythrolysis correlated with the severity of neuronal loss. The early erythrolysis was detectable by T2* MRI and was facilitated by hypertension. Early erythrolysis and clearance via the CD163 mechanism are potential areas of further investigation.

Nuclear factor-erythroid 2 p45-related factor 2 (Nrf2), a transcription factor, is another recently discovered cell-signaling regulator of microglia function and hematoma clearance (Zhao et al., 2015). Upregulation of Nrf2 improved hematoma clearance in mouse and rat models of ICH, and hematoma clearance is impaired in Nrf2 knock-out mice. In vitro experiments suggest it reduces oxidative stress through its transactivation of cytoprotective target genes essential to cellular defense such as SOD (Park and Rho, 2002) and HO-1 (Alam et al., 1999), as well as by upregulating phagocytosis, likely through upregulation of one of its target genes, CD36.

5. Conclusions

ICH is the most deadly stroke subtype, yet no intervention has demonstrated improved outcomes. In fact some measures of supportive care previously thought beneficial, including very aggressive blood pressure lowering and platelet transfusion, have failed to show benefit in recent years. However, with the recent acceleration of research into ICH, including more preclinical studies and therapeutic strategies, it is hoped that better-

informed clinical trials stand a greater chance of positive findings when looking for an elusive, effective treatment for ICH.

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Figure Legends

Fig. 1. Axial computerized tomography (CT) scan showing spontaneous cerebellar intracerebral hemorrhage with intraventricular extension causing compression of the 4th ventricle and brainstem.

Fig. 2. Deferoxamine (DFX) reduces reddish zone around hematoma at days 3 and 7 in a piglet autologous blood injection intracerebral hemorrhage model. Values are mean ± standard deviation, n = 4, cross-hatch (#) denotes $p < 0.01$ vs. vehicle. Reproduced with permission of Wolters Kluwer Health, Inc. (Gu et al., 2009).

Fig. 3. A schematic of potential methods for reducing the harmful effects of clot-derived neurotoxins in intracerebral hemorrhage. The hematoma contains constituents (e.g., hemoglobin and iron) that can damage perihematomal neural cells directly or indirectly (e.g., by inducing neuroinflammation) – red arrow. These damaging effects might be reduced by several approaches: (1) preventing hematoma expansion after ictus (limiting the size of the hemorrhage), (2) evacuating the hematoma (although as yet there is no definitive evidence for surgical evacuation), (3) accelerating hematoma resolution (e.g., using PPARγ agonists, CD47 blockade), (4) preventing the release of the neurotoxins from the hematoma (e.g., by promoting phagocytosis of erythrocytes over red blood cell lysis, detoxifying neurotoxin while within the hematoma), (5) preventing the uptake of the neurotoxin into perihematomal cells (e.g., potentially CD163 inhibition), (6) preventing

cellular toxicity (depends on the individual neurotoxin but includes inhibiting cell injury pathways, 'neuroprotection', and inducing protective pathways in the cell).

Fig. 4. (A) Erythrophagocytosis (arrows) at days 3 and 7 in a piglet autologous blood injection model of intracerebral hemorrhage, with hemosiderin deposition (arrowhead) noted at day 7. Scale bar, 10 μm. (B) Time course of CD47 levels in the hematoma. Values are mean ± standard deviation, asterisk (*) and cross-hatch (#) denote $p < 0.05$ and $p < 0.01$, respectively, vs. 4-h. Reproduced with permission of Wolters Kluwer Health, Inc. (Cao et al., 2016).

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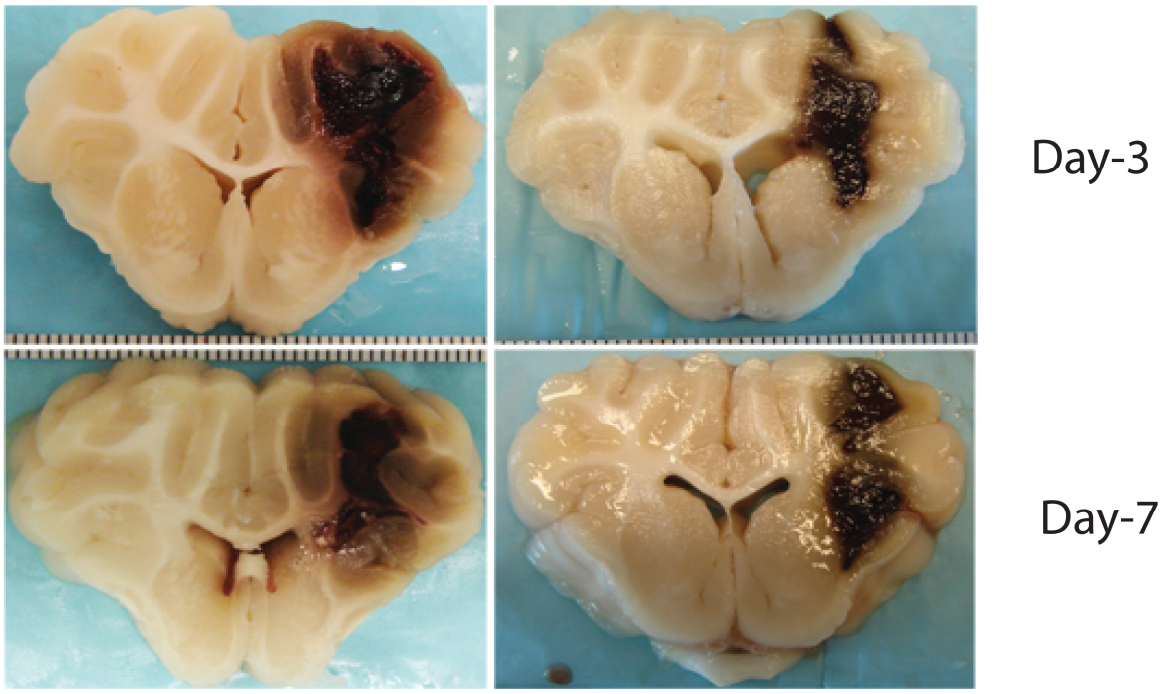
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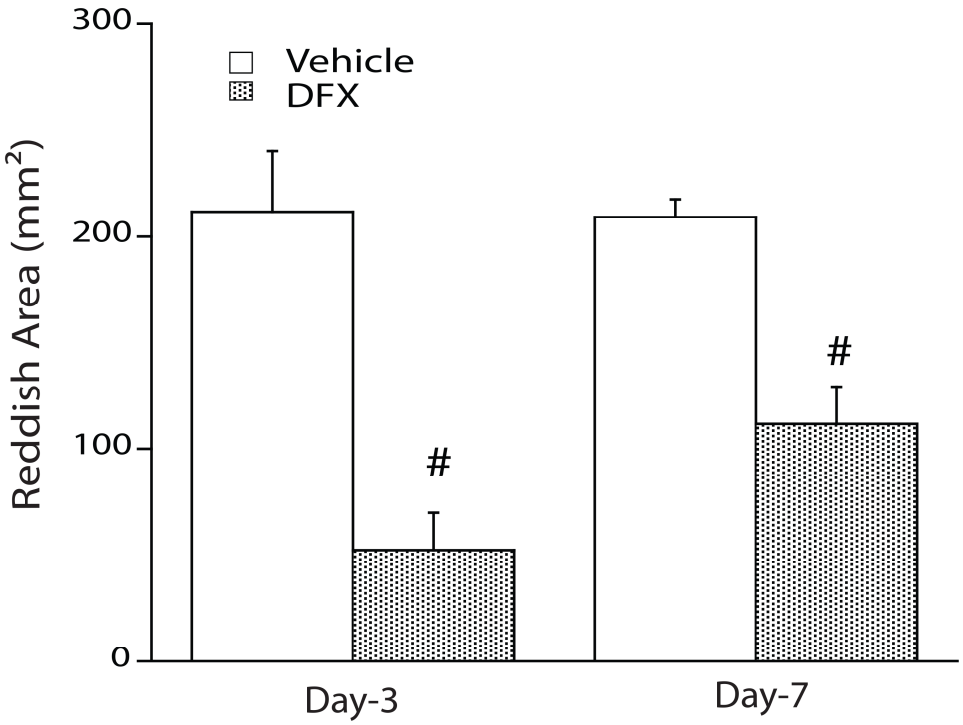
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Table 1: Clinical trials in intracerebral hemorrhage completed since 2013

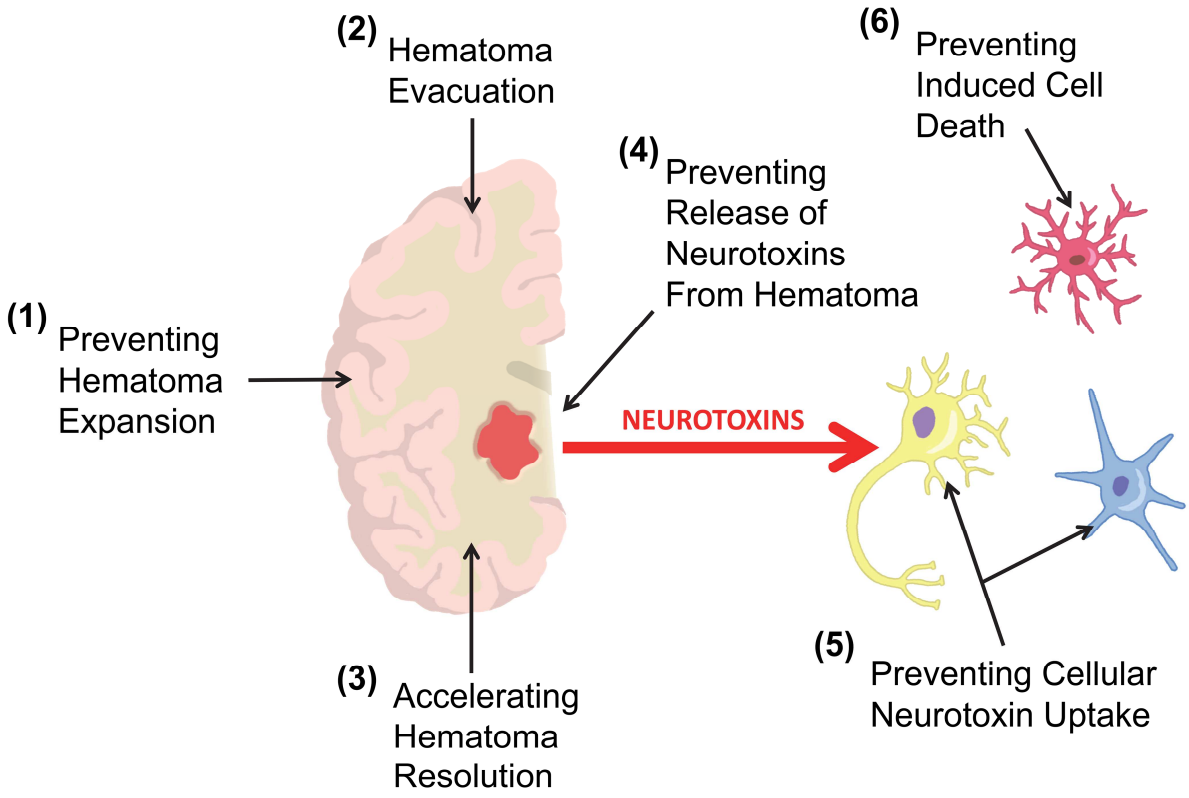
Year	Investigator	Acronym	Intervention	Target	Outcome
2013	Mendelow (Mendelow et al., 2013)	STICH II	Open surgery	Multiple	No benefit
2013	Anderson (Anderson et al., 2013)	INTERACT2	Blood pressure medications	Blood pressure, hematoma expansion	No benefit
2013	Butcher (Butcher et al., 2013)	ICH-ADAPT	Blood pressure medications	Cerebral blood flow, edema	No benefit
2016	Baharoglue (Baharoglu et al., 2016b)	PATCH	Platelets	Hematoma expansion	Worse outcome
2016	Qureshi (Qureshi et al., 2016)	ATACH-2	Blood pressure medications	Blood pressure, hematoma expansion	No benefit
2016	Hanley (Hanley et al., 2016)	MISTIE-2	Minimally invasive evacuation with tPA	Multiple	Safety, underpowered to determine benefit
2016	Vespa (Vespa et al., 2016)	ICES	Minimally invasive evacuation	Multiple	Safety, underpowered to determine benefit
2017	Hanley (Hanley et al., 2017)	CLEAR III	Intraventricular tPA	Multiple	No benefit
2017	Gladstone (NCT01359202)	SPOTLIGHT	Factor VIIa guided by “spot sign”	Hematoma expansion	No benefit (preliminary, unpublished)
2017	Flaherty (NCT00810888)	STOP-IT	Factor VIIa guided by “spot sign”	Hematoma expansion	No benefit (preliminary, unpublished)

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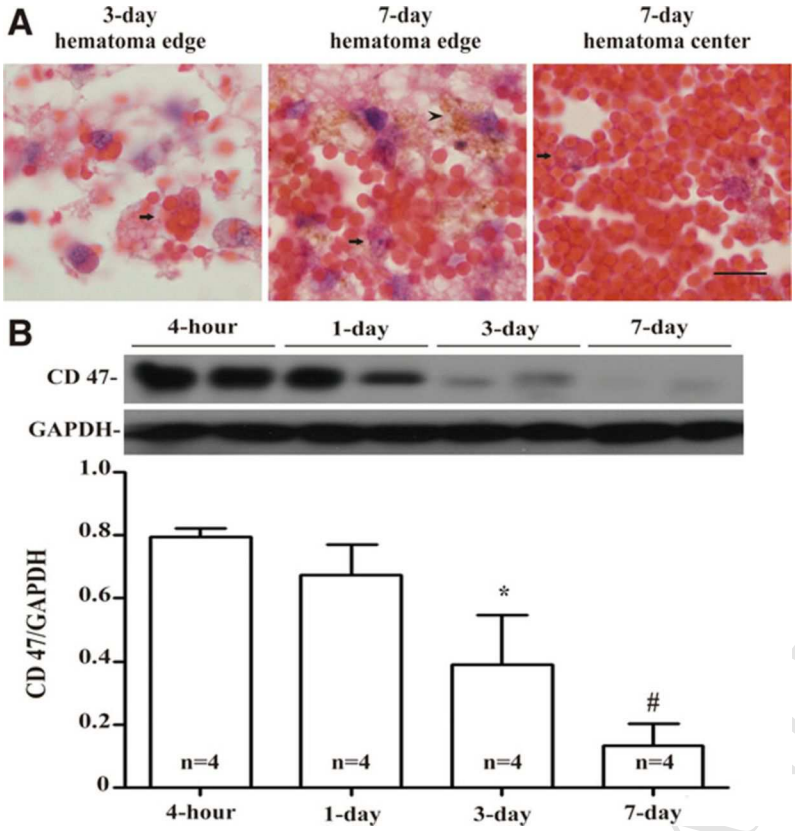

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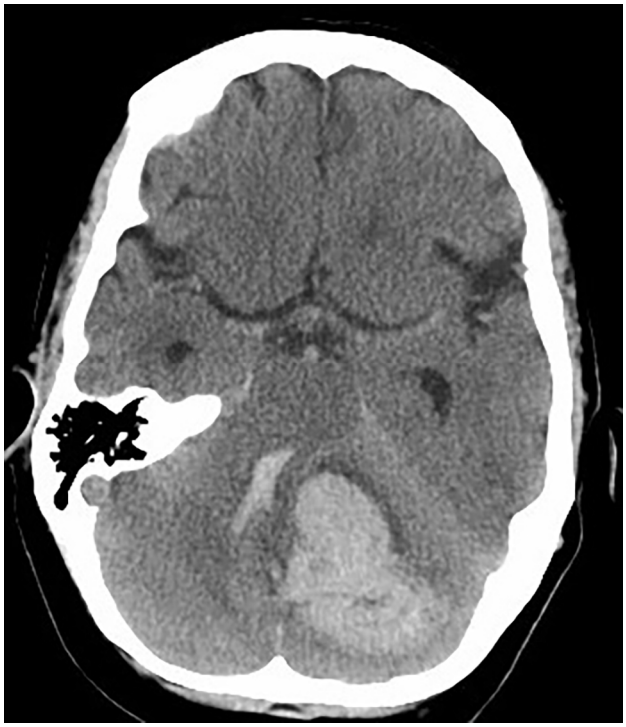
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Injury Mechanisms in Acute Intracerebral Hemorrhage

Highlights

1. Intracerebral hemorrhage remains a deadly hemorrhagic stroke subtype.
2. Trials of interventional strategies have failed to show a beneficial effect.
3. Multiple trials of minimally invasive clot removal strategies are underway.
4. Studies of hematoma clearance mechanisms may reveal pharmacologic targets.

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