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Intracerebral haemorrhage: mechanisms of injury and therapeutic targets

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Abstract

Intracerebral haemorrhage (ICH) accounts for about 10–15% of all strokes. ICH is associated with high mortality and morbidity and there has been no successful Phase III clinical trial for this condition. The last six years has seen a great increase in the number of pre-clinical and clinical studies focused on ICH. There have been significant advances in the animal models available to study ICH and in our understanding of the mechanisms underlying brain injury following haemorrhage. This has led to the identification of several therapeutic targets that are now being pursued into clinical trials. These advances are described in this review in addition to information on past and current clinical trials. Many of the former were based on very limited pre-clinical data and possible guidelines on the nature of pre-clinical results that justify proceeding to the clinic are discussed.

Keywords

intracerebral haemorrhage; brain oedema; thrombin; iron

Introduction

Intracerebral haemorrhage (ICH)is a stroke subtype that is associated with high mortality (~40% at one month[1]) and those that survive often have major neurological impairments. ICHaccounts for 10–15% of all strokes in the USA, Europe and Australia and 20–30% of strokes in Asia, with about two million cases worldwide per year.[2]In contrast to a marked reduction in overall age-adjusted stroke incidence, a recent meta-analysis found that the incidence of ICH has not declined between 1980 and 2008.[1] As yet, there is no proven (Phase III) medical or surgical treatment for ICH, although surgical decompression for cerebellar haemorrhages is widely accepted as potentially life-saving.[2, 3]

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Hypertension is the most common (~65%) cause of spontaneous ICH, with other major causes being: amyloid angiopathy, brain tumors, aneurysms, ateriovenous malformations, cerebral cavernous malformations and ateriovenous fistulae.[4, 5] However, ICH related to the use of anticoagulants is becoming increasingly frequent, now accounting for almost 20% of ICH in the USA.[6] Most case of ICH are ganglionic (putamen, caudate and thalamus), followed by lobar, cerebellar and pontine.[5]

In addition to symptomatic ICH,there are asymptomatic microbleeds. Studies on 'healthy' adults suggest that these occur in about 5% of the population[7] and rates of 11.1–23.5% have been reported in the elderly.[8] It has been estimated that there are approximately 2,000,000 silent first cases of ICH in the USA per year.[9] The long-term impact of such small haemorrhages is still uncertain. They are a marker of underlying vascular pathology and a risk factor for further cerebrovascular disease(e.g. the presence of microbleeds increases the risk of warfarin-associated ICH greater than 80-fold[10]). However, there is also the suggestion that they may impact brain function and contribute to vascular dementia and Alzheimer's disease.[11, 12]

Over the past twenty years there has been considerable progress made through animal and clinical studies in identifying mechanisms underlying ICH-induced brain injury[2, 5, 13–16]. The purpose of this review is to describe those injury mechanisms, potential therapeutic targets and comment on past and current clinical trials.

Natural History

Very large haemorrhages (>100ml) are associated with a very poor prognosis.[17] It should be noted that cerebrospinal fluid volume in humans is ~200 ml[18] and with large hemorrhages and associated perihaematomaloedema, this displacement capacity exhausted. With smaller haemorrhages, most patients survive the initial ictus but haematoma-induced secondary brain injury can result in severe neurological deficits and death.[5] In a subset of patients (~20–40%), there ishaematoma expansion during the first day after the initial ictus contributing to the mass effect of the ICHand such expansion is a predictor of worse outcome.[19–21] A rim of edema also forms around the haematomaadding to the mass effect and brain injury.[21] In humans, the edema increases rapidly after the ICH and peaks in about the second week after ictus (Figure 1).[21]The haematoma gradually resolves over weeks usually leaving a cavity with the destruction of brain tissue (brain atrophy, Figure 2).[22]

The location of an ICH is important in determining outcome and potential treatment. Thus,pontinehaemorrhages result in higher mortality and superficial haemorrhages may be more amenable to surgical removal.[23]Depending on location, bleeding from an ICH may extend into the ventricular system. Such intraventricular haemorrhages occur in ~40% of ICH patients and are a predictor of poor outcome.[24]

Seizures occur in about 8% of patients after ICH, mostly (~90%) within the first three days.[21] There are conflicting results on the impact of such seizures on clinical outcome.[21]

Animal Models of ICH

The major animal models that have been used to study ICH are direct blood or collagenase injection into different brain areas.[25, 26]These have both been performed in rodents and larger species. While the blood injection mimics the effects of an intracerebral haematoma in the brain, it does not have a disrupted vasculature as the source. In contrast, the collagenase injection does disrupt the vasculature, but there are concerns that the collagenase may have other non-haemorrhage related effects and that it causes disruption of multiple blood vessels including capillaries. Thus, there is need for caution in interpreting

results as there are apparent differences in the relative importance of different injury mechanisms between the two types of mode.[25] There are other less commonly used models including the spontaneously hypertensive stroke prone rat (SHRSP) and the hypertension related mouse models developed by Heistad and colleagues [27, 28]. Similarly, a mouse model of Alzheimer's disease results in haemorrhage.[29]

Recent advances have been made in examining known human risk factors for ICH using animal models. Thus, the blood injection model results in worse brain injury in aged compared to young rats[30] and, in a collagenase mouse ICH model, warfarin causes greater ICH.[31, 32]

For ischemic stroke, there has been considerable debate over the utility of animal models.[33] In reading the following sections on injury mechanisms and therapeutic approaches, it should, therefore, be noted that none of the preclinical studies have yet led to a successful Phase III clinical trial for ICH. However, the situation in ICH is somewhat different from ischemic stroke in terms of the number of clinical trials that have been undertaken and becausemany of the ICH trials were not based on direct preclinical data (e.g. haematoma evacuation and prevention of haematoma expansion trials) or were primarily based on preclinical data derived from non-ICH animal models, such as ischemic stroke. Thus, clinical trials on dexamethasone, mannitol and glycerol[34–36] were largely based on edema reduction in other neurological conditions and the CHANT and GAIN clinical trials of NXY-059[37] and gavestinel[38] were largely based on preclinical trials on ischemic stroke. Ongoing clinical trials which are examining agents which have undergone more preclinical testing will provide more information on the utility of ICH animal models.

Mechanisms of brain injury/therapeutic approaches

Primary injury

The initial bleed causes physical disruption of the cellular architecture of the brain and the mass of the haematoma may increase intracranial pressure which can compress brain regions, potentially impacting blood flow and leading to brain herniation. Because of the physical effects of the haematoma (mass effect), there have been many clinical trials examining the effect of clot removal. As yet, these trials have not shown a benefit for surgical evacuation.[39] One potential explanation for this lack of benefit is that the adverse effects due to the surgery negate the benefit of the evacuation. Two potential approaches are currently in clinical trial that may limit the former, the STICH II and MISTIE trials (Table 1; Fig.3). In the STICH II trial only superficial (< 1cm from cortical surface) lobar haemorrhages are being evacuated.[23] In the MISTIE trial, a minimally invasive approach with t-PA to assist evacuation is being used.[40] A similar trial is taking place in China (SATIH trial) as is a trial of lysis with ultrasound (SLEUTH trial[41]). It should be noted that ICH location is important for outcome and it is widely accepted that surgical decompression for cerebellar haemorrhage is potentially life-saving.[2, 3]

There have been relatively few pre-clinical studies examining the effects of clot evacuation. As it is difficult to remove haematomas in small animals, most evacuation studies have been in pig.[47, 48] Those studies have shown some benefit of very early evacuation after tPA-induced lysis, but there are problems in performing ultra-early clot evacuation in patients[49] where a subset of patients may be still bleeding or be susceptible to rebleeding.

Asa subset of ICH patients undergohaematoma expansion within the first day after ictus, preventing such expansion may be a method of limiting mass effect (and secondary injury). Two types of clinical trials have focused on such expansion. In the first type, agents have been used that alter the coagulation cascade or fibrinolysis. The initial Factor VIIa trials

showed promise in terms of reducing haematoma expansion but did not improve final outcome in patients.[43, 50] Factor VIIa use is associated with an increased rate of thromboembolic complications.[51] There has been, therefore, a focus on examining which patients may best benefit from Factor VIIa administration, either because there is evidence of haematoma expansion, the so-called spot sign (the current STOP IT and SPOTLIGHT trials), or because the patients were on anticoagulants or antiplatelet drugs at the time of ICH (http://www.strokecenter.org/trials/; PI Dr. A. Iorio). Other similar approaches that are being tested clinically are the use of platelet transfusions for patients on anti-platelet therapy (PATCH trial) and the use of aminocaproic acid, an antifibrinolytic agent (ATICH trial). Recently, in a small trial of 45 patients, Naidech et al. reported some benefit of early platelet transfusion in ICH patients with low platelet activity or who were known to have received anti-platelet therapy.[52]

There have been relatively few preclinical studies on the effect of haematoma expansion. Kawai et al.[53]didfind that Factor VIIa could reduce early haematomagrowth in a rat collagenase model. A growing number of groups are studying collagenase-induced ICH in warfarin treated animals.[31, 32]Illanes et al.[54]examined the effects of different methods of reversing warfarin anticoagulation on collagenase-induced ICH in mice and found smaller haemorrhages with prothrombin complex concentrate and frozen plasma and less effect with FVIIa and tranexamic acid.

The other approach focused on haematoma expansion are trials on lowering blood pressure (INTERACT [55], ICH ADAPT[56] and ATTACH[57] trials). It is still unknown whether these will show long-term therapeutic benefit but there is evidence of reduced haematoma expansion.[55, 57]There have been few preclinical examinations of the effects of blood pressure on haematoma expansion. Wu et al.[58]found no difference in haemorrhage volume between spontaneously hypertensive rats (SHR) compared to normotensive (WKY) controls after collagenase injection. However, SHR did have greater ICH-induced brain injury[58] suggesting that hypertension may have effects on ICH-induced brain injury other than by modifying haematoma volume. It is possible that acute changes in blood pressure (rather than prolonged hypertension) may be more important in haematoma expansion. Benveniste et al.[59]examined ICH after a brain biopsy and found no difference in haemorrhage volume between SHR and WKY rats, but found increased haemorrhage in normotensive WKY rats subjected to acute increases in blood pressure.

An alternate approach to reducing haematoma expansion is suggested by preclinical results from Liu et al.[60] They found that plasma kallikrein inhibits platelet aggregation and the haematomaexpansion could be reduced by plasma kallikrein inhibition or deficiency.

The extent to which peri-haematomalischaemiaoccurs after ICH is still controversial. With very large haematomas, intracranial pressure will rise, the brain herniates and blood flow will fall. If the tissue supplied by the vessel that ruptures has insufficient collateral supply and the vessel loses patency, this may also cause some drop in blood flow. Having said this, multiple clinical and animal studies have not reported changes in perihaematomal blood flow to levels expected to cause ischaemic damage but a few have.[61–66] It should be noted that interpreting blood flow in the perihaematomal tissue is complicated by changes in metabolism and edema formation. Thus, for example, Zazulia et al.[66]found that cerebral blood flow and the cerebral metabolic rate for oxygen were both decreased in the perihaematomal zone of patients, resulting in a reduced oxygen extraction fraction. These findings suggest that there is a zone of hypoperfusion without ischaemia. Recent data indicates that declines in cerebral metabolism may reflect mitochondrial damage rather than ischaemia.[67]The impact of oedemaon blood flow should also not be underestimated. Wagner et al.[68]reported that perihaematomal% water content in the white matter of pig increased

from 73 to 86%. In terms of water content (g/g dry weight), this represents a 127% change, while tissue swelling was 93%.

Secondary injury

Broadly, secondary injury after ICH may be caused by a cascade of events initiated by the primary injury (mass effect/physical disruption), by the body/tissue response to the haematoma (e.g. inflammation) and the release of clot components (e.g. haemoglobin/iron).Most recent preclinical studies have focused on the role of the last two. Compared to ischaemic stroke, there have been few clinical trials of agents targeting secondary brain injury in ICH (Table 1). This section describes the preclinical data, the evidence that these pathways occur in humans and whether these have then led to clinical trials (Table 1; Figure 3).

Thrombin—An initial tissue response to ICH is activation of haemostaticmechanisms to limit the bleeding. Thrombin plays a central role in that haemostasis. However, there is also much evidence that thrombin can participate in ICH-induced injury. Direct infusion of large doses of thrombin into brain causes inflammatory cell infiltration, mesenchymal cell proliferation, scar formation, brain oedema formation and seizures.[69]Thrombin has effects on multiple cells types including brain endothelial cells, leading to blood-brain barrier (BBB) disruption and brain oedemaformation[70, 71],neurons and astrocytes, which it can kill at high concentrations *in vitro*[72–74], and microglia, which it activates.[75] Thrombin activates potentially harmful pathways. For example, thrombin induces apoptosis in cultured neurons and astrocytes [76] and activates Src kinase[70, 77] which is thought to contribute to mitogenic stress, excitoxicity, vascular hyperpermeability and inflammation.[78]

Studies from our group and others have shown that thrombin inhibition can reduce ICH-induced injury[5, 79–81]. There is a brief report that thrombin also mediates brain injury in human ICH, with perihaematomal brain oedema being less after systemic treatment with argatroban, a thrombin inhibitor[82]. Drug administration was only started 24 hours after the haemorrhage to prevent rebleeding.

While high concentrations of thrombin may mediate ICH-induced brain injury, low concentrationsareneuroprotective.[72, 73, 83] Thus, the effect of thrombin may depend on haematoma size and proximity to the haematoma. In addition, there is evidence that thrombin is involved in brain recoveryand neurogenesisafter ICH.[84, 85]

Although the best-known effect of thrombin is cleavage of fibrinogen to fibrin, other effects are mediated by three protease-activated receptors (PARs). PAR-1, PAR-3 and PAR-4, are thrombin receptors.[79] Expression of thrombin receptor mRNA is found in neurons and astrocytes[86, 87] and thrombin receptor immunoreactivity has also been found in human brain tissue[88].Studies indicate that PAR-1 mediates some of the pathological effects of thrombin and are involved in ICH-induced pathophysiology.[81]

Inflammation—There is a pronounced inflammatory reaction after an ICH with activation of resident microglia, an influx of leukocytes into the brain and the production of inflammatory mediators.[13, 89–91]Multiple animal studies have indicated that inflammation plays an important role in ICH-induced injury but also brain recovery. The impact of modulating inflammation on human ICH-induced brain injury has yet to be determined.

There is an activation of microglia in the brain after animal models of ICH. This is an early response (starting at ~1h), that peaks after 3–7 days and persists 3–4 weeks. A number of, but not all, studies have shown a benefit of inhibiting microglia activation after ICH with tuftsin or minocycline.[89] However, as with cerebral ischaemia, the effects of microglia in

ICH-induced brain injury may be both detrimental and beneficial (e.g. clot resolution), and the net effect may be time-dependent.[89]

Neutrophils are the earliest leukocyte to enter the brain after ICH.[89] Evidence indicates that they participate in ICH-induced brain injury by producing reactive oxygen species, proinflammatory proteases and by disrupting the blood-brain barrier.[89]Monocytes also enter the brain from the blood-stream after ICH and a recent study indicated that neutrophil depletion reduced monocyte entry.[92] It appears that the toll-like receptor 4 on leukocytes is important in the infiltration of both neutrophils and monocytes.[93]

Two cell types that have received little attention in ICH are resident mast cells and infiltrating lymphocytes. Recent studies, however, have shown that both have a role in ICH-induced injury.[94, 95] As with ischaemic stroke, the role of these cells deserves further investigation.

ICH is associated with a marked upregulation of a wide array of inflammatory mediators in the brain in both animals and humans.[96, 97] These include marked increases in cytokines such as tumor necrosis factor-α and interleukin-1β, chemokines, adhesion molecules, and matrix metalloproteinases (MMPs) such as MMP-9 and −3. Evidence indicates that these inflammatory mediators are involved in ICH-induced brain injury in animals.[89, 98–100]

Blood-brain barrierbreakdown occurs after ICH. This may both contribute to inflammation by promoting leukocyte infiltration and be a consequence of inflammation as leukocyte-derived reactive oxygen species, pro-inflammatory cytokines, chemokines and MMPs have all been implicated in BBB disruption.[101]As well as promoting inflammation, BBB disruption contributes to vasogenic edema formation after ICH.

The cyclooxygenase inhibitor, celecoxib, has been examined in the ACE-ICH pilot clinical trial but the results have yet to be reported (http://clinicaltrials.gov).Another agent that has anti-inflammatory actions, pioglitazone, is currently undergoing clinical trial for ICH (SHRINC[102]), although this drug has multiple effects other than on inflammation. Similarly, two statins that have anti-inflammatory actions as well as other effects, rosuvastatin and simvastatin, have also been examined in clinical trials. The rosuvastatin trial was a preliminary study and showed some suggestion of a positive effect.[46]The simvastatin trial was closed because of poor enrollment (http://clinicaltrials.gov).

Complement—The complement system is involved in immune reactions, including cell lysis and the inflammatory response.[103] The plasma protein components of the complement system are normally excluded from the brain by the BBB, but they may enter the brain after ICH as part of the haemorrhage or following BBB breakdown and there is evidence of complement activation and formation of the membrane attack complex (MAC, consisting of C5b-9) in the brain after ICH.[104, 105] The MAC is involved in erythrocyte lysis and may, therefore, be involved inhaemoglobin and iron release resulting in perihaematomal tissue damage (see below; Figure 4). It also may also induce direct injury in perihaematomal neurons, glia and blood vessels. In addition, complement cascade activation produces C3a and C5a, powerful chemoattractants for leukocytes and activators of microglia and mast cells which may enhancethe inflammatory response ICH.[103] Multiple studies have shown that inhibiting the complement cascade by depleting components, antagonists or gene knockout, reduces ICH-induced brain injury (reviewed by Ducruet et al.[103]). There are, though, some conflicting results regarding C5, with a C5a inhibitor being protective[106] but C5 deficient mice having increased ICH-induced brain injury.[107] This difference may reflect some compensatory changes to C5 loss in the deficient mice. As with the inflammatory system, while complement activation may enhance brain injury early after ICH, there is

evidence that the complement cascade may also have beneficial effects on long-term brain repair.[103]

Haemoglobin, iron and free radicals—There is mounting evidence that haemoglobin and iron release from the haematoma is a major contributor to ICH-induced brain injury (Figure 4). Intracerebral injection of lysed erythrocytes into the rodent brain causes brain injury and this is mimicked by infusion of haemoglobin and iron.[108, 109]After ICH, there is a build-up of iron in tissue around the haematoma (Figure 5) [110, 111]and use of an iron chelator, deferoxamine, reduced ICH-induced brain injury in rat and pig models (Figure 6)[30, 112], although less or no protection was found in collagenase models.[113, 114]Deferoxamine is currently in clinical trial for ICH.[115]Inhibitors of haeme oxygenase, which are involved in the breakdown of haeme to biliverdin, carbon dioxide and iron, or deletion of haeme oxygenase-1, also reduce ICH-induced brain injury.[116–118]

One mechanism by which iron might cause tissue damage is through the generation of free radicals. There is evidence of free radical mediated damage after ICH[119–121] and free radical scavengers reduce ICH-induced injury in animals.[13, 122] However, it should be noted that there may be multiple sources of free radicals after ICH (e.g.[123]).NXY-059, a free radical spin trap agent, was examined in ICH patients as part ofthe CHANT trial and no evidence of benefit was found.[37]The reason(s) for this negative outcome are uncertain but may reflect insufficient BBB permeability or inability to neutralize the high levels of free radicals produced after ICH.[13]

Other blood components—While haemoglobin is the major intracellular component of erythrocytes, it is not the sole component. A recent study showed that intracerebral injection of carbonic anhydrase 1,another major component, could cause brain injury and treatment with a carbonic anhydrase inhibitor reduced ICH-induced injury in rats.[124]

Glutamate—While glutamate-induced excitoxicity plays a major role in cell death after cerebral ischaemia and there is some evidence that glutamate may also participate in ICH-induced brain injury.[16, 125, 126]However, some of the underlying mechanisms may be specific for ICH. The initial bleed results in an influx of glutamate from the blood stream and the production of thrombin after haemorrhage results in Src kinase activation which phosphorylates NMDA receptors and augments their function.[126] In contrast to cerebral ischaemia, glutamate receptor antagonists have not been examined in human ICH apart from one small trial with a NMDA antagonist,CP-101,606, which primarily focused on traumatic brain injury.[127]

Seizures—Clinical and subclinical seizures occur in about 8 and 30% of ICH patients, respectively.[21] The causes of such seizures are still unknown and there has been a paucity of animal studies examining ICH-induced seizures. However, the seizures may be related to increased extracellular glutamate and a down-regulation in GABA and potassium channels after ICH.[96] In addition, intracerebral thrombin can elicit seizure activity in rats.[128] Whether seizures impact outcome after ICH is a matter of controversy.[21]

Spreading Depression—Waves of spreading depression have been reported in a pig model of ICH[129] and in >60% of patients with ICH.[130] There has been considerable interest in the role of spreading depression in ischaemic injury[130] where the energy required to repolarize may compromise already damaged and energy-depleted cells. The impact on spreading depression on perihaematomal and more distant cells after ICH has received very little attention and deserves more investigation.

Cell death pathways—ICH results in peri-haematomal cell death and brain atrophy.[131] The cell death pathways involved appear to be a mixture of necrosis and apoptosis, although there has been debate about which predominates.[132, 133] A number of groups have used a variety of approaches in animal ICH models to reduce apoptosis and brain injury (e.g.[134,135]). Taurourodeoxycholic acid, an anti-apoptotic compound, is currently undergoing clinical trial (http://www.strokecenter.org/trials/; PI Dr. A. Qureshi). Citicoline, a membrane stabilization agent, is also being investigated.[44, 45]There is also evidence that autophagy occurs after ICH, although it is still uncertain whether this is a detrimental or a beneficial pathway.[136]

Endogenous defense mechanisms—After an ICH there is an upregulation of a variety of endogenous proteins that may serve to protect the brain from the injury mechanisms described above. Thus, for example, there is a marked upregulation of iron-handling proteins such as ferritin.[110] The transcription factor nuclear factor- erythroid 2-related factor 2 (Nrf2) that responds to oxidative stress may be involved in regulating some of the antioxidant defense mechanisms. Wang et al. found that brain injury after collagenase-induced ICH was enhanced in Nrf2 knockout mice.[137]

There has been considerable interest in using drugs to upregulate these defense mechanisms. Nrf2 can be upregulated by a range of agents including sulforaphane, a component of broccoli, which protects against ICH-induced brain injury in mice and rats via a Nrf2 dependent mechanism.[138]PPAR-gamma agonists may also exert some of their benefit after ICH by upregulating cellular defense mechanisms, including catalase.[139]

Pluripotent agents—Some of the agents that are being tested preclinically have multiple actions and this may be beneficial ICH. For example, minocycline acts as an iron chelator as well as an inhibitor of microglial activation[111] and pioglitazone affects haematoma resolution and upregulates endogenous defense mechanisms.[139] Erythropoietin, albumin and statinsare other examples of pluripotent agents that reduce ICH-induced brain damage in animal models.[140–142] That agents may have more than one protective effect makes them attractive potential therapeutics and pioglitazone (SHRINC[102]) and albumin (ACHIEVE; http://clinicaltrials.gov/) are being examined in clinical trials. Simvastatin (http://clinicaltrials.gov/) was also being examined but the trial was closed due to poor enrollment.

Hypothermia is an archetypal form of treatment that affects multiple treatments. It has been extensively studied in animal ICH models. Prolonged mild hypothermia improved functional recovery and brain oedema without affecting lesion size.[143, 144]There is a current clinical trial examining the use of ibuprofen to aggressively low temperature in ICH patients with fever (http://clinicaltrials.gov/).

Brain RecoveryAfter ICH

If patients survive the initial days after the ICH, there is gradual clot resolution and patients may recover some neurological function, although this recovery is almost always incomplete. The improvement of function may involve clot resolution, subsidence of the acute injury (e.g. reduced oedema), neuronal plasticity with surviving neurons (including the contralateral hemisphere) taking on new functions, and possibly neurogenesis. The recovery of function can be pronounced, as in rodent ICH models.[145]

A variety of methods have been used preclinically to try and enhance this recovery process. Microglia and blood-derived macrophages are involved in the clearance of extravasated erythrocytes by phagocytosis, thereby limiting the release of potentially toxic lysate products into the extracellular space (Figure 4). Zhao et al. have shown that it is possible to

enhance this phagocytosis by administration of peroxisome proliferator activated receptor (PPAR)-gamma agonists, rosiglitazone and pioglitazone.[139, 146]PPAR-gamma agonists speed haematoma resolution and reduce ICH-induced deficits in rodents[139, 146] and pioglitazone is in phase I clinical trial for ICH (SHRINC trial). As noted above, PPAR-gamma agonists may also act to protect the brain after ICH by upregulating cellular defense mechanisms.[139]

There has been much interest on how to implement rehabilitation in order to maximize neurological recovery. Auriat et al. found that in rats with ICH forced running had no effect on outcome but delayed exposure to an enriched environment and skilled reach training improved both neurological outcome and reduced lesion volume.[147–149] This improvement was associated dendritic complexity rather than neurogenesis.[149]

As with ischaemic stroke, there has been considerable interest in whether stem cells might improve outcome after ICH.A number of studies have demonstrated an improvement.[150] For example, Seyfried et al.[151]havefound that intravenously injected bone marrow cells migrate to the lesion site after ICH in rats and improved neurological outcome. One factor that may limit the impact of exogenous stem cells on outcome is cell survival. Lee et al.[152]found that genetically modifying human neural stem cells to overexpress Akt1 increased their survival in mouse ICH model and enhanced their protective effects on the brain.A clinical trial is currently underway in China to examine the effects of stem cell transplantation in ICH patients (http://www.strokecenter.org/trials/; PI: Dr. AnYihua).

Past Reflections/Future directions

In the past two decades there has been a marked increase in the amount of pre-clinical and clinical research on ICH. This has resulted in much new information about injury mechanisms and potential therapeutic targets. However, this has yet to result in any therapy for ICH. The mechanisms believed to be involved in ICH-induced brain injury differ in type, magnitude and timing from ischaemic stroke and this should be taken into account when designing clinical trials. In the past, in some cases, there has been very little published preclinical ICH evidence before a drug has been tested in human ICH patients (e.g. dexamethasone[34], gavestinel [a glycine antagonist[38]], mannitol[35]). Indeed, while there have been many complaints about animal models of cerebral ischaemiafailing to predict therapeutic efficacy, it is only very recently that clinical ICH trials have been based on preclinical testing. Time will tell on the utility of ICH preclinical models for informing clinical trials.

Search strategy and selection criteria

This review focuses on research on ICH in the period January 2005-April2012 to cover the period since our last review in Lancet Neurology was submitted.[5] All papers referencing ‘intracerebral haemorrhage/hemorrhage’ and ‘intracerebral haematoma/hematoma’ during that period in MEDLINE in English were reviewed. Articles were selected for their conceptual importance and primacy. Where issues are controversial, evidence on both sides of the issue are given.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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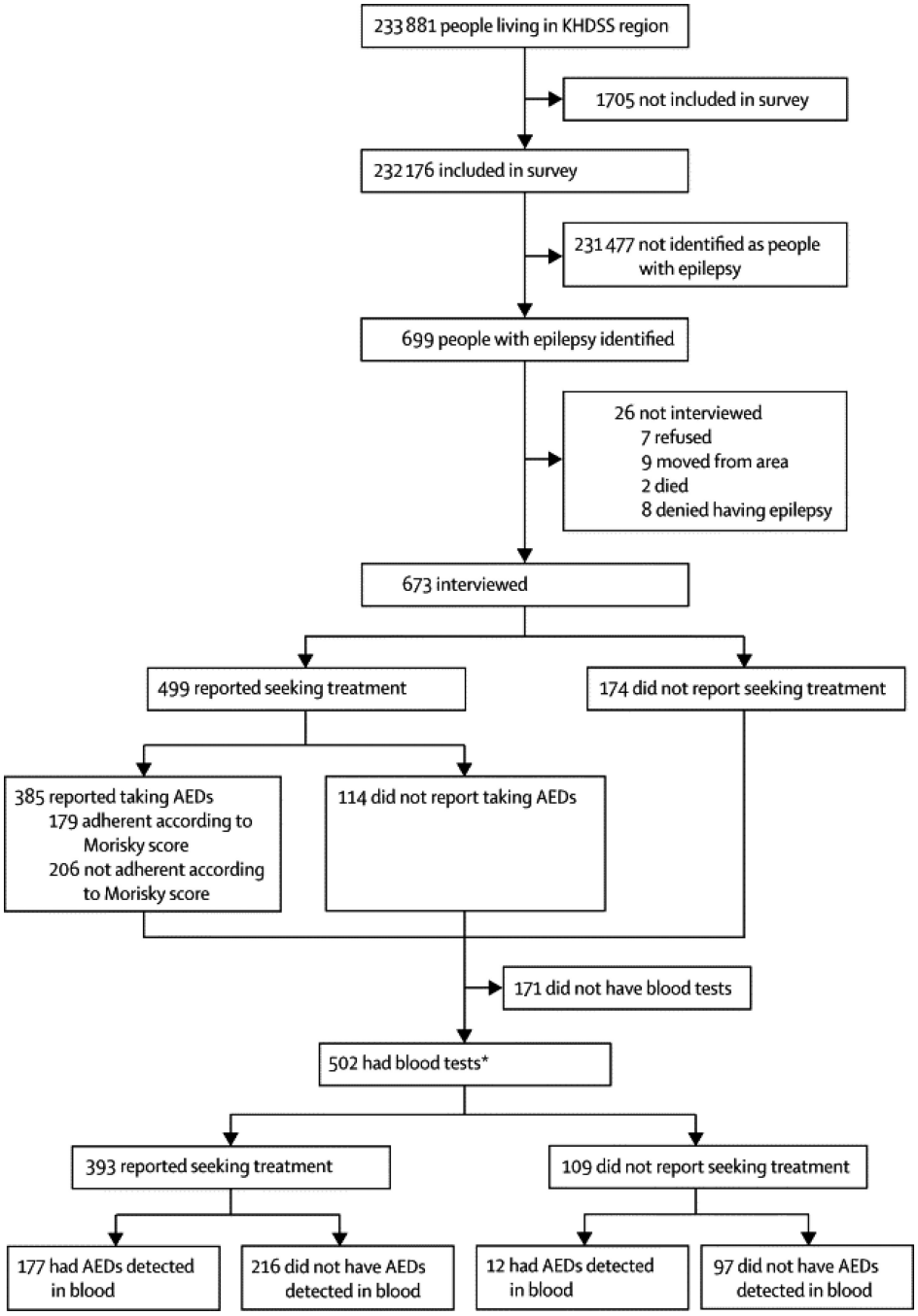

Figure 1.
CT scan showing perihaematomaloedema (hypodensity zone) at 14 days after intracerebral haemorrhage. Note the marked perihaematomaloedema with midline shift.

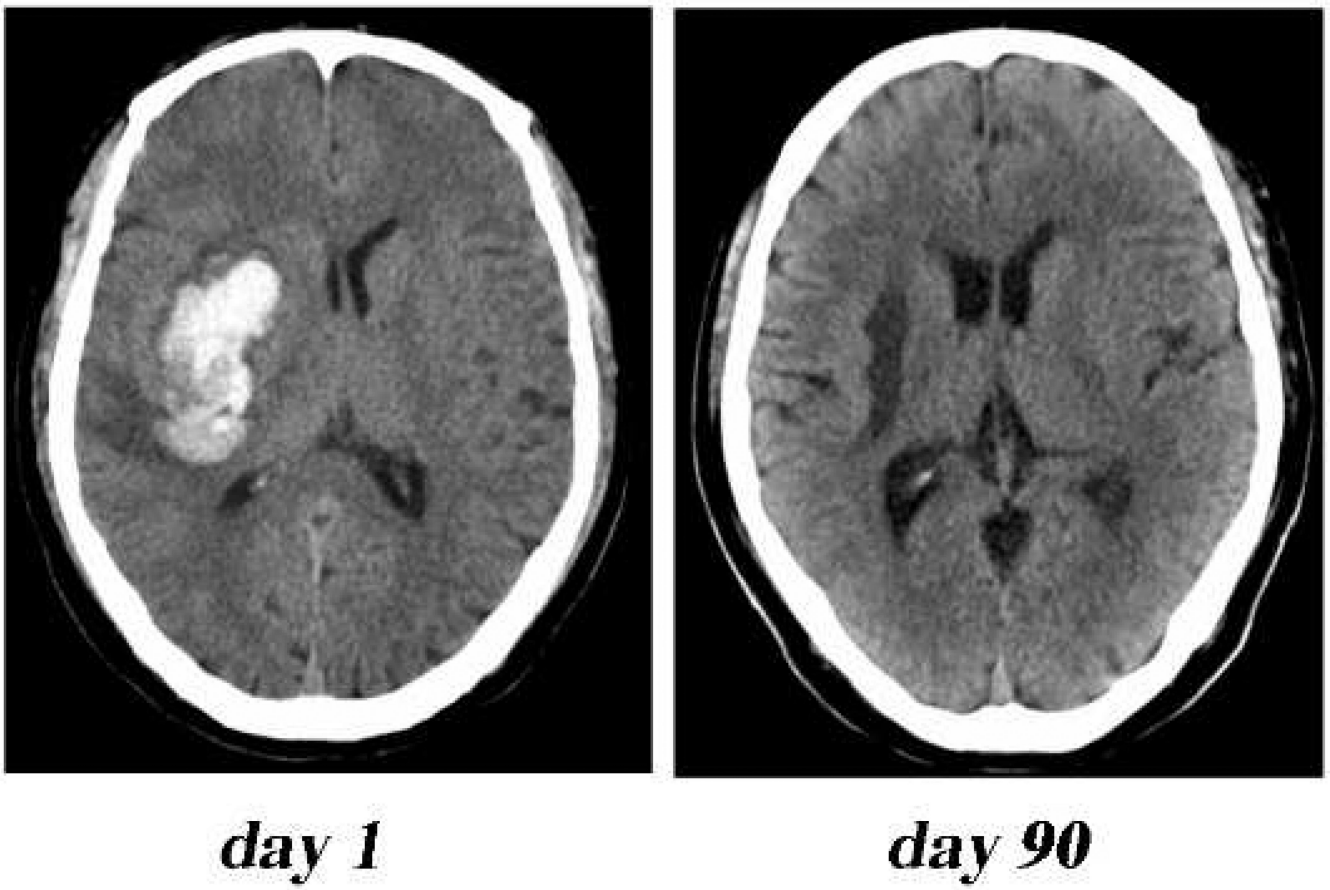

Figure 2.
CT scan showing marked brain tissue loss (atrophy) at day 90 after intracerebral haemorrhage. Note the dilated ipsilateral ventricle, fluid filled cavity and enlarged sulci.

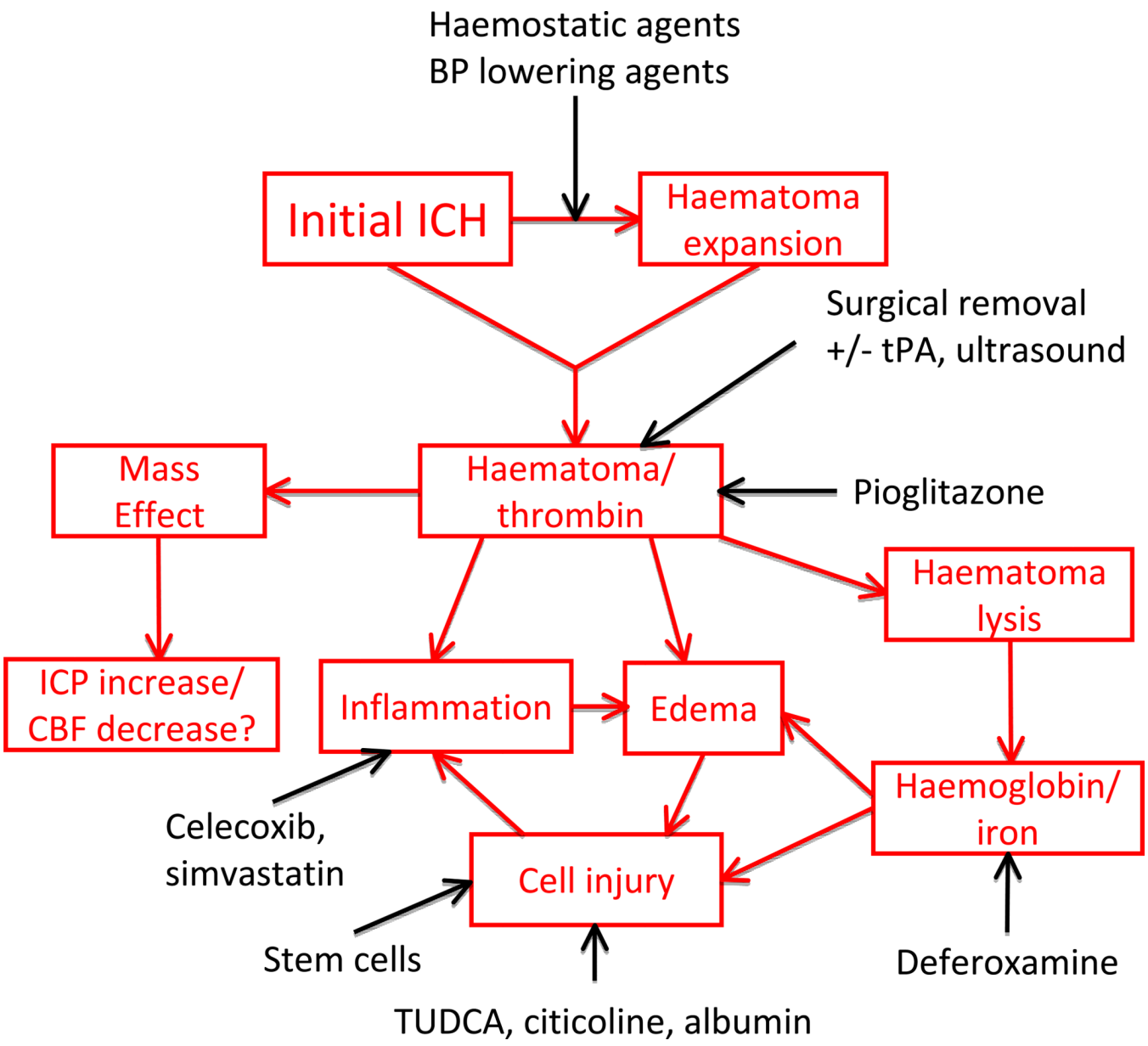

Figure 3.

Current clinical trials for ICH in relation to proposed injury mechanisms. Note that surgical removal of the haematoma and prevention of haematoma expansion may potentially reduce injury by affecting multiple downstream mechanisms. Pioglitazone accelerates haematoma resolution in rodents but it also has multiple other effects (on free radical and inflammation induced damage. Similarly, as well as inhibiting inflammation, simvastatin has multiple actions on different systems and albumin has effects on edema and vascular integrity as well as cell injury. ICH, intracerebral haemorrhage; tPA, tissue plasminogen activator, TUDCA, tauroursodeoxycholic acid.

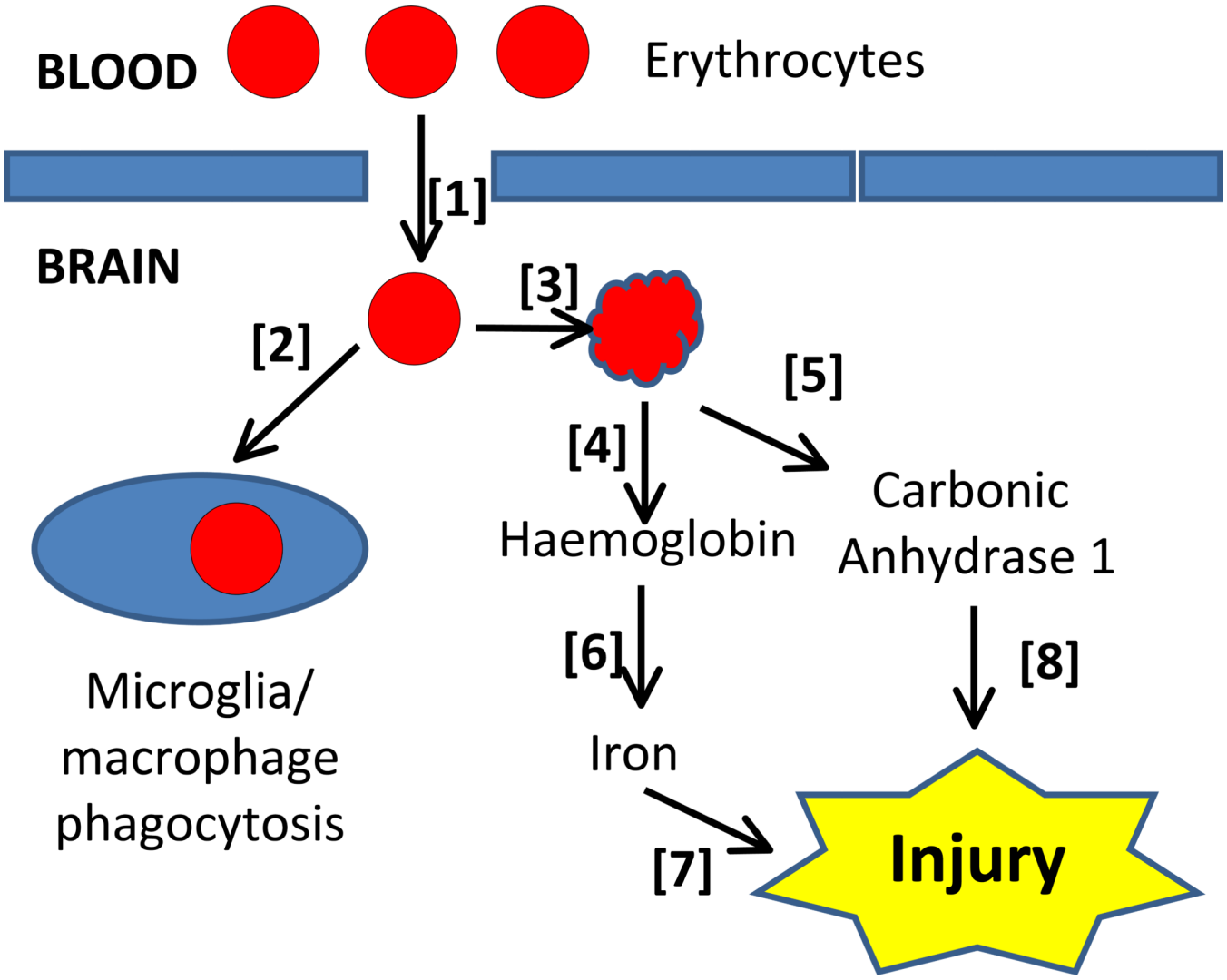

Figure 4.

After an ICH [1], erythrocytes may eventually be engulfed by microglia/macrophages [2] or lyse [3] because of complement activation or energy depletion. Erythrocyte lysis will result in the release of haemoglobin [4] and other intracellular contents such as carbonic anhydrase 1
[5]. Haeme from haemoglobin is degraded by haeme oxygenase [6] to release iron. Both iron and carbonic anhydrase 1 have been implicated in inducing brain injury after ICH [7] and [8].

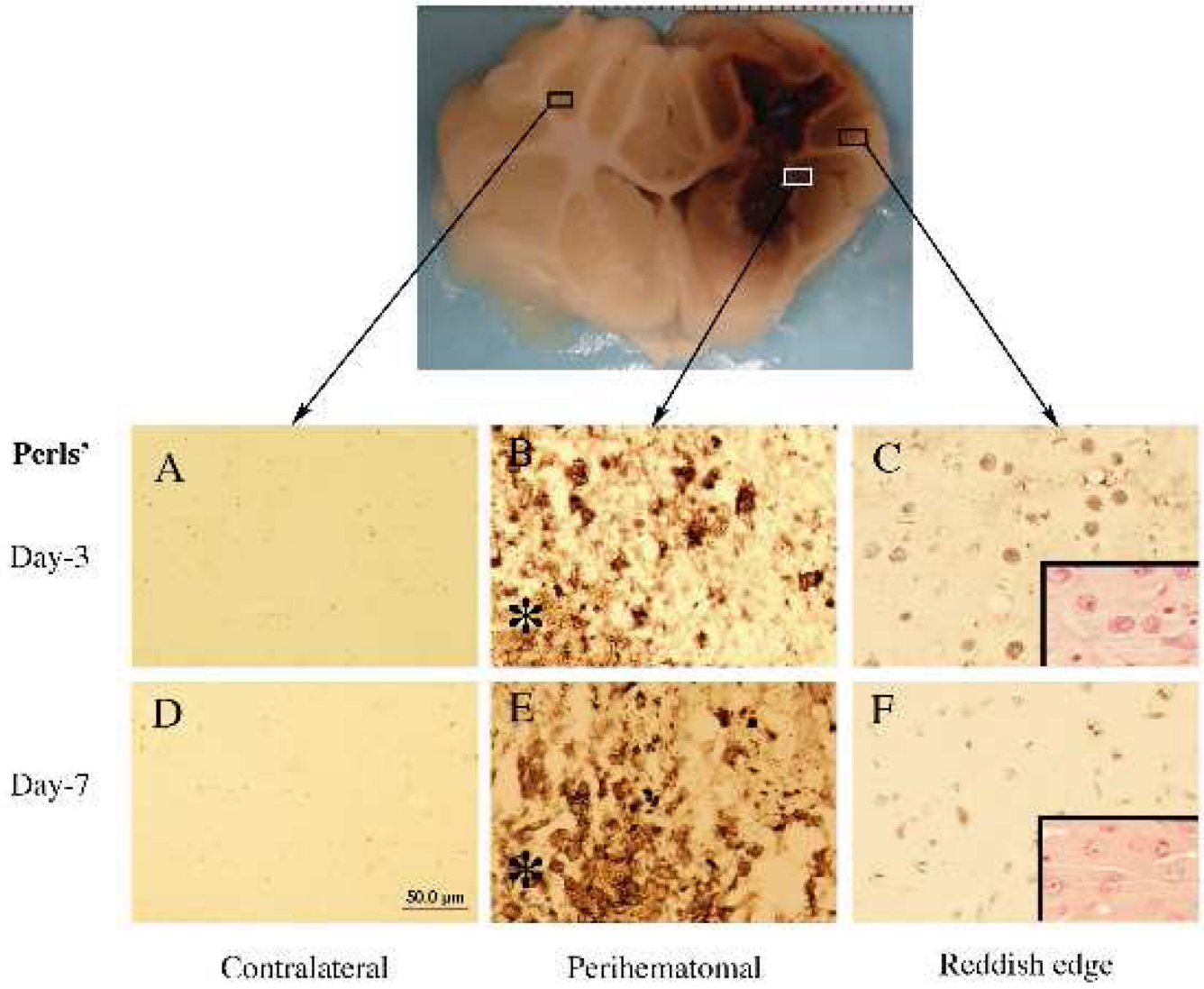

Figure 5.
Iron histochemistry (Perls' staining) in the brain 3 days after intracerebral haemorrhage in pigs. Asterisk indicates the haematoma. Insets in C and F: hematoxylin and eosin staining. Scale bar (A–F)=50 μm. Figure reprinted with permission from Gu et al., *Stroke*, 2009;40:2241–2243.[112]

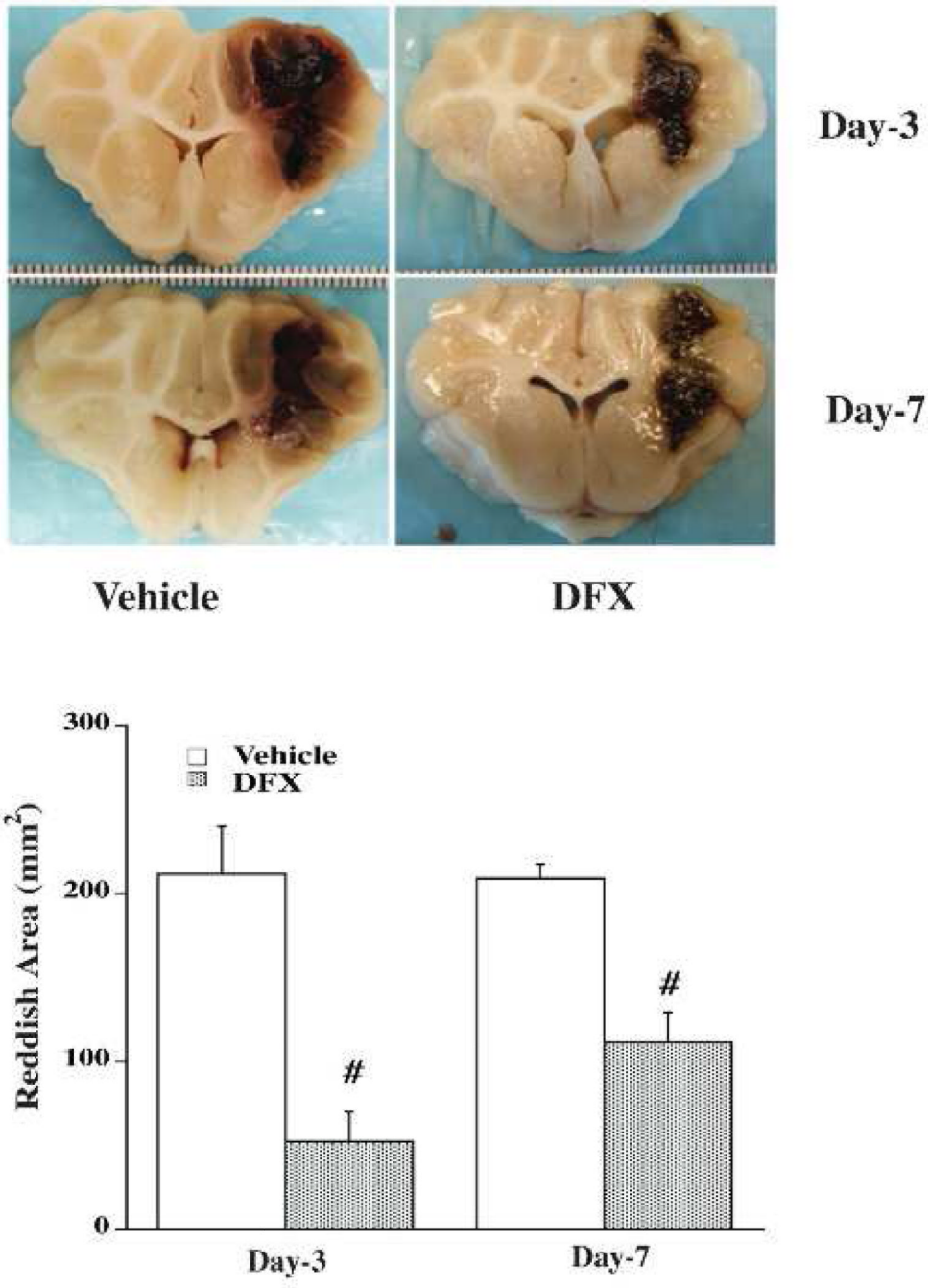

Figure 6.
Deferoxamine reduces reddish zone around haematoma at day 3 and day 7 in a pig intracerebral haemorrhage model. Values are means ± SD, n=4, # $p<0.01$ vs. vehicle. Figure reprinted with permission from Gu et al., *Stroke*, 2009;40:2241–2243.[112]

Table 1

Current and past clinical trials for intracerebral haemorrhage. See http://www.strokecenter.org/trials/ and http://clinicaltrials.gov/ for ongoing trials and the references cited in the table for details of past trials. The simvastatin trial was terminated due to poor enrollment.

Agent	Study Name	Target	Outcome
Surgical Evacuation	Multiple	multiple	No benefit[39]
Surgical Evacuation	STITCH II	multiple	Ongoing
Surgical Evacuation/tPA	MISTIE	multiple	Ongoing
Surgical Evacuation/tPA	SATIH	multiple	Ongoing
Surgical Evacuation/ultrasound	SLEUTH	multiple	Ongoing
Surgical evacuation with	Pre-SICH	multiple	No benefit [42]
Factor VIIa			
Blood pressure lowering agents	ATACH	blood pressure/haematoma expansion	Ongoing
Blood pressure lowering agents	INTERACT	blood pressure/haematoma expansion	Ongoing
Blood pressure lowering agents	ADAPT	blood pressure/haematoma expansion	Ongoing
Factor VIIa	FAST	haematoma expansion	No benefit[43]
Factor VIIa (for spot sign patients)	SPOTLIGHT	haematoma expansion	Ongoing
Factor VIIa (for spot sign patients)	STOP IT	haematoma expansion	Ongoing
Factor VIIa (for anticoagulant patients)		haematoma expansion	Ongoing
Platelet Transfusion (for anti-platelet patients)	PATCH	haematoma expansion	Ongoing
Aminocaproic Acid	ATICH	anti-fibrinolytic/haematoma expansion	Ongoing
NXY-059	CHANT	free radicals	No benefit[37]
Mannitol		edema	No benefit[35]
Glycerol		edema	No benefit[36]
Dexamethasone		edema	No benefit[34]
Gavestinel	GAIN	glycine antagonist	No benefit[38]
Citicoline		membrane stabilization	Preliminary[44, 45]
Rosuvastatin		multiple	Preliminary[46]
Simvastatin		multiple	Terminated
Pioglitazone	SHRINC	PPARγ-agonist	Ongoing
Deferoxamine	DFO-ICH	iron chelation	Ongoing
Celecoxib	ACE-ICH	cyclooxygenase	Ongoing
Tauroursodeoxycholic acid	IV TUDCA	apoptosis	Ongoing
Albumin	ACHIEVE	multiple	Ongoing
Ibuprofen		fever	Ongoing
Stem cell transplantation		multiple	Ongoing
Acupuncture		multiple	Ongoing