Intracranial haemorrhage: therapeutic interventions and anaesthetic management

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Editor’s key points
- Intracranial haemorrhage (ICH) requires timely treatment to maximize functional outcome.
- Efforts to reduce haematoma expansion, and thereby improve outcome, have involved recombinant factor VIIa (rFVIIa) and reduction in arterial pressure.
- Reversal of anti-coagulation is an increasingly important consideration in ICH patients.
- Multicentre trials are underway to improve management of these complex patients.

Intracranial haemorrhage
Stroke is the fourth leading cause of death in the USA1 and second only to ischaemic heart disease worldwide.2 While the majority of strokes are ischaemic in origin (see review by Anastasian in this issue),3 10–15% are due to intracranial haemorrhage (ICH).1,4 ICH has been traditionally divided into primary (spontaneous) and secondary. ICH is considered spontaneous if it results from rupture of small arteries and arterioles that have been damaged by chronic hypertension (60%) or amyloid angiopathy (30%),5–7 whereas secondary causes include trauma, aneurysms and vascular malformations, vasculitis, haemorrhagic conversion of infarct, and substance abuse. Primary ICH comprises 85% of all intracerebral haemorrhages,5 and affects 4 million people globally, with a 30 day mortality of 40–50%.8–9 Of the survivors, only 20–25% are able to function independently at 6 months.10–11

A PubMed literature search from 1980 through 2014 was performed utilizing the following key words: intracerebral haemorrhage, anaesthesia, therapy, and guidelines. Recent articles and clinical trials were surveyed and are summarized in this review with particular attention to three areas: pathophysiology of ICH, recent therapeutic innovations, and published guidelines reflecting standard management.

Aetiology of ICH
The two most prominent aetiologies of ICH include chronic hypertension and amyloidosis. Chronic hypertension leads to lipohyalinosis of cerebral arterioles, whereby there is breakdown of vasculature smooth muscle and intimal hyalinization, weakening the vessels, especially at their bifurcations.7 Amyloid angiopathy is defined by amyloid deposition in the media and adventitia of the arterioles, leading to fibrinoid necrosis. In contrast to hypertension-related haemorrhages, which occur most frequently in deep brain structures basal ganglia and thalamus, haemorrhages due to amyloid angiopathy are predominately lobar in nature.

Pathophysiology of ICH
First, there is the insult of the initial haemorrhage. The initial haemorrhage volume, in conjunction with level of consciousness, has long been established as an important predictor of mortality.16 Secondly, haematoma expansion occurs.

Summary. Intracranial haemorrhage (ICH) is a devastating cause of stroke. Although the total incidence of ICH has remained stable worldwide, the proportion associated with the use of anticoagulant medications is increasing. Innovative interventions developed to improve patient outcomes often require peri-procedure anaesthetic management. This non-systematic review examines the pathophysiology of ICH at a clinical level, reports on novel therapeutic interventions, many of which are currently in clinical trials, and reviews the current published recommendations for the management of patients with ICH.

Keywords: anaesthesia; anticoagulation; arterial pressure; intracranial haemorrhage; neurosurgery
in 30% of ICH patients and is correlated not only with mortality but also with decreased incidence of recovery to independent function.\textsuperscript{17} 18 Finally, the extent of perihaematoma brain oedema is significantly correlated with continued neuronal damage and post-haemorrhage mortality.\textsuperscript{19}

**Table 1** Determination of the ICH score. GCS score indicates GCS score on initial presentation (or after resuscitation); ICH volume, volume on initial CT calculated using ABC/2 method; and IVH, presence of any IVH on initial CT. Reproduced from\textsuperscript{15}, with permission

<table>
<thead>
<tr>
<th>Component</th>
<th>ICH score points</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS score</td>
<td></td>
</tr>
<tr>
<td>3 – 4</td>
<td>2</td>
</tr>
<tr>
<td>5 – 12</td>
<td>1</td>
</tr>
<tr>
<td>13 – 15</td>
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<tr>
<td>ICH volume (ml)</td>
<td></td>
</tr>
<tr>
<td>$\geq$ 30</td>
<td>1</td>
</tr>
<tr>
<td>$\leq$ 30</td>
<td>0</td>
</tr>
<tr>
<td>IVH</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Infratentorial origin of ICH</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>$\geq$ 80</td>
<td>1</td>
</tr>
<tr>
<td>$\leq$ 80</td>
<td>0</td>
</tr>
<tr>
<td>Total ICH score</td>
<td>0 – 6</td>
</tr>
</tbody>
</table>

**Initial haemorrhage**

Therapeutic interventions throughout this cascade of events are limited and the subject of ongoing investigations of safety and efficacy. Surgical evacuation of the haematoma can be beneficial in decreasing ICP and minimizing the effects of haematoma expansion and perihaemorrhagic oedema. The decision to bring a patient to the operating theatre for acute evacuation of an ICH depends on the location and the size of the haemorrhage. A Cochrane database meta-analysis reported an overall benefit of surgery compared with conservative therapy [odds ratio (OR) 0.71; $P<0.001$; 95% confidence interval (CI) –0.58 –0.88];\textsuperscript{20} however, patients with an ICH in deep brain structures and those with intraventricular haemorrhage leading to hydrocephalus did worse with early surgery, while those with superficial (<1 cm from the surface) cortical haematomas had better outcomes. STICH II, a trial to assess early surgical therapy in patients with superficial (1 cm from cortical surface) ICH, did not find a significant improvement in outcome in the entire early surgery group, although there was 21% crossover from the conservative management group to surgery due to neurological deterioration.\textsuperscript{21}

In a subgroup analysis of patients with poor prognosis, as determined by a formula based on age, Glasgow coma scale (GCS), and haemorrhage volume, there was a survival advantage to early surgery (OR 0.49, 95% CI 0.26 –0.92; $P=0.02$). Subgroup meta-analysis of raw data from multiple early surgical intervention trials concluded that early surgery may have benefit in any of these subgroups: patients between ages 50 and 69, GCS $>9$, haematoma volume of 20 –60 ml, or surgical evacuation within 8 h of ictus.\textsuperscript{22}

Cerebellar haemorrhage is the one subgroup in which surgical evacuation is recommended if the patient has a large haematoma (>3 cm), is deteriorating neurologically, or has brainstem compression or hydrocephalus.\textsuperscript{23} Decompressive craniectomy, utilized as a treatment for malignant intracranial hypertension and brain oedema in traumatic brain injury and middle cerebral artery thromboembolic stroke, has not been prospectively studied in ICH. A review of several case–control studies suggests that patients with GCS $<8$ and haematoma volume $<60$ ml who underwent decompressive craniectomy in conjunction with haematoma evacuation had a favourable outcome in 41% of cases with an overall mortality of 28%.\textsuperscript{24} Comparative data in patients who had only medical management or had haematoma resection without decompressive craniectomy suggest a mortality of 91% and favourable outcome in only 5% of patients.\textsuperscript{16} 22

Since both the extent of ICH expansion and the development of significant peri-haemorrhagic oedema are correlated with initial haematoma volume, some have rationalized that evacuation of the haematoma might diminish the damage resulting from these processes.\textsuperscript{12} Recent trials have suggested that there may be benefit from minimally invasive (endoscopic) clot removal as a stand-alone treatment or in combination with thrombolysis of the clot in some patient populations.\textsuperscript{25} 26

MISTIE III, a multicentre randomized trial (phase III) is underway to investigate the outcome and safety of clot lysis with rtPA (NCT01827046).

Intraventricular haemorrhage, often secondary to an ICH in the basal ganglia or thalamus, occurs in 45% of ICH patients.\textsuperscript{27} Intraventricular (IVH) volume has been established as an independent predictor of poor outcome in ICH patients, independent of hydrocephalus,\textsuperscript{27} 29 perhaps because of the toxic effects of intraventricular blood on the brainstem and other periventricular structures.\textsuperscript{30} The presence of IVH increases
the mortality of ICH to between 50% and 80%. The Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Haemorrhage (CLEAR) trial (phase III) is now enrolling patients to evaluate the use of endoscopically directed recombinant tissue plasminogen activator (rTPA) to lyse clot in IVH and determine if this improves outcome (NCT 00784134).

Haematoma expansion

Haematoma expansion usually occurs within the first 24 h after the initial haemorrhage, and occurs in up to 30% of patients. For each 10% increase in haematoma volume, there is a 5% increase in the hazard ratio for mortality, and each 1 ml in volume increase leads to a 7% decrease in the likelihood of the patient being able to function independently. Risk factors for expansion include initial haemorrhagic volume, early presentation for medical care after symptom onset, use of antithrombotic and antiplatelet medications, and the presence of the 'spot sign', a marker of continued bleeding on computed tomography angiography (CTA) (Fig. 2). Although it has a positive predictive value of 61%, many patients without a spot sign go on to suffer significant haematoma expansion. Additionally, genetic factors play a role in that presence of the apolipoprotein E allele increases the risk of secondary haematoma expansion in lobar ICH.

Clinical trials aimed at reducing haematoma expansion have focused on either utilization of recombinant factor VIIa (rFVIIa) or reduction in arterial pressure. Although a phase II trial confirmed a reduction in haematoma volume, morbidity, and mortality after rFVIIa treatment, a phase III trial failed to demonstrate any outcome benefit. Although currently it is not recommended to treat patients without a history of anticoagulant use with rFVIIa, ongoing trials in the USA and Canada (STOP-IT (NCT00810888) and SPOTLIGHT (NCT01359202)) are designed to evaluate the safety and efficacy of rFVIIa in preventing haematoma expansion utilizing refined selection criteria based on the CTA spot sign.

Control of systemic arterial pressure

Since the expansion of volume of an intracranial haematoma is associated with increased mortality, several studies have attempted to minimize the ultimate size of the haematoma by reducing arterial pressure. The INTERACT2 (Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial) trial assessed the effect of a reduction in systolic arterial pressure to <140 mm Hg within 1 h of randomization on outcome as measured by death or major disability at 90 days. Patients were treated with i.v. medications, including α-blockers, β-blockers, calcium channel blockers, and other medications as per local practice. Although small differences found in the primary outcome measures failed to reach statistical significance (P=0.06), there were proportionally more patients with outcomes of either ‘no disability’ or ‘mild disability’ in the treatment group (P=0.04). Haematoma size and expansion were assessed in a subgroup of patients who had repeat neurological imaging and there was no difference found between groups. Concerns have been raised regarding the study in that there was no standardized medication utilized to bring about the reduction in arterial pressure and that the time to randomization was >4 h, possibly reducing any potential benefit. Over 50% of the patients were from China, which may make it difficult to generalize the results to other populations, although the authors’ subgroup analysis did not find any difference between this group and the rest of the study population. A post hoc analysis of systolic arterial pressure variability in this study population revealed a significant association between increased variability and poor outcome, suggesting that avoiding wide swings in arterial pressure may benefit ICH patients.

The Antihypertensive Treatment in Acute Cerebral Haemorrhage (ATACH2) trial is utilizing a single agent, nicardipine, to rapidly reduce systolic arterial pressure to 110–140 mm Hg within 4 h. Preliminary data suggest a decrease in both haematoma expansion and in-hospital mortality (www.atach2.com, NCT01176565). Although INTERACT2 failed to reach statistical

![Fig 2 ICH spot sign and haematoma expansion. (A) CT demonstrating acute intracerebral haemorrhage of 18 ml. (B) CT angiogram demonstrating multiple spot signs in the anterior portion of haemorrhage. (C) CT 7 h after first: significant haematoma expansion to a calculated volume of 119 ml. Reproduced from with permission](https://academic.oup.com/bja/article-abstract/113/suppl_2/ii17/227880/187972/2880)
significance and ATACH2 is not complete, the results suggest that rapid reduction in blood pressure in ICH patients in whom ICP is not a concern, will not cause harm and may be of benefit.

Peri-haemorrhagic oedema

Secondary injury due to the development of peri-haemorrhagic oedema is another target for clinical therapy in ICH. Perihematomatoma oedema can develop within 3 h of haemorrhage, but peaks 10–20 days after the initial haemorrhage, and increases morbidity and mortality. Several trials are aimed at reducing oedema and direct neurotoxicity due to haemoglobin, thrombin, and iron. Thrombin, a serine protease, has been demonstrated to promote both early and delayed oedema formation by disrupting the blood–brain barrier, inducing apoptosis, potentiating glutamate, and activating microglia. Perihematomatoma oedema is reduced in ICH associated with thrombolysis therapy when compared with spontaneous ICH, and was reduced in the MISTIE II trial of minimally invasive lytic with rtPA. Additionally, haemoglobin and iron may increase brain oedema, and although the iron chelator defer-oxamine reduced ICH-induced brain oedema in animals, a human trial was halted because of an increased incidence of acute respiratory distress syndrome (NCT1662895). The inflammatory response, neutrophil infiltration, cytokine and complement activation, and production of tissue matrix metalloproteases all play a role in tissue oedema. While early studies of corticosteroid therapy failed to show benefit and led to increased complications, several current ongoing trials are directed towards reducing oedema and improving patient outcomes. Hypothermia was found to potentially limit ICH perihemorrhagic oedema in two retrospective case-controlled studies. Accordingly, a prospective, multicentre, randomized controlled phase II trial is currently underway (NCT01607151). Similarly, a small trial of fingolimid, a sphingo-mized controlled phase II trial is currently underway.

Anticoagulant-associated ICH

While research is directed towards the discovery of treatments to improve the outcome of ICH, the use of anticoagulants for the prevention of thromboembolic stroke and coronary stent thrombosis has increased both the incidence and severity of ICH. Atrial fibrillation is associated with 15–25% of ischaemic strokes, and warfarin therapy decreases the risk of ischaemic stroke in patients with atrial fibrillation by 62%. Unfortunately, as the prevalence of patients receiving anticoagulation and antiplatelet medications has increased, so has the incidence of anticoagulant-associated intracerebral haemorrhage (AAICH) (0.8/100 000 persons in 1988 to 45.9/100 000 in 1999). The incidence of AAICH as a percentage of ICH increased from 5% to 17%.

Antithrombotic medication

Significant haemorrhage is the major complication of warfarin therapy. In fact, ICH causes 90% of bleeding-related deaths in patients on warfarin. Warfarin increases the risk of ICH sevenfold and is associated with a 60% mortality rate, perhaps because the use of anticoagulant medication is associated with larger initial haematoma size. A meta-analysis of aspirin use showed a statistically significant absolute risk increase of 12 ICH events per 10 000 patients; however, this was counterbalanced by an absolute risk reduction of 39 ischaemic strokes per 10 000 patients. Combining aspirin and warfarin in elderly patients doubles the risk of ICH compared with the use of warfarin alone. Of interest, almost all studies of anticoagulant safety and efficacy exclude patients at high risk for bleeding, such as the very elderly.

Haematoma expansion occurs in 54% of patients with AAICH, almost twice that of patients not on antithrombotic medication, with a median time of expansion occurring at 21 h. Thus, urgent reversal of antithrombotic effect is important in survival. Various professional societies have recommended protocols to reverse warfarin in the setting of ICH (Table 2). All recommendations include administration of prothrombin complex concentrate (PCC), pooled plasma products containing factors II, IX, and X. Four-factor PCC, which also includes factor VII, is preferred. Alternatively, fresh-frozen plasma (FFP) or three-factor PCC plus factor VII can be administered. The use of FFP as the sole reversal is less effective and is associated with a slower time to INR correction and large volume of administration, which might not be tolerated in some patients. Studies suggest that the PCC can achieve the target INR within 15 min in 89% of patients. There is a risk of a prothrombotic event (deep vein thrombosis, myocardial infarction) in as many as 1.5% of patients receiving PCC. Because the half-life of PCC can be as brief as 6 h, i.v. vitamin K (5–10 mg i.v. every 12 h up to 25 mg) should also be administered and should normalize the INR within 24 h. If the initial dose of PCC or FFP does not reduce the INR to 1.4–3.0 min after administration, consideration should be given to repeating the dose.

The newer oral anticoagulants, dabigatran (direct thrombin inhibitor), and rivaroxaban and apixaban (factor Xa inhibitors), have been shown to be as effective as warfarin in preventing thromboembolic events in patients with atrial fibrillation (Fig. 3). In a meta-analysis, the incidence of ICH was significantly less in patients treated with the newer agents compared with those treated with warfarin (RR 0.49, 95% CI 0.17–1.09). Although reversal agents currently are not available, a number of pre-clinical and clinical trials are ongoing. Neurologists, in response to a survey, indicated that if necessary to treat life-threatening haemorrhage, they would try to reverse the effects of dabigatran with FFP (53%), PCC (61%), factor VIIa (24%), or haemodialysis (24%).

Although increasingly used in patients with atrial fibrillation, the direct thrombin and factor Xa inhibitors are not used in
patients with mechanical valves because the RE-ALIGN study found that patients given dabigatran had a higher incidence of stroke, MI, and valve thrombosis. Warfarin remains the standard oral anticoagulant in this population.

**Dual antiplatelet therapy**

The use of dual antiplatelet therapy (DAPT) after percutaneous coronary interventions with drug-eluting stents (DES) for the treatment of coronary artery disease is also associated with an increased incidence of ICH. Various drug combinations for DAPT have been evaluated for their effectiveness at preventing stent thrombosis while minimizing the risk of haemorrhagic complication, and have resulted in the combination of aspirin and P2Y12-ADP-receptor inhibitors as the mainstream of DES maintenance therapy. Commonly used P2Y12-ADP inhibitors include clopidogrel, prasugrel, and ticagrelor. Ticagrelor is unique in that it is not a pro-drug and has a relatively rapid onset and offset in inhibition of platelet activity. In the PLATO (PLATelet inhibition and patient Outcomes) trial, the incidence of ICH was 0.34% and 0.19% for ticagrelor- and clopidogrel-treated patients, respectively. Although the absolute incidence of ICH in patients on DAPT is low, the mortality is very high (55%). Accordingly, the management of a patient on DAPT in the setting of a ICH is guided by the patient’s risk of neurological deterioration and permanent injury vs the risk of coronary stent thrombosis. Ideally, the patient should be cared for in the setting where there is both neurological critical care and interventional cardiology. Quantitative assessment of platelet inhibition due to P2Y12 inhibitor and aspirin is helpful in guiding therapy. In spite of a history of prior antiplatelet medication use in patients with ICH, only 9–21% demonstrated inhibition of platelet activity on assay evaluation. Naidech and colleagues reported better functional outcome in a very small study in patients receiving early platelet transfusion. American Heart Association/American Stroke Association Guidelines consider the evidence for platelet transfusion for ICH in patients taking antiplatelet medication to be Class IIB.

**Management of ICH**

The American Heart Association/American Stroke Association and European Stroke Organization have developed guidelines for the management of ICH (Table 3), many of which will occur in the operating theatre. Few of these recommendations are based on strong randomized clinical trial data, but rather represent the consensus opinion of experts in the field based upon the available evidence. Many of the recommendations, such as those regarding timing of surgical intervention and reversal of anticoagulant medications, are summarized above.

**Management of elevated ICP**

ICP may be acutely increased in the setting of ICH, and emergent interventions to control elevated ICP should be undertaken when indicated. Placement of an external ventricular drain (EVD) allows direct monitoring of ICP and possible drainage of cerebrospinal fluid to reduce ICP. If ICH is associated with the use of antithrombotic or antiplatelet medications, those medications should be reversed before placement of the EVD. Initial interventions to decrease ICP include elevating the head of the bed, administration of mannitol or hypertonic saline.
Fig 3 Sites of action of antithrombotic medications. Reproduced from71, with permission

Table 3 Summary of American Heart Association/American Stroke Association and European Stroke Organization Guidelines for Management of ICH. Data from23 64

<table>
<thead>
<tr>
<th>Diagnostic studies</th>
<th>CT/MRI/angiography to rule out ischaemic stroke or secondary ICH (i.e. aneurysm or AVM rupture)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurointensive care</td>
<td>Patients have better outcome when managed in ‘stroke’ units</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Reversal of any antithrombotic/antiplatelet therapy as rapidly as feasible given other potential contraindications (consultation with other specialities)</td>
</tr>
<tr>
<td>Airway/respiration</td>
<td>Ensure adequate airway protection, ventilation and oxygenation: intubation and mechanical ventilation if necessary</td>
</tr>
<tr>
<td>Intracranial pressure</td>
<td>Control of ICP using medical measures or placement of an external ventricular drain</td>
</tr>
<tr>
<td>Haemodynamic management</td>
<td>Within 6 h of onset of ICH, acute reduction (in &lt; 1 h) of arterial pressure to a target SAP &lt; 140 mm Hg is safe and may be superior than the previous target of SAP &lt; 180</td>
</tr>
<tr>
<td>Anticonvulsant medication</td>
<td>Prophylactic use of anticonvulsants is not recommended</td>
</tr>
<tr>
<td></td>
<td>Treat clinical seizures with antiepileptic medications</td>
</tr>
<tr>
<td></td>
<td>Continuous EEG monitoring may be indicated in patients with a more severely depressed mental status than expected from degree of brain injury</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Monitor blood glucose and avoid hyperglycaemia (&gt; 180 mg dl⁻¹) or hypoglycaemia</td>
</tr>
<tr>
<td>Temperature</td>
<td>Avoid hyperthermia. The duration of fever in ICH patients is associated with poor outcome</td>
</tr>
<tr>
<td>Deep vein thrombosis prophylaxis</td>
<td>Utilize pneumatic compression devices</td>
</tr>
</tbody>
</table>
saline, sedatives, and paralytics (intubation and mechanical ventilation). Mild hyperventilation can be useful; however, more significant levels of hyperventilation are not recommended without the guidance of jugular venous oxygen saturation or a cerebral oximeter to ensure adequate tissue oxygenation.

Control of systemic arterial pressure

Maintenance of adequate cerebral perfusion pressure has long been a mainstay of appropriate anaesthetic management in patients with neurological disease; however, the risks of modest arterial pressure reduction in ischaemic stroke may not apply in ICH where there is no significant perihaematoma penumbra in the acute setting. Cerebral autoregulation is not usually impaired in acute ICH; however, progressive impairment of autoregulation beginning post-haemorrhage days 3–5 is associated with poor outcome at 90 days.80

Seizure prophylaxis

Fewer than 7% of ICH patients present with seizure. Although subclinical seizure activity may be seen in up to 25% of patients with ICH,81 this is not associated with an increase in morbidity or mortality. In fact, increased mortality was noted in patients receiving prophylactic antiepileptic medication, specifically, phenytoin.82 The use of antiseizure medication, therefore, should be reserved for those patients with clinical or EEG demonstrated seizure activity.

Blood glucose

Hyperglycaemia is an independent predictor of mortality within the first 28 days of ICH;83 however, ‘tight’ glucose control has been found to be associated with depleted cerebral glucose level84 and also increased mortality when compared with conventional glucose control of a goal of <180 mg dl⁻¹.85 Thus, the AHA/ASA recommendation is to avoid blood glucose >180 mg dl⁻¹.

Conclusions

Intracerebral haemorrhage is a devastating injury for which prompt, effective treatment can impact meaningful survival. As more aggressive therapies are developed which require anaesthetic care, anaesthesiologists will have greater impact on these patients. Continuation of recommended management guidelines throughout the perioperative period and implementation of novel therapeutic strategies in conjunction with neurosurgeons and neurologists will hopefully increase functional survival in these patients.

Author’s contribution

P.F.M. conceived and wrote the entire manuscript.

Declaration of interest

None declared.

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Intracranial haemorrhage


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