Update in Management of Acute Spontaneous Intracerebral Haemorrhage

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EPIDEMIOLOGY
Although ICH represents only about 9% of all stroke, it accounts for 10-30% of hospital admissions. ICH leads to catastrophic disability, morbidity, and a 6 month mortality of 30-50%. Long term outcomes are poor, only 20% of patients regain functional independence at 6 months.2,3

ICH is a common disorder, with an estimated frequency of 37,000-52,000 each year in the USA. The overall incidence of ICH is 12-15 cases per 100,000 people per year. ICH results in staggering medical costs, about 125,000 per patient per year, with an overall cost of $6 billion annually in the USA.2

RISK FACTORS AND CAUSES OF BLEEDING
There are several modifiable risk factors for spontaneous ICH. Hypertension is by far the most important and prevalent risk factor, directly account for about 60-70% of cases.2 ICH is a particular risk in hypertensive patients younger than 55, smokers, and patients who are noncompliant with antihypertensive regimens. Other modifiable risk factors include smoking and heavy alcohol use. Chronic alcoholism may increase the risk of ICH by causing cirrhosis, thrombocytopenia, or both. Low serum cholesterol is associated with increased risk of ICH, especially among
hypertensive patients. Genetic risk factors, include the ApoE ε2 and ε4 alleles, predispose to lobar haemorrhages by increasing the vasculopathic effect of amyloid deposition in cortical blood vessels. Hypertension is the main cause of spontaneous ICH. Chronic hypertension causes degeneration, fragmentation, and fibrinoid necrosis of small penetrating arteries in the brain, which can eventually result in spontaneous rupture. In some people, chronic hypertension may cause discrete microaneurysm at the bifurcation of the arterioles (Charcot-Bouchard aneurysms). Persistently raised intraluminal arterial pressure, which commonly found in hypertensive patients, damages small-vessel walls. These degenerative changes are most common in the distal portions of medium and small arterioles ranging from 100-600 µm in diameter. Hypertensive ICH typically occurs in the basal ganglia (putamen, thalamus, or caudate nucleus), pons, cerebellum, or deep hemispheric white matter.

The second most common cause of primary ICH is cerebral amyloid angiopathy, which accounts for about 15% of cases. This disorder is characterized by the deposition of amyloid-β peptide in small to medium sized blood vessels of the brain and leptomeninges, which results in vascular fragility. The typical clinical syndrome of amyloid angiopathy ICH is spontaneous lobar haemorrhage in elderly patients with a history of cognitive decline. This type of ICH is less severe than hypertensive ICH. Other major causes of ICH are brain tumors, aneurysms, arteriovenous malformation (AVM), cavernous angiomas, and arteriovenous (AV) fistula.

Ganglionic haemorrhages are the most common forms of ICH, followed by lobar, and then cerebellar or pontine. Location is important both in terms of outcome, potential surgical intervention, and underlying cause. In general, fewer lobar haemorrhages than those in other regions are hypertensive in origin.

**CLINICAL MANIFESTATIONS**

Rapid recognition and diagnosis of ICH are essential because of its frequently rapid progression during the first several hours. The classic clinical presentation includes the onset of a sudden focal neurological deficit while the patient is active, which progresses over minutes to hours. This smooth symptomatic progression of a focal deficit over a few hours is uncommon in ischemic stroke and rare in subarachnoid hemorrhage. Headache is more common with ICH than with ischemic stroke, although less common than in subarachnoid hemorrhage. Vomiting is more common with ICH than with either ischemic stroke or subarachnoid hemorrhage. Increased blood pressure and impaired level of consciousness are common. However, clinical presentation alone, although helpful, is insufficient to reliably differentiate ICH from other stroke subtypes.

Therefore, CT or MRI is essential for confirming diagnosis. Rapid progression to coma with motor posturing suggest massive supratentorial haemorrhage, bleeding into the brainstem or diencephalon, or acute obstructive hydrocephalus due to intraventricular haemorrhage. Over 90% patients have acute hypertension exceeding 160/100 mm Hg, whether or not there is a history of hypertension. Dysautonomia in the form of central fever, hyperventilation, hyperglycemia, and tachycardia or bradycardia is also common.

**PATHOPHYSIOLOGY**

ICH can occur anywhere in the brain. The haematoma spread between the white matter tracts, resulting in islands of viable brain tissue within the haematoma itself. Bleeding usually stops shortly after the initial ictus, but in a substantial minority of patients the haematoma continous to expand, usually within the first hour after presentation. Early haematoma expansion portends a worse outcome. Once the haematoma forms, vasogenic cerebral edema forms around the clot as osmotically active serum proteins are released from the haematoma. Edema formation peaks at about 48 hours and usually begins to resolve by 5 days, but it may persist longer. Edema contributes to neurologic deterioration by causing tissue shifts, raised ICP and transtentorial herniation. As the haematoma is absorbed and edema resolves, a slitlike haematoma cavity containing hemosiderin remains, with surrounding brain atrophy.
In recent years, understanding the pathophysiology of ICH has been changed. The two most important new concepts are that many hemorrhage continue to grow and expand over several hours after the onset, a process known as early haematoma growth, and that most of the brain injury and swelling that happens in the days after ICH is the result of inflammation caused by thrombin and other coagulation end-products. Early haematoma growth is common and associated with neurological deterioration and poor clinical outcome. The mechanisms that lead to early haematoma growth during the acute stage of ICH remain unclear. A sudden increased ICP, local tissue distortion and shear forces, and disruption of the normal cerebral anatomy can lead to a multifocal bleeding process in some patients, with enlargement of the haematoma resulting from the addition of discrete “satellite” haemorrhages to the periphery of the existing clot. Other changes include vascular engorgement related to a reduction to venous outflow, early transient ischaemia, breakdown of the blood-brain barriers, and possibly the transient creation of a local coagulopathy may contribute to early haematoma growth.

DIAGNOSIS

Initial clinical diagnostic evaluation of ICH at the hospital involves assessment of the patient’s presenting symptoms and associated activities at onset, time of stroke onset, age, and other risk factors. The patient or witnesses are questioned about trauma; hypertension; prior ischemic stroke, diabetes mellitus, smoking, use of alcohol and prescription, over-the-counter, or recreational drugs such as cocaine; use of warfarin and aspirin or other antithrombotic therapy; and hematologic disorders or other medical disorders that predispose to bleeding, such as severe liver disease. The physical examination focuses on level of consciousness and degree of neurological deficit after assessment of airway, breathing, circulation, and vital signs.

CT scan is the method of choice to evaluate the presence of ICH. Careful inspection of the pattern and topography of bleeding can sometimes give important clues about a secondary cause of ICH, such as associated subarachnoid blood (suggestive of aneurysm), multiple inferior frontal and temporal haemorrhages (suggestive of trauma), or fluid-fluid levels within the haematoma (indicative of coagulopathy). Demonstration of active contrast extravasation into the haematoma with CT angiography might help to predict haematoma expansion and is predictive of poor outcome. A CT scan determines the exact site and size of the haematoma, extension into the ventricular system, degree of surrounding edema, anatomical disruption, and excludes other pathologies.

MRI is as sensitive as CT for the detection of ICH in the acute stage, but is most commonly done as a follow-up study to detect vascular flow voids, which are indicative of an AVM, chronic microbleeds on gradient echo imaging suggestive of amyloid angiopathy, or a contrast-enhancing neoplasm. Sensitivity of MRI for ICH is 100%. In the HEME Study, MRI and CT were equivalent for the detection of acute ICH but MRI was significantly more accurate than CT for the detection of chronic ICH. MRI has additional potential advantage of demonstrating small microbleeds on gradient echo images that are not visible by CT.

TREATMENT

The management of patients with ICH include both medical and surgical approaches. Potential treatments of ICH include stopping or slowing the initial bleeding during the first hours after onset; removing blood from the parenchyma or ventricles to eliminate both mechanical and chemical factors that cause brain injury; management of complications of blood in the brain, including increased ICP and decreased cerebral perfusion; and good general supportive management of patients with severe brain injury.

Rapid neurological decline and depressed consciousness lead to loss of normal reflexes that maintain an open airway, which mandates immediate endotracheal intubation and mechanical ventilation. High blood pressure should be corrected immediately to minimize the potential for haematoma expansion and to maintain adequate cerebral perfusion pressure (CPP), which is calculated as mean arterial pressure (MAP) minus ICP. American Stroke Association guideline
recommend that MAP be maintained at or below 130 mm Hg for patients with ICH and a history of hypertension. In patients who have had craniotomy, MAP should be maintained at or below 100 mm Hg. In all cases, systolic blood pressure (SBP) should be maintained above 90 mm Hg, and in patients with an ICP monitor, CPP should be maintained above 70 mm Hg.2,3

Emergency measures for ICP control are appropriate for stuporous or comatose patients, or those who present acutely with clinical signs of brainstem herniation. The head should be elevated to 30 degrees, 1.0-1.5 g/kg of 20% mannitol should be given by a rapid infusion followed by bolus doses of 0.25 to 1.0 g/kg as needed, and the patient should be hyperventilated to a pCO2 of 28-32 mm Hg. Corticosteroids such as dexamethasone are not suggested in the management of ICH because of their failure to demonstrate efficacy in ICH.2,3

Eptacog alfa (recombinant activated factor VII or rFVIIa), is a powerful initiator of haemostasis holds great promise as an effective emergency treatment for non-coagulopathic spontaneous ICH, but formal approval of rFVIIa for this indication will depend on the result of an ongoing phase III trial (The FAST Trial) comparing placebo with doses of 20 µg/kg and 80 µg/kg. Patients with ICH receiving warfarin should be reversed immediately with fresh frozen plasma or prothrombin-complex concentrates and vitamin K. Treatment should never delayed in order to check coagulation tests. Patients with ICH who have had anticoagulation therapy with unfractionated or low-molecular-weight heparin should be reversed with protamine sulfate, and patients with thrombocytopenia or platelet dysfunction can be treated with a single dose of desmopressin (DDAVP), platelet transfusions, or both.2,3

To minimize ICP and reduce the risk of ventilator-associated pneumonia in mechanically ventilated patients, the head should be elevated 30 degrees. Isotonic fluids such as 0.9% saline should be given as the standard intravenous replacement fluid. Solutions containing dextrose should generally be avoided unless hypoglycemia is present, because hyperglycemia can be detrimental to the injured brain. A state of euvolesmia should be maintained by the monitoring of fluid balance, central venous pressure, and body weight.2,3

The 30 day risk of clinically evident seizures after ICH is about 8%. Convulsive status epilepticus may be seen in 1–2% of patients, and the risk for epilepsy is 5–20%. Lobar location is an independent predictor of early seizure. The American Heart Association guidelines recommend antiepileptic treatment in selected patients for up to 1 month, after which therapy should be discontinued if there are no seizures.2,3

Fever after ICH is common, particularly after intraventricular haemorrhage, and should be treated aggressively. Paracetamol and cooling should be given to all patients with sustained fever in excess of 38.8 °C. As is the case with all critically ill patients with neurological disorders, enteral feeding should be started within 48 hour to reduce the risk of malnutrition. A small-bore nasoduodenal feeding tube can lower the risk of aspiration events.2,3

The decision about when to operate remains controversial. The STICH trial, a landmark trial of 1033 ICH patients, showed that emergent surgical haematoma evacuation within 72 hours of onset does not improve outcome in comparison to a policy of initial medical management.2,7

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adult 2007 Update recommend:6

**Recommendations or Surgical Approaches:**

**Class I:** Patients with cerebellar hemorrhage >3 cm who are deteriorating neurologically or who have brain stem compression and/or hydrocephalus from ventricular obstruction should have surgical removal of the hemorrhage as soon as possible (Class I, Level of Evidence B).

**Class II:** 1. Although stereotactic infusion of urokinase into the clot cavity within 72 hours of ictus apparently reduces the clot burden and risk of death, rebleeding is more common, and functional outcome is not improved; therefore, its usefulness is unknown (Class IIb, Level of Evidence B) 2. Although theoretically attractive, the usefulness of minimally invasive clot evacuation utilizing a variety of mechanical devices and/or endoscopy awaits further testing in clinical trials; therefore, its current usefulness is unknown (Class IIb, Level of Evidence B); 3.
For patients presenting with lobar clots within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered (Class IIb, Level of Evidence B).

Class III: 1. The routine evacuation of supratentorial ICH by standard craniotomy within 96 hours of ictus is not recommended (Class III, Level of Evidence A). (See possible Class II exception above for patients presenting with lobar clots within 1 cm of the surface.)

Recommendations for Timing of Surgery:
Class II: No clear evidence at present indicates that ultra-early craniotomy improves functional outcome or mortality rate. Operative removal within 12 hours, particularly when performed by less-invasive methods, has the most supportive evidence, but the number of subjects treated within this window is very small (Class IIb, Level of Evidence B). Very early craniotomy may be associated with an increased risk of recurrent bleeding (Class IIb, Level of Evidence B).
Class III: Delayed evacuation by craniotomy appears to offer little if any benefit with a fairly high degree of certainty. In those patients presenting in coma with deep hemorrhages, removal of ICH by craniotomy may actually worsen outcome and is not recommended (Class III, Level of Evidence A).

Recommendations for Decompressive Craniotomy:
Class II: Too few data currently exist to comment on the potential of decompressive craniectomy to improve outcome in ICH (Class IIb, Level of Evidence C).

PREVENTION
Hypertension remains the most important target for ICH prevention. Data on how and when to switch from intravenous medications used to control blood pressure in ICH patients during the hospitalization to oral long-term medications are not available. This change in antihypertensive regimen often begins after the patient is clinically stable, able to swallow medication or to take oral medications through a gastrointestinal tube, and near discharge from the acute care hospital.

Smoking (particularly in the young), heavy alcohol use, and cocaine use have also been associated with an increased risk of ICH and should be strongly discouraged after ICH.

REFERENCES