CME

The Acute Management of Intracerebral Hemorrhage: A Clinical Review

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Intracerebral hemorrhage (ICH) is a devastating disease with high rates of mortality and morbidity. The major risk factors for ICH include chronic arterial hypertension and oral anticoagulation. After the initial hemorrhage, hematoma expansion and perihematoma edema result in secondary brain damage and worsened outcome. A rapid onset of focal neurological deficit with clinical signs of increased intracranial pressure is strongly suggestive of a diagnosis of ICH, although cranial imaging is required to differentiate it from ischemic stroke. ICH is a medical emergency and initial management should focus on urgent stabilization of cardiorespiratory variables and treatment of intracranial complications. More than 90% of patients present with acute hypertension, and there is some evidence that acute arterial blood pressure reduction is safe and associated with slowed hematoma growth and reduced risk of early neurological deterioration. However, early optimism that outcome might be improved by the early administration of recombinant factor VIIa (rFVIIa) has not been substantiated by a large phase III study. ICH is the most feared complication of warfarin anticoagulation, and the need to arrest intracranial bleeding outweighs all other considerations. Treatment options for warfarin reversal include vitamin K, fresh frozen plasma, prothrombin complex concentrates, and rFVIIa. There is no evidence to guide the specific management of antiplatelet therapy–related ICH. With the exceptions of placement of a ventricular drain in patients with hydrocephalus and evacuation of a large posterior fossa hematoma, the timing and nature of other neurosurgical interventions is also controversial. There is substantial evidence that management of patients with ICH in a specialist neurointensive care unit, where treatment is directed toward monitoring and managing cardiorespiratory variables and intracranial pressure, is associated with improved outcomes. Attention must be given to fluid and glycemic management, minimizing the risk of ventilator-acquired pneumonia, fever control, provision of enteral nutrition, and thromboembolic prophylaxis. There is an increasing awareness that aggressive management in the acute phase can translate into improved outcomes after ICH. (Anesth Analg 2010;110:1419–27)

Intracerebral hemorrhage (ICH) is a spontaneous extravasation of blood into brain parenchyma. The overall incidence is 12 to 15 cases per 100,000 population per year,[1] and it is the cause of 10% to 15% of first-ever strokes.[2] It is more common in the elderly[3] and in those of African[4] or Asian ethnicity,[5] and the incidence is substantially increased in those receiving anticoagulant therapy.[6] Although ICH accounts for only 10% to 30% of all stroke-related admissions to hospital, it is one of the major causes of stroke-related death and disability. Overall mortality approaches 50% at 30 days,[7,8] and approximately half of all ICH-related mortality occurs within the first 24 hours after the initial hemorrhage.[9] Functional outcome in survivors is also poor with fewer than 20% being independent at 6 months.[2] In up to 40% of cases, the hemorrhage extends into the ventricles (intraventricular hemorrhage [IVH]) and this is associated with obstructive hydrocephalus and worsened prognosis.[5] Other factors associated with poor outcome include large hematoma volume (>30 mL), posterior fossa location, older age, and admission mean arterial blood pressure (MAP) >130 mm Hg.[8,9]

More than 85% of ICH occurs as a primary (spontaneous) event related to rupture of small penetrating arteries and arterioles that have been damaged by chronic arterial hypertension or amyloid angiopathy. Sixty percent to 70% of primary ICH is hypertension related[10] and, in the elderly, amyloid angiopathy accounts for up to one-third of the cases.[11] Secondary ICH can be related to multiple causes (Table 1).[11]

This review discusses the current understanding of the pathophysiology of spontaneous and anticoagulation-related ICH and presents consensus evidence for its acute management.

RISK FACTORS

Nonmodifiable risk factors for ICH include male gender, older age, and African or Asian ethnicity.[3–5] Cerebral amyloid angiopathy is an important risk factor in the elderly and can occur in isolation or in association with Alzheimer disease or familial apolipoprotein syndromes.[11,12] Amyloid angiopathy usually results in lobar

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Table 1. Causes of Intracranial Hemorrhage (ICH)
Primary ICH
Hypertension
Amyloid angiopathy
Secondary ICH
Coagulopathy
Trauma
Arteriovenous malformation
Intracranial aneurysm
Dural venous sinus thrombosis
Cavernous angioma
Intracranial neoplasm
Dural arteriovenous fistula
Hemorrhagic conversion of cerebral infarct
Cocaine abuse
Vasculitis

(often multiple) hematomas, and recurrent hemorrhage occurs in 5% to 15% of patients per year.

There are several modifiable risk factors for ICH and attention has focused on their prevention in an attempt to reduce its incidence. Hypertension is one of the most important, especially in the elderly or in those with untreated or uncontrolled hypertension, when the risk of ICH is doubled.[3,10,11] Fifty percent of hypertensive-related hemorrhage occurs in deep structures (basal ganglia and thalamus) and 30% in superficial (lobar) areas.[11] The risk of recurrent hypertensive ICH is <1.5% if arterial blood pressure (BP) is well controlled.[13] Warfarin anticoagulation is associated with an 8- to 19-fold increase in the risk of ICH.[14,15] High-dose aspirin is also associated with increased risk in the elderly (particularly in those with untreated hypertension), although the risk from other antiplatelet drugs is less clear.[16] Alcohol intake, either moderate or heavy acute use or chronic abuse (>60 mg/d), is also a risk factor for ICH,[17] as is the recreational use of cocaine.[3] The effect of cholesterol is uncertain, but recent evidence suggests that therapeutic reduction of cholesterol level reduces the incidence of stroke overall but is associated with a small increase in the risk of ICH.[18] Any purported detrimental association between ICH and smoking, or beneficial effect of physical activity, remains inconclusive.

PATHOPHYSIOLOGY

In the majority of cases, chronic changes in the cerebral vasculature are the underlying pathophysiologic events leading to ICH. Chronic hypertension leads to changes in the walls of small- to medium-sized cerebral arterioles (100–600 μm in diameter) including degeneration in the vessel wall smooth muscle, the development of small miliary aneurysms associated with thrombosis/microhemorrhages, and intimal hyalinization in the distal vessels or at bifurcation points.[19] These changes are termed lipohyalinosis and are usually located in the deep structures of the brain including the thalamus, basal ganglia, periventricular gray matter, pons, and cerebellum. Cerebral amyloid angiopathy results in fibrinoid changes in small- to medium-sized vessels secondary to the deposition of amyloid protein in the media and adventitia; these changes are associated with apolipoprotein Ee2 and Ee4 genotypes.[12]

ICH was previously considered a single hemorrhagic event, but it is now known that it is a complex, dynamic process with 3 distinct phases: (1) initial hemorrhage, (2) hematoma expansion, and (3) perihematoma edema.[20–22] Disease progression and outcome are primarily influenced by 2 of these factors: hematoma expansion and perihematoma brain edema.

After the initial hemorrhage, expansion of the hematoma occurs to some extent in most patients. In one study, hematoma volume increased to a substantial degree (>33% from baseline or >12.5 mL) in the first 24 hours in approximately one-third of patients.[23] In another study, 38% of patients had an increase in hematoma volume of >33% within 3 hours of the ictus and, in two-thirds of these, the hematoma growth was present within 1 hour of the baseline scan, suggesting continued bleeding in the hyperacute phase.[20] The mechanisms of early hematoma growth are unclear but likely to be related to sudden increases in intracranial pressure (ICP), causing local tissue distortion and disruption, vascular engorgement secondary to obstructed venous outflow, blood-brain barrier disruption, and a local coagulopathy secondary to release of tissue thromboplastin.[5] Hematoma expansion is an important cause of early neurological deterioration, the severity of which depends on original hematoma size and subsequent expansion rate.[20] There is an exponential increase in mortality when the hematoma volume exceeds 30 mL.[24] The 30-day mortality of patients with hematoma volume >60 mL in association with a Glasgow Coma Scale (GCS) score <8 is >90% compared with 19% for those with a hematoma volume <30 mL and a GCS score >9.[7]

Perihematoma brain edema develops early, evolves over many days, and is the primary cause of neurological deterioration after the first day.[25] It occurs mainly as a result of an inflammatory response secondary to local release from the hematoma of thrombin and other end products of coagulation, and also because of cytotoxic mediators and disruption of the blood-brain barrier.[22,26] Although the presence of an ischemic penumbra around the area of the ICH was previously a concern, recent evidence does not confirm the presence of perihematoma tissue ischemia unless the hematoma is massive. One study, using multisequence magnetic resonance imaging (MRI) protocols, found no evidence of potentially salvageable ischemic penumbra in the acute phase after ICH, suggesting that perihematoma hypoperfusion is a consequence of reduced metabolic demand rather than true tissue ischemia.[27] It is now clear that perihemorrhagic tissue damage is primarily related to the inflammatory and cytotoxic response described above.[19,28,29] Although therapies directed toward ICH-related edema are currently lacking, it is possible that antiinflammatory drugs, targeted at perihematoma edema, might have therapeutic potential to ameliorate secondary brain injury after ICH.[19]

CLINICAL PRESENTATION

A rapid onset of focal neurological deficit with clinical signs of increased ICP, such as a change in consciousness, headache, and vomiting, are strongly suggestive of a diagnosis of ICH. In conscious patients, the initial clinical features depend on the location and size of the hematoma.[9] A small- or moderate-volume lobar hematoma can present with limited initial symptoms, or with nonspecific signs of increased ICP with or without a focal neurological deficit.

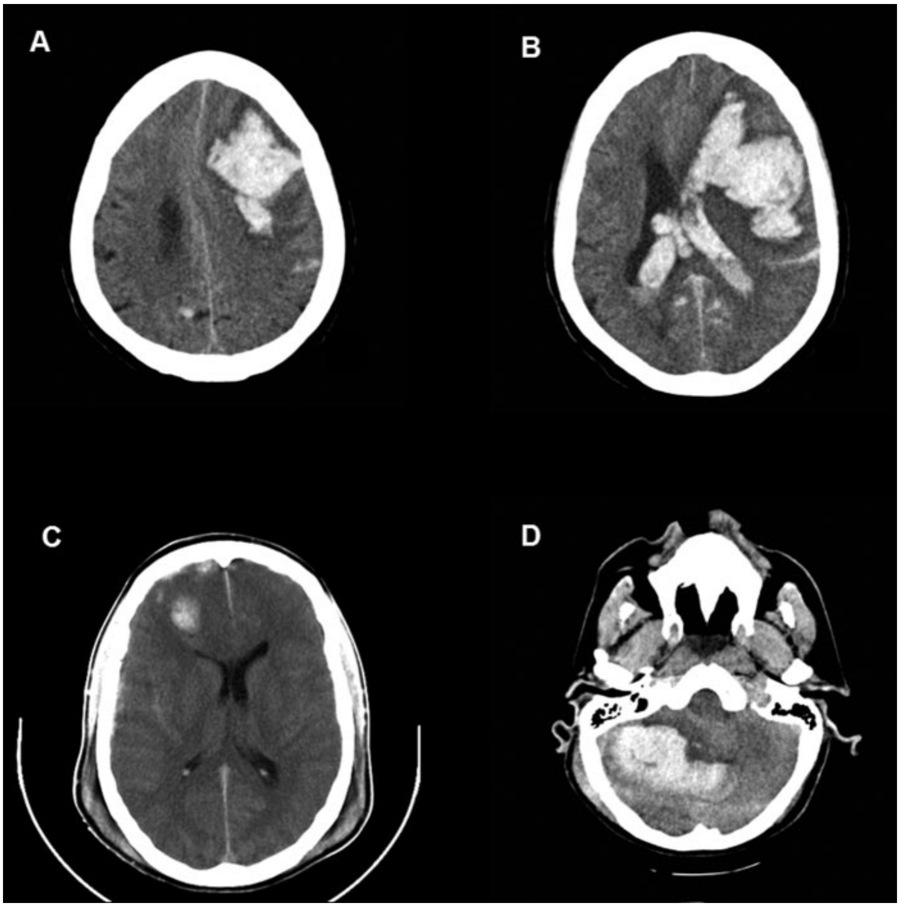

Figure 1. Computed tomographic scans showing intracerebral hemorrhage. A, Supratentorial lobar hematoma. B, Supratentorial hematoma with intraventricular extension. C, Traumatic intracerebral hemorrhage. D, Posterior fossa hemorrhage.

Even a small-sized lesion in the posterior fossa can, however, be fatal. Larger hematomas, whatever their location, can result in immediate loss of consciousness and rapid progression to death because of critically increased ICP or direct brainstem compression.[30] More than 90% of patients present with acute hypertension (>160/100 mm Hg),[31] and dysautonomia, causing hyperventilation, tachycardia, bradycardia, central fever, and hyperglycemia, is also common. Clinical deterioration occurs in 30% to 50% of patients, usually within the first 24 hours, and may be attributable to any combination of hematoma expansion, perihematoma edema, hydrocephalus, and seizures.

DIAGNOSIS AND INTERVENTION

ICH cannot be differentiated from other causes of stroke by clinical examination alone.[32] A cranial computed tomographic (CT) scan confirms the diagnosis, allows estimation of hematoma volume, and identifies mass effect and intraventricular extension (Fig. 1). The pattern of bleeding may indicate the potential cause of the ICH, and extravasation of contrast into the hematoma predicts hematoma expansion.[33] MRI is as sensitive as computed tomography for acute detection of ICH and superior in identifying perihematoma edema.[34] MRI is most frequently used as a follow-up investigation to identify arteriovenous malformation (AVM), amyloid angiopathy, or associated neoplasm.

Angiography should be performed in appropriate cases to exclude a vascular cause of secondary ICH such as aneurysm or AVM. In one study, abnormalities on angiography were present in 48% of normotensive patients younger than 45 years, in 49% of patients with lobar hemorrhage, and in 65% of those with isolated IVH.[35] Cerebral angiography should be considered in young patients with no obvious risk factors for ICH and in all cases of primary IVH. Patients with preexisting hypertension, the elderly, and those with a deep hematoma are less likely to benefit from angiography. However, with the availability of high-quality noninvasive imaging provided by CT angiography, vascular imaging is increasingly being performed in the acute phase after ICH, although this will risk missing so-called angiographically occult AVMs.

ACUTE MANAGEMENT

Although ICH remains the form of stroke with the least satisfactory treatment options, recent advances in our understanding of its pathophysiology, and the beneficial effect of some interventions, have resulted in a shift away from therapeutic nihilism. ICH is a medical emergency, and delays in treatment result in worse outcome. Initial management should focus on urgent stabilization of cardiorespiratory variables and treatment of intracranial complications.[2,5] Airway management, including endotracheal intubation and mechanical ventilation, is a priority in the unconscious patient or in those with a deteriorating conscious level.[36] Increased ICP can be related to a direct effect of the hematoma, the development of cerebral edema, or hydrocephalus. The usual emergency measures to control ICP should be considered in unconscious patients or in those who present with clinical signs of brainstem herniation. Early placement of a ventricular drain in patients with hydrocephalus can be life saving.

BP CONTROL

BP monitoring and management is critical after ICH, but the targets for treatment remain controversial. Even in previously normotensive patients, hypertension is a very common finding[31] and associated with worse outcome, probably because excessive hypertension is a cause of hematoma expansion.[37,38] In a recent multicenter study, systolic BP (SBP) >140 to 150 mm Hg after ICH doubled the risk of subsequent death or dependency.[39]

The risks of a sudden therapeutic reduction in BP after ischemic stroke are well known,[40] but it is possible that these same concepts may not apply after ICH because of the absence of an ischemic penumbra around small-volume ICHs.[27] A small, single-center study suggested that BP reduction in patients with acute ICH is safe and that aggressive reduction might reduce the risk of neurological deterioration in the first 24 hours after admission.[41] Two recently completed multicenter studies have provided more robust preliminary data on BP control after ICH. In the INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT), 203 patients were randomized to a low-target SBP of 140 mm Hg to be achieved within 1 hour and maintained for at least 24 hours after ICH, and 201 were randomized to a more conservative SBP target of 180 mm Hg.[42] This pilot study established the safety of decreasing BP early after ICH, determined by the absence of a significant excess risk of death, dependency, or cardiovascular morbidity, and demonstrated a tendency toward reduction of hematoma expansion within the first 6 hours. However, this study excluded patients with the severest injury (admission GCS score 3–5) and therefore those who would presumably be most at risk from acute therapeutic reductions in BP. The study was also not powered to detect clinical outcomes, so INTERACT2 has been designed to assess in 2800 patients whether early intensive BP-decreasing therapy can reduce death and disability after ICH. The Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) study evaluated the feasibility and safety of 3 escalating levels of antihypertensive treatment with IV nicardipine in patients with ICH-related acute hypertension.[43] Preliminary data from this study suggest that reduction of SBP to 110 to 140 mm Hg in the first 24 hours after ICH is well tolerated and associated with a reduced risk of hematoma expansion, neurological deterioration, and in-hospital mortality.* Only patients with a presentation GCS score >8 and hematoma volume <60 mL are being recruited into the ATACH study, so its results will be relevant only to the less severe end of the ICH spectrum.

The continued controversy over the targets for BP control after ICH is reflected in current management guidance. The American Heart Association/American Stroke Association recommends cautious management of severe hypertension with continuous infusion of antihypertensive drugs such as labetalol, esmolol, or nicardipine according to the following guidelines.[2] If SBP is >200 mm Hg or mean arterial blood pressure (MAP) >150 mm Hg, aggressive BP reduction, guided by frequent BP monitoring (at least every 5 minutes), should be considered. If SBP is >180 mm Hg (or MAP >130 mm Hg) and there is no evidence or suspicion of increased ICP, a modest reduction in BP to 160/90 mm Hg (MAP 110 mm Hg) is recommended. The European Union Stroke Initiative (EUSI), however, recommends BP targets determined by the patient's premorbid state.[44] An upper limit of SBP of 180 mm Hg and a diastolic BP of 105 mm Hg is recommended for patients with known hypertension or signs of chronic hypertension (e.g., electrocardiogram or retinal changes) and, if treatment is necessary, the recommended target BP is 160/100 mm Hg (or MAP 120 mm Hg). In patients without known hypertension, the upper recommended limits are 160/95 mm Hg, and the target BP is 150/90 mm Hg (or MAP 110 mm Hg). However, the EUSI also recommends that mean BP reduction should always be limited to ≤20% of baseline. In patients with an ICP monitor in place, both sets of guidance recommend that BP management should be targeted to maintain cerebral perfusion pressure between 60 and 70 mm Hg.[2,44] The optimal timing of conversion from IV to oral antihypertensive therapy is unknown but, in stable patients, sometime between 24 to 72 hours is usually recommended.[11]

Data to guide management of the lower limits of BP after ICH are virtually nonexistent. Individualized management based on premorbid BP, age, cause of ICH, and presence of increased ICP is recommended, but SBP should be maintained >90 mm Hg in all cases.[5]

HEMOSTATIC THERAPY

There has been interest in the application of hemostatic therapy to minimize hematoma expansion and improve outcome after ICH. In 2005, a phase IIb placebo-controlled study showed that treatment with recombinant factor VII (rFVIIa), a potent initiator of hemostasis, within 4 hours of ICH significantly reduced hematoma growth in association with reduced mortality and improved functional outcome in survivors at 3 months.[45] This improvement was seen despite a small increase in thromboembolic complications in the rFVIIa-treated patients (7% vs 2% for rFVIIa and placebo, respectively, $P = 0.12$). However, a subsequent phase III trial in 841 patients, the Factor VII for Acute Hemorrhagic Stroke (FAST) study, failed to replicate these clinical outcomes.[46] In this 2-dose study (rFVIIa 20 and 80 μg/kg), the dose-related reduction in hematoma expansion did not translate into a beneficial effect on the risk of death or severe disability. Post hoc analysis of the FAST data suggests that rFVIIa might be effective in a subgroup of younger patients (<70 years) with baseline ICH volume <60 mL if administered within 2.5 hours of the onset of symptoms.[47] On balance, current evidence suggests that any potential benefit of rFVIIa is offset by a modest increase in the risk of thromboembolic complications.[48] Early investigation with CT angiography might identify patients most at risk of hematoma expansion and who therefore might have the most to gain from treatment with rFVIIa.[49] Further studies are therefore urgently required to define more

*Available at: http://www.strokecenter.org/trials/TrialDetail.aspx?tid=602. Accessed December 14, 2009.

Table 2. National Guidelines for the Reversal of Warfarin Anticoagulation

Organization	Recommendations
American Heart Association/American Stroke Association (2007)[2]	IV vitamin K PCC, FFP or rFVIIa PCC—no dose specified FFP—no dose specified rVIIFa—no dose specified
American College of Chest Physicians (2004)[56]	IV vitamin K (10 mg) PCC rFVIIa may be considered as alternative to PCC
European Union Stroke Initiative (2006)[44]	IV/PO vitamin K (5–10 mg)—one or two doses Either FFP or PCC PCC 10–50 IU/kg—repeat until INR <1.5 FFP 10–40 mL/kg
British Committee of Standards in Haematology (2006)[57]	IV vitamin K (5–10mg) PCC or FFP PCC 50 IU/kg FFP 15 mL/kg
Australasian Society of Thrombosis and Haemostasis (2004)[58]	IV vitamin K (5–10 mg) PCC and FFP (to replace lack of factor VII in this PCC) PCC 25–50 IU/kg FFP 150–300 mL

FFP = fresh frozen plasma; PCC = prothrombin complex concentrate; IU = international units.

accurately the potential target population that might benefit from rFVIIa.

ANTICOAGULATION AND ICH

Oral Anticoagulation

ICH is the most serious complication of warfarin anticoagulation. The risk of ICH approximately doubles for each increase of one in the international normalized ratio (INR),[50] and an INR >3 is associated not only with larger initial hematoma volume[51] but also with an increased frequency of hematoma expansion and higher incidence of neurological deterioration in the first 24 to 48 hours.[52] Warfarin-related ICH has a very high mortality, with reported rates up to 67%.[14,15] The need to arrest intracranial bleeding outweighs all other considerations and, although there is often a reluctance to reverse anticoagulation in patients considered to be at high risk of thrombotic complications (e.g., those with mechanical heart valves),[53] the evidence overwhelmingly supports the correction of coagulopathy in all patients.[54,55] There is a relatively short time window for treatment and options include vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and rFVIIa. There are currently no standardized guidelines for the reversal of anticoagulation in patients with warfarin-related ICH, but various national guidelines have been published.[2,44,56–58] All recommend discontinuation of warfarin and a combination of vitamin K and FFP or PCCs, although the detailed regimens vary (Table 2).

Intravenous vitamin K (5–10 mg), which supports endogenous synthesis of clotting factors, should be administered to all warfarin anticoagulated patients with ICH.[54,59,60] Vitamin K takes approximately 6 hours to reach therapeutic levels but has an effect that lasts beyond the relatively short half-lives of FFP and PCCs. FFP contains factors II, VII, IX, and X and is an effective way of correcting the INR acutely. However, it has a short duration of action and, because large volumes (20–40 mL/kg) may be required, there is a risk of intravascular volume overload and heart failure.[54] FFP has other disadvantages; it must be compatibility tested and thawed before use, it carries the general risks of blood transfusion, and factor IX levels may remain low despite adequate correction of other coagulation factors. Although there are no studies that definitively evaluate the efficacy or optimal dose of FFP after oral anticoagulation–related ICH,[59] more predictable and reliable correction of the INR is achieved when the time between diagnosis and initiation of treatment is short. In one study, every 30-minute delay in FFP infusion was associated with a 20% reduction in the probability of successful correction of INR at 24 hours.[61] Commercially available PCCs are pooled plasma products containing high (but varying) concentrations of factors II, IX, and X, with or without factor VII, depending on the individual product.[62] PCCs are available in smaller volumes than FFP, do not require compatibility testing or thawing, and are effective treatments for warfarin overanticoagulation that avoid the risks and delays associated with FFP. Several nonrandomized trials in the setting of warfarin-related ICH confirm that PCCs can correct INR faster than FFP, although improvements in outcome have not been demonstrated.[63,64] The optimal PCC dose for warfarin reversal has also not been established, but it is usually administered in a dose-dependent manner, according to the INR, body weight (15–50 IU/kg), and nature of the individual preparation.[54] PCCs are associated with higher thromboembolic complications than FFP, although these are dose related and their incidence in warfarin reversal seems to be low.[59] PCCs are widely used to reverse warfarin anticoagulation in some European countries but rarely in the United States. Whatever combination of treatments is chosen, the INR should be checked 30 minutes after the initial infusion and, if it has not decreased to between 1.2 and 1.5, consideration should be given to administration of further doses of FFP or PCC.[60]

rFVIIa is a promising candidate for rapid reversal of warfarin anticoagulation after ICH,[65] but there is currently no strong evidence to support its widespread use for this indication. Its short half-life means that repeated doses are necessary and the increased incidence of thrombotic events in nonanticoagulated patients with ICH raises concern about its use in a group of patients who are already at high risk of thromboembolism. Furthermore, its high cost is likely to be a significant impediment to widespread use.

The optimal time for resumption of oral anticoagulation is unresolved. However, in the acute phase, the risk of recurrent ICH from restarting warfarin exceeds the risks of systemic thromboembolism from withholding it.[66] In patients with prosthetic heart valves, the risk of valve thrombosis in the absence of warfarin has been estimated at 1.8% per year and of ischemic stroke at 4% per year, producing an overall risk of valve-related thromboembolism of 0.2% to 0.4% over a 2-week period.[67] Oral anticoagulation is usually withheld for between 7 and 10 days after ICH.[44,54,55] Beyond this time, the risk of thromboembolic events in the absence of anticoagulation outweighs that of recurrent ICH after its reintroduction.[68,69] However, survivors of lobar ICH with atrial fibrillation should not be offered long-term anticoagulation because the risks of recurrent hemorrhage outweigh the potential benefits.[69] The role of IV heparin, or subcutaneous low-molecular-weight heparin (LMWH), as temporary therapy prior to reinstitution of warfarin is unclear.[54]

Antiplatelet Drugs

With an increasingly elderly population, there has been a dramatic increase in the number of patients receiving long-term antiplatelet medication. Aspirin is associated with an absolute risk increase in ICH of 12 events per 10,000 persons, although this must be put into the context of an overall benefit of aspirin in terms of reduced risk of myocardial infarction and ischemic stroke.[70] High-dose aspirin increases the risk of ICH further in the elderly, particularly in association with untreated hypertension.[16] The risk of ICH is increased even more by the combination of aspirin and clopidogrel.[71] Antiplatelet therapy is also an independent predictor of hematoma expansion.[23] There are no data confirming the efficacy of platelet replacement or other specific interventions after antiplatelet therapy–related ICH, and further studies on this issue are required.

NEUROSURGERY

The value of placement of a ventricular drain in patients with hydrocephalus is undisputed, but the timing and nature of other neurosurgical interventions are more controversial.[72,73] One meta-analysis failed to show a statistically significant reduction in the odds of death with surgical intervention (odds ratio, 0.84; 95% confidence interval, 0.67–1.07) compared with standard medical therapy.[74] The Surgical Trial in Intracerebral Hemorrhage (STICH) randomized 1033 patients with supratentorial ICH to surgery within 72 hours or conservative management; no outcome benefit of hematoma evacuation compared with standard medical therapy was demonstrated.[75] Although STICH suggests that early surgery is ineffective, it does not confirm that it is useless in all cases because the study was based on clinical equipoise; patients who the local investigator thought might benefit from hematoma evacuation were not recruited into the study. The STICH trial also did not set out to differentiate deep-seated ICH with IVH and hydrocephalus from more superficial lobar ICH for which the prognosis is much better. Only 222 patients with lobar ICH were randomized, possibly because so many neurosurgeons believed that such patients should undergo surgery. There is some evidence to support this view; a post hoc analysis of the STICH data showed that a subgroup of patients with superficial hematomas and no IVH gained benefit from surgery.[76] Because the mean time to surgery was >24 hours, STICH also does not exclude the possibility that earlier surgery might have been beneficial in some patients. However, there is evidence from other sources that ultraearly surgery (within 4 hours of ictus) is associated with an increased risk of rebleeding and higher mortality (>75%).[77] These controversies provided impetus for the continuing STICH-II study that will evaluate the role of early surgery in superficial supratentorial lobar hematomas in patients without IVH.† In contrast to supratentorial lesions, there is better evidence that patients with a posterior fossa hematoma benefit from early surgical evacuation because of the high risk of deterioration.[78] The place of decompressive craniectomy after ICH is not established, although in a small series, 6 of 11 patients (54.5%) treated with hemicraniectomy had a good functional outcome.[79] These findings suggest that a randomized controlled trial of decompressive craniectomy after ICH is warranted.

Hematoma aspiration via minimally invasive surgery (MIS) offers some advantages over conventional surgery, including the possibility for local anesthesia, reduced operating time, and reduced tissue trauma.[80] Thrombolysis, with or without clot aspiration, can also be performed using MIS, but one meta-analysis concluded that, although intraventricular thrombolysis is safe, there is no definite evidence of efficacy.[81] However, preliminary data from the Minimally Invasive Surgery plus rtPA for Intracerebral hemorrhage Evacuation (MISTIE) trial suggest that MIS plus recombinant tissue plasminogen activator (rtPA) offers greater clot resolution than conventional medical therapy.[82] A recent preliminary report of the Clot Lysis Evaluating Accelerated Resolution on Intraventricular Hemorrhage (CLEAR-IVH) trial also confirms that low-dose rtPA can be safely administered to stable IVH clots and may increase lysis rates.[83]

OTHER INTENSIVE CARE MANAGEMENT

Patients with depressed conscious level require ventilatory support as well as cardiovascular and ICP monitoring and management in an intensive care unit. However, close observation in an intensive care environment is recommended for many nonventilated patients for at least the first 24 hours because the risk of neurological deterioration is greatest during this period.[25] Systemic medical complications, including pneumonia, neurogenic lung injury, hyperglycemia, and fever, are common after ICH and associated with increased intensive care unit and hospital length of stay and worsened outcome.[84] There is substantial evidence that management in a specialist neurointensive care unit results in improved outcomes after ICH.[85] The exact reasons for this remain unclear, although the delivery of consensus-based, protocolized treatment strategies by a dedicated multiprofessional team familiar with the interactions between the injured brain and nonneurological organ systems, as well as early transfer to a multidisciplinary stroke rehabilitation unit, are likely to play a role. Attention has also focused on the major role that therapeutic nihilism and self-fulfilling prophesies of doom can have on determining outcome when patients with ICH are cared for by nonspecialist teams.[86]

Control of ICP

There is a high risk of increased ICP after large-volume ICH, particularly in the presence of IVH.[87] Although there is limited evidence for the monitoring and management of ICP after ICH, many neurocritical care units continuously monitor ICP in all sedated ICH patients requiring mechanical ventilation. Although the majority of the evidence base

†Available at: http://www.ncl.ac.uk/stich/. Accessed December 14, 2009.

and consensus guidance for the treatment of intracranial hypertension relates to traumatic brain injury, similar principles are applied empirically to the ICH patient population. Standard medical treatment of increased ICP should therefore be initiated as appropriate, a detailed discussion of which is beyond the scope of this review.

Anticonvulsant Therapy

Approximately 8% of patients with ICH develop clinical seizures within 30 days of the ictus, and continuous electroencephalographic monitoring demonstrates subclinical seizure activity in up to 25%.[88] Seizures are more likely to occur in the presence of a lobar hematoma.[89] The use of prophylactic anticonvulsant medication after ICH is controversial, although one small study showed that it does reduce the risk of early seizures.[89] Current guidance does not recommend universal prophylaxis, but that therapy should be considered in selected patients with lobar ICH.[2,44] If seizures do occur, they should be treated aggressively in the usual manner.

Glycemic Control

Hyperglycemia worsens cerebral ischemic injury, and admission hyperglycemia is associated with increased 30-day mortality after ICH.[90] However, the targets for glycemic control are unclear, and there is increasing evidence that "tight" glycemic control with insulin infusion can be associated with a critically low cerebral extracellular glucose concentration after brain injury.[91] Until further data become available, systemic glucose levels should not be treated in the acute phase after ICH unless >10.0 mmol/L (180 mg/dL).[92]

General Therapy

General measures, including fluid management, fever control, provision of enteral nutrition, and prevention of aspiration pneumonia and bedsores, are the same as for patients with ischemic stroke.[2,44,93] Thromboembolic prophylaxis with compression stockings and intermittent pneumatic compression is recommended in all patients from admission. Subcutaneous low-molecular-weight heparin should be considered after 24 to 48 hours, when it does not seem to result in an increased risk of recurrent hemorrhage.[94]

SUMMARY

ICH is a devastating disease, and the long-standing controversy over its optimal management remains largely unresolved. However, there is optimism that new insights into its pathophysiology will lead to the introduction of targeted management strategies. A greater understanding of the dynamic processes that occur after ICH is likely to result in the development of therapies aimed at the prevention of neurological deterioration and improve outcome by minimizing hematoma expansion, perihematoma edema, and secondary neuronal damage. An awareness of the adverse effects of systemic physiological disturbances is also likely to lead to the introduction of evidence-based treatments that were previously delivered on an empirical basis. Continuing randomized, controlled trials will clarify the correct approach to early BP management and the indications for surgical interventions after ICH. Promising future treatments include the development of antiinflammatory drugs that inhibit or reduce perihematoma edema, surgical techniques that maximize hematoma removal while minimizing damage to normal tissue, and thrombolytic therapy for IVH. There is a short time window for the stabilization and acute management of patients with ICH, and an increasing recognition that focused management in a specialist neurocritical care unit is associated with improved outcome. The days of treatment nihilism are being replaced by an appreciation that aggressive management in the acute phase can translate into improved outcomes.

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