Modern Treatment Options for Intracerebral Hemorrhage

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Opinion statement

Spontaneous intracerebral hemorrhage (ICH) is a devastating neurological event with a 30-day mortality of approximately 40%. Recent research provides new insights into the pathophysiology of ICH-associated edema, with potential molecular and cellular targets for future therapy. Neuroimaging techniques such as gradient echo MRI are yielding insights into cerebral microbleeds and the microangiopathies associated with hypertension and cerebral amyloid angiopathy. Recent literature provides new medical treatment strategies for fever, acute hypertension, and perihematomal edema, and methods of reducing intracranial pressure. Two randomized controlled trials have provided crucial evidence regarding surgical and medical intervention for acute ICH intervention. Recombinant factor VIIa appears to lessen growth of ICH when administered within 4 hours of ictus. Further study of potential efficacy and safety is underway in an international phase III trial. In addition, the Surgical Trial in Intracerebral Hemorrhage reported results from an international randomized trial of 1033 patients who did not show benefit for surgical evacuation of ICH, compared with medical therapy alone. Less invasive surgical methods for hematoma evacuation, studied previously over the past decade, continue to be investigated.

Introduction

Spontaneous intracerebral hemorrhage (ICH) is more than twice as common as subarachnoid hemorrhage but equally as deadly [1], carrying a 1-month mortality of 40% [2, Class IIIa2]. Although ICH was once thought to be a monophasic event, clinical-radiographic studies demonstrated that hematoma growth occurs during the first 24 hours after onset [3••, Class IIa]. In the study reported by Brott *et al.* [3••, Class IIa], growth in ICH volume by more than one third occurred in 38% of ICH patients over the first 24 hours and was associated with neurologic deterioration.

Diagnosis of ICH is by established history, neurologic examination, and noncontrast head CT [4••]. Patients with ICH frequently progress to coma, requiring intubation, mechanical ventilation, and critical care management of blood pressure, temperature, fluids, and electrolytes. Secondary complications from ICH include intraventricular extension, hydrocephalus, increased intracranial pressure (ICP), seizures, aspiration or ventilator-associated pneumonia, deep venous thrombosis, pulmonary embolus, and myocardial injury. Poor prognostic predictors include ICH volume 30 cm^3 or more, age older than 80 years, infratentorial location, low presenting Glasgow Coma Scale (GCS) [5••, Class IIIa2], and the presence of intraventricular blood [6, Class II]. Additional prognostic factors include QTc dispersion on electrocardiogram [7], extreme ends of high or low systolic blood pressure (SBP) around an inflection point of 130 mm Hg [8, Class IIa], and high serum glucose at admission [9, Class IIIa2]. This article focuses on recent literature providing new medical and surgical treatments for spontaneous (nontraumatic) ICH.

ETIOLOGY AND PATHOGENESIS

Spontaneous ICH occurs in approximately 37,000 to 50,000 Americans annually [4••]. It is estimated that approximately one of five cases (7,000–10,000) of ICH may occur in the setting of warfarin anticoagulation [10••]. Clinical risk factors for ICH include advancing age,

hypertension [11], International Normalized Ratio (INR) intensity more than 3.5 [12], and prior stroke. Neuroimaging factors predictive of future and recurrent ICH include leukoaraiosis severity, evidence of recent or prior stroke, and the presence of cerebral microbleeds [13–18].

Location is an important feature of ICH. Anatomic patterns include cerebral hemispheric (deep, lobar, or involvement of deep and lobar tissue), brainstem, and cerebellum. Deep cerebral hemispheric brain parenchyma includes the putamen, globus pallidus, thalamus, caudate, internal capsule, and other deep white matter loci. The location of ICH provides clues toward pathogenesis. The attributable risk of hypertension for nonlobar ICH is approximately 0.5, suggesting hypertension causes approximately 50% of deep (nonlobar) ICH. In contrast, lobar ICH is attributed to cerebral amyloid angiopathy in approximately one third of cases [11]. Advancing age is a very important risk for ICH occurring at all locations, but the attributable risk of advancing age for spontaneous ICH in general, or by location, has not been established. Other causes of nontraumatic ICH include bleeding from arteriovenous malformations, aneurysms, cavernous angiomas, moyamoya, venous sinus thrombosis, venous angiomas, neoplasm, stimulant drug use, and vasculitis [19].

Chronic hypertension is associated with pathologic changes termed lipohyalinosis, a process affecting small penetrating arteries or arterioles (50–200 μm), often at branch points. Pathologic studies describe microaneurysm (Charcot-Bouchard) formation, which are thought to rupture and cause ICH [20,21]. Cerebral amyloid angiopathy is a disorder caused by amyloid protein deposition within the walls of blood vessels in cortical-subcortical locations. Amyloid-laden blood vessels are fragile and prone to bleed. Cerebral amyloid angiopathy also affects leptomeningeal blood vessels covering the surface of the brain (pial), which can bleed and cause subarachnoid hemorrhage [17].

EVALUATION AND DIAGNOSIS

Patients with ICH present with altered level of consciousness, sudden headache, neck pain, vomiting, or focal neurologic deficits and have CT evidence of a focal accumulation of intracerebral blood. Neurologic deficits depend on the area of brain or brainstem affected. Occasionally a patient becomes unconscious or rapidly comatose because of massive ICH, increased ICP, brainstem compression, generalized seizure, or post-ictal state. Given the acuity and severity of presentation, patients are typically brought to the emergency department for evaluation.

A history should be collected from the patient if possible. However, if the patient is aphasic, unconscious, or comatose, the information should be collected from witnesses. Time of onset of symptoms, history of trauma or fall, past medical and surgical history, allergies, medications, family history, smoking, illicit drug use, and alcohol history should be obtained in an efficient manner. Emergent noncontrast head CT should be performed without delay unless the patient is medically unstable. Although MRI technology is emerging [22], CT remains the diagnostic test of choice for detecting ICH because of its widespread availability, rapid acquisition time, and high sensitivity for acute intracranial blood. Standard laboratory tests include complete blood count with platelet count, prothrombin time, activated partial thromboplastin time, serum glucose, electrolytes, blood urea nitrogen, creatinine, and an electrocardiogram. CT typically shows a spherical or ellipsoid accumulation of intraparenchymal blood (Fig. 1). ICH location is deep (nonlobar) in 50% of cases and lobar in one third [11]. Extension of the hematoma into the ventricles is common [6, Class II] and can cause dilated ventricles (hydrocephalus). Intracerebral hematoma volume (cm^3) can be easily and reliably calculated by the formula ABC/2 [23], in which A and B are the largest perpendicular diameters of the hematoma in centimeters, and C is the number of vertical CT slices multiplied by the slice thickness (cm).

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Treatment

Medical management

- Standard medical therapy includes blood pressure, temperature, glucose, and electrolyte regulation, while preventing complications during hospitalization including pneumonia, deep venous thrombosis, and pulmonary embolism. Medical therapies that have failed to show benefit in ICH include 10% intravenous glycerol [25], gavestinel [26], dexamethasone [27,28], and epsilon-aminocaproic acid [29]. For standard medical therapy in acute ICH, one is referred to the comprehensive reviews of Manno *et al.* [30•] and the Stroke Council, American Heart Association Guidelines [4••].

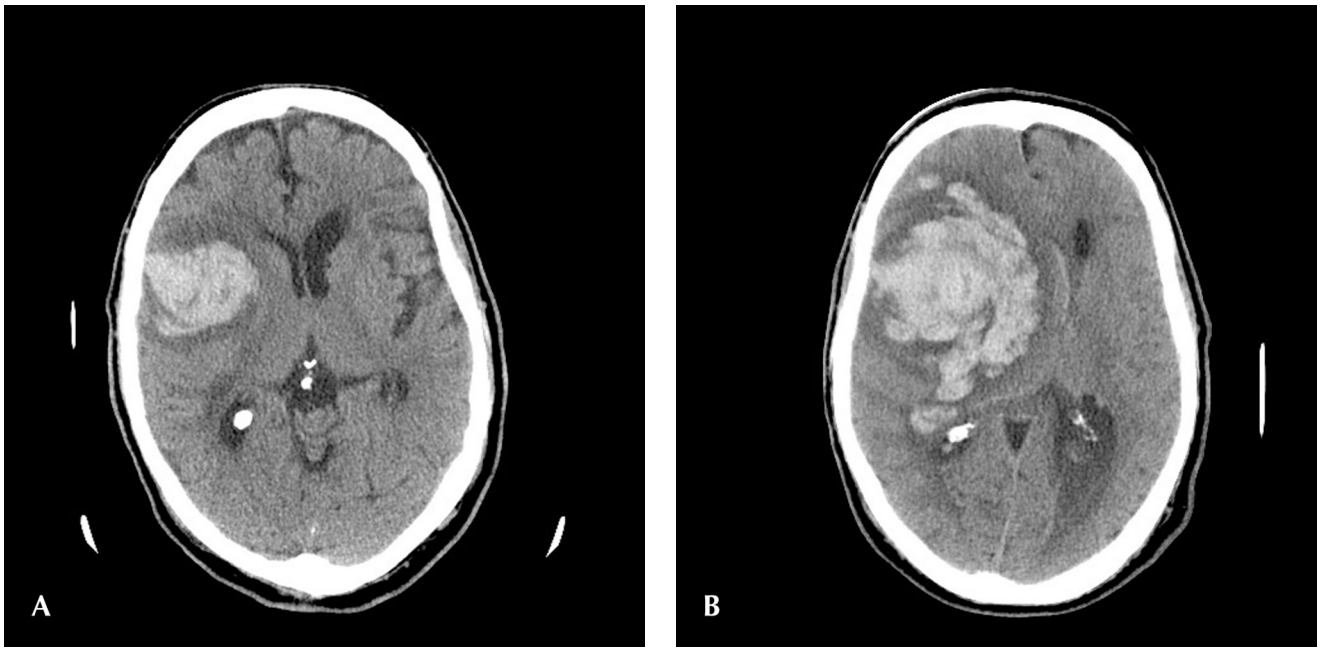

Figure 1. A, An 81-year-old patient with acute intracerebral hemorrhage (ICH). ICH volume is calculated by the formula ABC/2 [23]. A and B are perpendicular diameters of the hematoma on the CT slice with maximal hematoma size. The vertical diameter, C, is obtained by counting the number of vertical slices that display the hematoma (10, not shown) multiplied by slice thickness (0.5 cm/slice). The values obtained for A (4 cm), B (4.5 cm), and C (5 cm) are then multiplied together and divided by 2. Hematoma volume by this method in this case is 45 cm^3. **B**, Hematoma enlargement in this patient's case (1 hour and 42 minutes after the first CT) is approximately 390% enlarged (6.7 cm $\times$ 9.6 $\times$ 14 slices at 0.5 cm/slice) to 227 cm^3. Hematoma enlargement can be calculated as percentage of change in ICH volume by the formula $(F - I)/I \cdot 100$, in which F represents later CT-measured ICH volume (cm^3) and I represents the earlier CT-measured ICH volume [24, Class I].

Treatment of hypertension

- Arterial blood pressure treatment guidelines in acute ICH are conservative within the first few hours, with treatment typically avoided unless SBP exceeds 230/140 mm Hg, SBP is sustained greater than 180 to 230 mm Hg, or sustained diastolic blood pressure (DBP) is greater than 105 to 140 mm Hg [4••]. Considerable controversy remains regarding whether high arterial blood pressure contributes to intracerebral bleeding and if lower blood pressures can cause perihematomal ischemia or hematoma enlargement [31].
- The natural history of hypertension in acute ICH is thought to decline within 6 hours of acute ICH before reaching a plateau [32, Class IIIa2; 33]. Qureshi *et al.* [33] found a decline in mean arterial pressure (MAP) of approximately 2 mm Hg per hour (mean values ± 1.9, range -8.5 to +0.6) within the 24 hours, with a faster slope of MAP decline in ICH patients with higher mortality ($P = 0.04$). Because blood pressure declines naturally after acute ICH, overaggressive treatment may be unwise. Typically, short-acting intravenous medications such as labetalol, esmolol, and enalaprilat are administered [4••] for ICH-related hypertension in the first few hours.
- Newer studies provide insight into antihypertensive treatment in acute ICH. In a positron emission tomography (PET) regional cerebral blood flow (rCBF) study, Powers *et al.* [31] randomized 14 ICH patients (1–45 cm^3 ICH volume) to pharmacologic MAP reduction with labetalol or nicardipine. A MAP reduction of 11% to 21% occurred (143 ± 10 to 119 ± 11 mm Hg), with no change in pre- and post-treatment rCBF [31]. Dog experiments of acute ICH with a pharmacologically reduced MAP (within normal autoregulatory limits of cerebral perfusion pressure) showed no detriment

in rCBF around or distant to the hematoma [34]. Qureshi *et al.* [35] treated 27 acute ICH patients with hypertension to keep SBP less than 160 mm Hg and DBP less than 90 mm Hg and found a low rate of neurologic deterioration and hematoma expansion when patients were treated within the first 6 hours. Zazulia *et al.* [36] used PET to measure cerebral metabolic rate of oxygen consumption ($CMRO_2$), CBF, and oxygen extraction fraction (OEF) in 19 ICH patients and found reduced perihematomal CBF, $CMRO_2$, and OEF, suggestive of reduced perihematomal metabolism.

- Although newer studies provide a lower blood pressure threshold for antihypertensive treatment, larger randomized controlled trials are needed in acute ICH to investigate whether aggressive blood pressure control impacts early hematoma growth and clinical outcomes.

Treatment of fever

- Fever is detrimental in brain-injured patients [37,38•,39,40]; fever increases basal metabolic rate (BMR) [41] and increases $CMR0_2$. ICH patients with fever (temperature ≥ 38° C) should be physically examined, and when clinically appropriate, should undergo laboratory testing or imaging to determine the source of infection. Fever of neurologic origin may occur when blood extends into the subarachnoid or intraventricular space, but ascribing fever to neurologic origin should be a diagnosis of exclusion. In patients with fever and ICH, acetaminophen is typically administered first, with caution in elderly or hepatic disease patient populations.
- Intracerebral hemorrhage patients with persistent fever that is refractory to acetaminophen and without infectious cause may require cooling devices to become normothermic. Such patients have been the subject of recent study (Table 1) [37,38•; 42•, Class I; 43••]. Diringer *et al.* [38•] prospectively studied 296 patients admitted to neurologic intensive care units, comparing conventional treatment (acetaminophen and a cooling blanket) against conventional treatment plus use of an intravascular catheter-based cooling device. The intravascular cooling device and conventional treatment reduced fever burden (area under curve, degrees C-hours) by 64%, compared with conventional treatment alone. Mayer *et al.* [42•, Class I] performed a randomized controlled trial in 47 patients in the neurologic intensive care unit with fever (≥ 38.3° C for 2 hours after receiving acetaminophen), administering a conventional cooling blanket or hydrogel-coated water-circulating cooling pads applied to the trunk and thighs. Patients treated with the cooling pads experienced a 75% reduction in fever burden, spent less time febrile ($P < 0.001$), spent more time normothermic, and reached normothermia faster than when treated with a conventional cooling blanket. However, cooling pads caused more shivering compared with the cooling blanket.

Treatment of shivering

- Shivering represents an expected physiologic response to cooling [43••] but raises BMR and oxygen consumption similar to fever [41,46]. Shivering represents a formidable thermoregulatory defense of the autonomic system [43••], is difficult to control in unanesthetized patients, and often requires several methods of treatment [42•, Class I; 45,46]. A stepwise approach to reduce shivering was used in the study by Mayer *et al.* [42•, Class I] (Table 2). Thiopental or fentanyl reduces hyperthermia and also reduces $CMRO_2$. In selected intubated, mechanically ventilated patients with refractory fever and increased ICP, treatment with acetaminophen, cooling devices, $CMRO_2$-reducing sedatives, and competitive neuromuscular blocking agents can be used as a method of last resort.

Table 1. Methods for cooling febrile* ICH patients

1. Acetaminophen 650 mg enterally or rectally every 6 hours as needed for fever
2. Surface cooling (air and/or water conductive) blanket
3. Increasing intravenous fluid rate of infusion (especially with cool fluids)
4. Cooling device (if available):
   Cooling pads applied to trunk or thighs [42•, Class I] or
   Central venous catheter–based cooling device [38•]
5. In mechanically ventilated patients, sedative-analgesic infusion can be increased (eg, propofol, fentanyl)

*Fever is defined as core temperature > 38° C [44•]. Goal of cooling therapy is normothermia (37° C). Medical causes of fever should be investigated and treated when clinically appropriate [44•]. Harmful side effects from cooling include vasoconstriction, adrenergic hyperactivation [43••], and postoperative myocardial events [45].
ICH—intracerebral hemorrhage.

Table 2. Treatment algorithm to reduce shivering*

1. Apply heated polyvinyl chloride-lined boots and mittens
2. Warm the face and neck with a standard face tent with warmed, humidified air
3. Apply a warming blanket that circulates warm air inside the blanket over the patient's body
4. Meperidine intravenously (25–75 mg every 2 hours) as needed
5. Oral buspirone 30 mg every 8 hours orally or by nasogastric tube
6. In mechanically ventilated patients, sedative infusion rate (propofol, fentanyl, dexmedetomidine) can be increased, and if refractory, competitive neuromuscular blocking agents can be administered with sufficient sedation

*Although meperidine is very effective in reducing shivering, it can be combined with dexmedetomidine or buspirone for additive or synergistic effects, respectively, in lowering the shivering threshold [43••,46,47]. Meperidine can cause sedation, seizures, and central nervous system toxicity.
(*Modified from* Mayer *et al.* [42•, Class I].)

Hematoma growth

- Intracerebral hemorrhage growth (volume increase of at least 33%) occurs in approximately 38% of patients, with 26% of hematoma growth occurring between the baseline and 1-hour CT scan, and the remaining 12% of patients with hematoma growth between the 1- and 20-hour CT scans [3••, Class IIa]. Hematoma growth (Fig. 1) is associated with neurologic deterioration [3••, Class IIa; 31, Class IIIa2], and hematoma volume is a powerful predictor of 30-day mortality [2]. Factors that have been associated with hematoma enlargement include presentation within 6 hours of ictus, antiplatelet or anticoagulant therapy, and liver disease [32, Class IIIa2; 48, Class III].
- Antiplatelet therapy or platelets less than 100,000/μL was independently predictive of hematoma growth more than 40% on CT scans performed within 24 hours [32, Class IIIa2]. In patients taking antiplatelet agents (eg, aspirin, clopidogrel, ticlopidine), warfarin, or both, it is crucial to stop the medication. When thrombocytopenia less than 50,000/μL is present, transfusion of platelets is warranted.
- Although it seems intuitive that high blood pressure during ICH may contribute to ICH growth, there are limited data to support a cause and effect relationship. Kazui *et al.* [49, Class IIIa2] found that SBP greater than 200 mm Hg at admission correlated with hematoma expansion. Brott *et al.* [3••, Class IIa] failed to confirm a relationship, and Toyoda *et al.* [32, Class IIIa2] also did not find an association of increasing levels of hypertension with ICH growth. Furthermore, two studies report reduced hematoma enlargement in acute ICH patients when SBP was treated to 150 mm Hg or less [35; 50•, Class IIIa2].

Treatment to reduce hematoma growth

- Because ICH volume correlates strongly with mortality, reducing hematoma growth and volume appears to be the logical target for therapeutic intervention. In a landmark randomized controlled trial, Mayer *et al.* [51••, Class I] investigated a drug, recombinant factor VIIa (rFVIIa), on early hematoma growth. rFVIIa (NovoSeven; Novo Nordisk) is a cloned product of endogenous activated coagulation factor VII and has US Food and Drug Administration (FDA) label indication for bleeding episodes in hemophiliac patients with factor inhibitors [52]. Three hundred and ninety-nine patients with acute ICH were randomized to receive placebo or 40 μg/kg, 80 μg/kg, or 160 μg/kg of rFVIIa within 1 hour after a baseline CT scan. The primary outcome of the study was to assess hematoma growth at 24 hours. The study found a dose-dependent effect on reducing hematoma growth, with a mean increase of 29%, 16%, 14%, and 11% in the placebo, 40 μg/kg, 80 μg/kg, and 160 μg/kg doses, respectively ($P = 0.01$). Clinical outcomes were secondary measurements by the modified Rankin Scale (mRS). The mRS assessed at 90 days and found 69% of placebo-treated patients dead or severely disabled (mRS = 4–6), compared with 49% to 55% for the rFVIIa-treated patients ($P = 0.004$). Mortality at 90 days was 29% for placebo-treated patients, compared with 18% in rFVIIa-treated patients. Thromboembolic events of myocardial infarction or ischemic stroke occurred in 7% of rFVIIa-treated patients, compared with 2% of placebo patients ($P = 0.12$).

Recombinant factor VIIa (NovoSeven)

Standard dosage	To address the safety issue and an optimal dose, Novo Nordisk and the NovoSeven Investigators are conducting a phase III trial in the United States and Europe. More than 170,000 doses of rFVIIa have been administered to hemophiliac patients, for whom the drug was originally manufactured, and only 17 serious thromboembolic complications have been reported [53].
Main drug interactions	Reverses warfarin anticoagulation.
Main side effects	Although this study certainly has implications for an effective drug for acute ICH, issues regarding drug safety and the incidence of thromboembolic complications remain. Despite the randomized trial data provided by Mayer *et al.* [51••, Class I] of rFVIIa limiting hematoma growth, the FDA will not approve label indication for rFVIIa for acute ICH until safety and potential dose-response issues are clarified.
Special points	Pending completion of the ongoing phase III trial, we do not recommend use of rFVIIa outside of a clinical trial protocol.
Cost/cost effectiveness	Another important issue is the cost of rFVIIa, which is approximately $1020 to $1369 per 1.2-mg vial [54•, Class IIIa2; 55•].

Warfarin-related intracerebral hemorrhage

- Warfarin-related spontaneous ICH occurs in approximately 7,000 to 10,000 patients annually [10••] or about one of every five cases of spontaneous ICH. Risk factors for warfarin-related ICH include [56] age, hypertension, cerebrovascular disease, prior ICH, intensity and duration of anticoagulation, and cerebral amyloid angiopathy. Warfarin-related intracerebral hematomas are thought to be larger [57; 58, Class IIIa1; 59•, Class IIIa2; 60] and continue to grow after 24 hours, which is rare in spontaneous ICH not associated with anticoagulation. Thirty-day mortality is also higher in warfarin-related ICH (50%) [59•, Class IIIa2], compared with patients not anticoagulated with ICH (40%) [2, Class IIIa2]. In patients with atrial fibrillation, the risk for warfarin-related ICH is the same for an INR less than 2 and for the 2 to 3 range, yet

increases when INR is 3.5 to 3.9 (adjusted odds ratio = 4.6 [CI = 2.3–9.6]) [12]. The intensity of anticoagulation also contributes to hematoma expansion [61] and worse outcomes [58, Class IIIa1]. Therefore, patients with symptomatic, warfarin-related ICH with an INR more than 1.3 should have emergent anticoagulation reversal.

Treatment of acute warfarin-related intracerebral hemorrhage: recombinant factor VIIa

- Recent, small retrospective studies have investigated the use of rFVIIa in warfarin-related ICH [54•, Class IIIa2; 62]. In a study of seven patients with spontaneous warfarin-related ICH, 15 to 90 μg/kg of rFVIIa were administered with standard therapy (vitamin K and fresh frozen plasma [FFP]) and rapidly normalized the INRs [54•, Class IIIa2]. The study also demonstrated a later increase in the INR, suggesting rFVIIa's short half-life of 2.5 hours [52], necessitating full doses of vitamin K and FFP for complete anticoagulation reversal. In a similar study, Brody *et al*. [62] studied rFVIIa use in 13 patients with warfarin-related ICH along with standard therapies of vitamin K and FFP, compared with 15 patients who received FFP and vitamin K without rFVIIa. Patients were administered rFVIIa (mean dose 4.8 mg, range 2.4–9.6) if there was worsening neurologic status (GCS < 8 rFVIIa group vs standard group, $P < 0.01$). They found a fourfold faster decrease in INR with rFVIIa use, compared with FFP. There were no differences between groups in surgical intervention, intensive care unit or hospital length of stay, and discharge GCS. Five patients in the rFVIIa group died (42%), whereas two died in the standard group (13%), but the difference was not statistically significant. Both studies demonstrated favorable safety profiles, with one patient developing disseminated intravascular coagulation in the setting of pre-existing renal failure [62].
- Recombinant factor VIIa appears promising as therapy for warfarin-related ICH, particularly for emergency warfarin anticoagulation reversal. Although promising, similar issues remain regarding the use of rFVIIa for warfarin-related ICH, including optimal dose, safety, and cost. In the studies investigating warfarin-related hemorrhage and rFVIIa [53; 54•, Class IIIa2; 62–64,65•], thromboembolic complications appear uncommon but have not been prospectively studied in large populations.

Summary treatment recommendations for warfarin-related intracerebral hemorrhage

- The first step in anticoagulation reversal in warfarin-related ICH is discontinuation of warfarin. The next step is intravenous bolus administration of rFVIIa (10–40 μg/kg) [54•, Class IIIa2; 66•] while simultaneously ordering and administering complementary therapies of vitamin K_1 (phytonadione) and FFP [67••]. Five to 10 mg of intravenous vitamin K_1 should be administered slowly over 30 minutes [67••,68], noting warfarin resistance up to a week occurring in doses greater than 5 μg. Intravenous vitamin K carries a risk (3/10,000) of anaphylaxis [69] and uncertain risk (possibly rare) of anaphylactoid reaction [70]. Fifteen cm^3/kg of FFP should be administered to fully reverse anticoagulation [71]. In locations where rFVIIa is unavailable, prothrombin complex concentrates and vitamin K can be administered [72•]. In locations where rFVIIa and prothrombin complex concentrates are unavailable, intravenous vitamin K and FFP should be given without delay. Coagulation parameters should be assessed after treatment and daily until anticoagulation is reversed. We consent, prescribe, and document rFVIIa use in this setting. Patients or their legal representatives are informed regarding potential benefit, the potential for thromboembolic complications, and issues regarding cost.

Intraventricular hemorrhage and hydrocephalus

- Intraventricular hemorrhage (IVH) commonly results from extension of ICH into the ventricles. Volume of intraventricular blood, like volume of intracerebral blood, is an independent predictor of mortality [6, Class II]. Standard treatment for IVH with acute obstructive hydrocephalus includes drainage of cerebrospinal fluid (CSF) by external ventriculostomy [6, Class II]. Infusion of urokinase into the ventricles of patients with IVH by ventriculostomy speeds clot resolution within the ventricles [73] and may improve 30-day mortality [74–77]. Rebleeding into the ventricles with urokinase treatment occurred in 6.25% of patients [75]. Use of recombinant tissue plasminogen activator (rtPA) has also proceeded at some institutions [78•]. A large, multicenter prospective phase IIb trial (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage) is investigating the optimal dose of intraventricular rtPA to expedite removal of IVH [79].

Perihematoma edema

- Three phases of perihematomal edema occur after ICH [80]. The first phase is early (first few hours) and includes separation of clot and plasma (clot retraction) [80]. The second phase, over the next 2 days, involves plasma protein extravasation, activation of the coagulation cascade and complement, and an inflammatory process triggered by fibrin and thrombin. The third phase (after day 3) involves erythrocyte lysis and hemoglobin-mediated neuronal toxicity. Perihematoma edema volume increases up to 75% of the hematoma size in hyperacute ICH patients and is strongly predictive of functional outcome [81,82]. Heparinized blood injected into pig brain [83] is associated with minimal perihematomal edema. Patients who suffered an ICH after rtPA administration [84] develop significantly less perihematoma edema than do those patients with spontaneous ICH. Similarly, pig brains injected with autologous blood containing rtPA showed reduced perihematomal edema and ICH volume [85]. Leukocytes recruited to the perihematomal area secrete inflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-α [86]. Erythrocyte lysis with hemoglobin release leads to hemoglobin breakdown products such as iron, biliverdin that interact with free radicals, generating neurotoxic excitatory amino acid glutamate [86], and upregulation of matrix metalloproteases (MMPs). The inflammatory cytokines and MMPs serve as potential future therapeutic targets of intervention to reduce perihematomal edema.

Treatment of increased intracranial pressure

- Standard methods to control increased ICP, including head of bed elevation (30 to 45 degrees), mannitol (0.25–0.5 g/kg every 4 hours), furosemide, hyperventilation, sedation/paralysis, and ventriculostomy to drain CSF, are treatments described in Stroke Council, American Heart Association Guidelines [4••].
- A recent study compared high-dose mannitol (approximately 1.4 g/kg) with lower-dose (approximately 0.7 g/kg) mannitol in patients with preoperative temporal lobe ICH associated with pupillary enlargement [87]. Patients who received high-dose mannitol had reversal of pupillary enlargement and better 6-month clinical outcomes.
- Hypertonic saline (2% to 3% and in 23.4% concentrations) is emerging as a new treatment option for reducing ICP. Recent studies indicate that hypertonic saline may be as effective as mannitol for reducing ICP and

with similar safety in brain-injured patients [88–91]. Hypertonic (3%) saline/acetate was studied in 27 patients with cerebral edema and increased ICP, eight of whom had spontaneous ICH [91]. Hypertonic saline infusion increased serum sodium concentrations to 145 to 155 mmol/L and reduced ICP in patients with traumatic brain injury and postoperative brain edema, but not in patients with ICH or cerebral infarction. Suarez *et al*. [92] studied 20 patients (one with basal ganglia ICH) retrospectively who were treated with 30-mL intravenous boluses of 23.4% saline (8008 mOsm/L) with intracranial hypertension refractory to standard ICP management, including mannitol (1 g/kg). Approximately 80% of patients had a decrease in ICP by more than 50% of the pretreatment value in approximately 20 to 30 minutes. In a dog model of ICH, hypertonic saline (3% and 23.4%) was equally as effective as 1 g/kg mannitol in reducing ICP [89]. Longer duration of effect was noted with hypertonic saline (especially 3%), compared with mannitol.

Treatment of seizures

- Anticonvulsants should not be routinely prescribed unless seizure occurs. When a seizure does occur, most neurologists treat acutely with intravenous lorazepam (Ativan; Wyeth, Madison, NJ) and follow with infusion of fosphenytoin or phenytoin to prevent early and late seizure recurrence. Prolonged anticonvulsant therapy is considered on a case-by-case basis. If no further seizures occur after 1 month, therapy can be discontinued [4••]. Nonconvulsive status (NCSE) may occur in up to 10% of patients with ICH in the neurointensive care unit [4••], and is difficult to detect clinically unless there are subtle motor manifestations such as eyelid twitching. Some neurointensive care units propose continuous electroencephalography monitoring to improve detection of NCSE.

Surgical management

Surgical therapy

- Meta-analysis of seven surgical trials for supratentorial ICH showed no benefit for surgery [93]. The Surgical Trial in Intracerebral Hemorrhage (STICH) was an international prospective randomized trial of 1033 patients comparing early surgery (503) versus initial conservative management (530) for patients with spontaneous ICH for whom best treatment was deemed uncertain [94••, Class I]. Favorable outcome was defined as good recovery or moderate disability on the Glasgow outcome scale. Twenty-six percent of patients randomized to early surgery had a favorable outcome, compared with 24% of patients randomized to conservative treatment ($P = 0.414$). The authors concluded that there was no overall benefit of early surgical evacuation of ICH compared with conservative medical therapy. Application of the results of STICH is limited with regard to very early surgery because 73% ($n = 339$) of patients in the early surgery arm did not undergo surgery until 12 hours from randomization, and only 16% ($n = 74$) underwent surgery within 12 hours of ictus. In addition, of the patients initially randomized to conservative treatment, 26% ($n = 140$) of patients later underwent surgery. Most patients (> 75%) underwent craniotomy, but other less invasive techniques were also used, including endoscopic and stereotactic methods of hematoma evacuation.

Emerging surgical therapies

- Although the STICH trial suggested no benefit of surgical treatment in supratentorial ICH, several recent studies have investigated newer surgical methods. Nishihara *et al*. [95] report use of novel transparent endoscopic tools for hematoma evacuation by using a burr-hole approach in 82 patients. Patients were treated within 24 hours of ICH onset. Vespa *et al*. [96] performed a pilot, nonrandomized study of ICH evacuation with frameless stereotactic aspiration and thrombolysis using rtPA in 28 ICH patients and found an ICH volume reduction of 77% after surgery. Early clinical improvements were suggested by the difference in mean admission versus discharge National Institutes of Health (NIH) stroke scale (24 vs 16, $P < 0.001$). An earlier trial investigated stereotactic intracerebral hematoma evacuation with catheter-injected urokinase in 71 patients with ICH [97]. Hematoma volume was reduced, but there was no significant difference in mortality between surgical (56%) and nonsurgical patients (59%) at 180 days. Murthy *et al*. [98] performed decompressive craniectomy with clot evacuation for large hemispheric ICH (ICH volume > 48 cm^3) in 12 patients. Eleven patients survived to discharge, six with good functional outcome (mRS = 0–3). An NIH-sponsored safety study (Minimally Invasive Surgery Plus Recombinant Tissue Plasminogen Activator for Intracerebral Hemorrhage Evacuation) is investigating minimally invasive surgery in combination with rtPA for intraparenchymal hemorrhage removal [79].

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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