Neurosurg Focus 30 (6):E22, 2011

State of the art in managing nontraumatic intracerebral hemorrhage

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Nontraumatic intracerebral hemorrhage constitutes a major public health problem worldwide. Intracerebral hemorrhage leads to a high rate of morbidity and mortality. To date, no medical or surgical trials have clearly attested to the benefit of a particular therapy. The aim of this review was to summarize the best evidence for management decision-making in intracerebral hemorrhage. *(DOI: 10.3171/2011.3.FOCUS1145)*

Key Words • nontraumatic intracerebral hemorrhage • surgical management • hematoma

Nontraumatic intracerebral hemorrhage constitutes a major public health problem worldwide, accounting for 2 million (10%–15%)[81] of about 15 million strokes worldwide each year.[60] In the US, on average, someone has a stroke every 40 seconds.[60] Its direct cost is around US$12.7 billion of the US$73.7 billion related to stroke care annually.[60] Despite active research, it is still the least treatable cause of stroke and a leading cause of morbidity, disability, and death worldwide.[75] During the first month after ICH onset, the proportion of patients that die has varied from 22% to 62%.[17,24,39] Only 20% of persons who survive achieve functional independence at 6 months post-ICH.[39]

Incidence varies on the basis of age, race, and demographics. The incidence of ICH increases exponentially with advancing age, with rates doubling every 10 years after the age of 35 years.[19] Intracerebral hemorrhage is more common in Asian, African, and Hispanic American populations.[57,67] These differences are mostly predominant in hemorrhages in deep cerebral locations and in young and middle-aged people. Differences might be explained by the decreasing incidence in some populations that can easily access medical care and blood pressure control.[55,77]

Intracerebral hemorrhage commonly affects both supratentorial and infratentorial structures. In one study of 1014 ICHs, 50% were in a deep location (periventricular white matter, caudate nucleus, globus pallidus, putamen, internal capsule, or thalamus), 35% were lobar (gray matter or subcortical white matter), 10% were cerebellar, and 6% were in the brainstem (midbrain, pons, or medulla).[37]

In this review, we discuss the major risk factors and clinical and radiological features of ICH, as well as the clinical trials on managing this condition.

Risk Factors and Etiologies

Age increases the incidence of ICH, and men and postmenopausal women appear to have a greater risk.[6] Alcohol consumption doubles the risk of ICH when consuming more than 2 standards units of alcohol per day.[34] Sympathomimetics, such as amphetamines, increase the risk of ICH,[34] and smoking produces only a small increase in the risk of ICH.[6]

Hypertension is the most significant modifiable risk factor[70] and is estimated to be the cause of 50%–70% of all ICHs.[6,19,83] Hypertension is nearly as common in primary lobar hemorrhage as in deep, cerebellar, and pontine hemorrhages.[15] The more the stage of hypertension increases, the more the risk of ICH is important.[79] Regardless, hypertension is a very prevalent condition, and its existence should not exclude other causes of ICH, especially among young people.

Cerebral amyloid angiopathy is a risk factor for spo-

Abbreviations used in this paper: AVM = arteriovenous malformation; CAA = cerebral amyloid angiopathy; DAF = dural arteriovenous fistula; DS = digital subtraction; ICH = intracerebral hemorrhage; INR = International Normalized Ratio; rFVIIa = recombinant activated factor VII.

radic ICH. It is characterized by the deposition of congophilic material, usually amyloid-beta protein, in the walls of cortical and leptomeningeal bloods vessels. The incidence of CAA increases with age so that nearly 50% of all individuals older than 80 years have affected cortical and leptomeningeal blood vessels.[87] The major clinical manifestation of CAA is lobar hemorrhage, commonly associated with variations in the gene encoding apolipoprotein E.[64] Cerebral amyloid angiopathy is estimated to be the cause of 50% of lobar hemorrhages in elderly people.[91]

Anticoagulant therapy is a significant cause of secondary ICH. The incidence of anticoagulant-associated ICH quintupled during the 1990s probably due to the increasing use of this therapy.[36] Anticoagulant-associated ICH is estimated to be the cause of nearly 20% of all ICHs.[36] This condition is related to a higher risk of hematoma expansion and a higher mortality rate.[36] Patients on anticoagulant therapy often suffer from chronic hypertension or CAA, and thus these anticoagulant agents might exacerbate an existing risk.[45]

The other well-known causes of ICH are hemorrhagic transformation of ischemic stroke, vascular abnormalities (aneurysm, AVM, DAF, and cavernous malformation), venous thrombosis, vasculitis, arteritis, coagulopathy, and neoplasia.

Clinical and Radiological Features

Both ICH and ischemic stroke cause focal neurological deficits such as hemiparesis, hemisensory loss, aphasia, ophthalmoplegia, and visual fields cuts. Intracerebral hemorrhage produces blood leakage into the brain, causing compression, increasing intracranial pressure, and scattering in ventricles and subarachnoid spaces. Thus, ICH can cause additional symptoms such as headache, nausea, vomiting, progressive deterioration, and coma. Clinically, however, it is not always easy to distinguish an ischemic process from a hemorrhagic process. Intracerebral hemorrhage should be most suspected in patients presenting with a sudden focal deficit, including several vascular territories, that gradually increases over the time.

The immediate recommended imaging procedure to establish whether a process is ischemic or hemorrhagic is CT of the head.[16] In cases of ICH, CT provides information on the location of the hematoma, its size, the existence of accompanying blood in ventricles or subarachnoid space, and the presence of perihematoma edema. The existence of accompanying bleeding in the subarachnoid space points to AVM or aneurysm, perihematoma edema points to intracranial tumor, ICH located in the basal ganglion points to chronic hypertension, and lobar ICH points to CAA.

Although CT is the first-line diagnostic approach, MR imaging with gradient echo sequences can detect hyperacute ICH with equal sensitivity and overall accuracy. Furthermore, MR imaging is more accurate for the detection of microhemorrhages.[35]

Surgically treatable causes of ICH should be considered. These causes include vascular abnormalities such as aneurysm, AVM, DAF, cavernous malformation, and tumor. When a vascular abnormality is suspected, DS angiography is considered the standard imaging protocol. However, this technique is invasive and painful and requires a high level of skill. Neurological complications occur in 1.3% of cases,[90] and the mortality rate is about 0.1%.[44] There is also a high frequency of silent embolism in up to 23% of cases.[13] Compared with DS angiography, both CT angiography and MR angiography are noninvasive techniques. Moreover, CT angiography can be performed immediately after the initial noncontrast CT with a single bolus of intravenous contrast medium to allow rapid diagnosis and treatment. The procedure allows one to acquire images from the aortic arch to the vertex in a single acquisition within 11–16 seconds. Furthermore, CT angiography is becoming part of the standard protocol in patients presenting with ICH at many institutions.[12,48,93]

Authors of many studies have been evaluating the diagnostic accuracy of CT angiography in terms of its ability to detect cerebral aneurysms and have reported good results.[12] In 2003, in a meta-analysis of 21 studies published between 1995 and 2002, Chappell et al.[21] documented a 93% rate of sensitivity and 87.8% rate of specificity. More recently, with the current-generation, high-speed, multislice, dual-source CT scanners, authors have reported sensitivities between 95.1% and 98%[1,22,31,53] and specificities between 94.1% and 100%.[1,22,31,53] However, based on an aneurysm size < 3 mm, diagnostic accuracy decreases (sensitivity: 86.1%; specificity: 94.1%).[31] Computed tomography angiography is also highly accurate in displaying the vascular anatomy and characterizing the aneurysm for choosing the most appropriate treatment.[1,48,86] Magnetic resonance angiography is less accurate than CT angiography in detecting aneurysms, with a sensitivity between 55% and 93%.[5,49,51,78] Although MR angiography shows promise in acute ICH, its accessibility, availability, and scan time remain major disadvantages. As regards AVMs, few studies have evaluated the diagnostic accuracy of CT angiography in detecting these lesions. In a prospective study of 45 patients, Eshwar Chandra et al.[33] showed that CT angiography correctly predicted 83% of AVMs. Computed tomography angiography and MR angiography seem to have good accuracy. Magnetic resonance imaging is superior in demonstrating the exact anatomical relationships of AVMs.[69] However, MR angiography tends to underestimate AVM size.[68] The reason for this difference between MR angiography and CT angiography is the ability of MR to separate out the draining veins.[68] Furthermore, a small lesion in the presence of a hematoma can be missed.[10] Regarding DAFs, CT angiography and MR angiography have not been shown to be sensitive enough on their own to identify these lesions.[26,28,56] Indeed, the lack of temporal resolution and the peripheral location of dural feeders makes CT angiographic identification difficult.[93] As regards cavernous malformations, MR imaging is currently the best technique to make the diagnosis, with the T2* gradient recalled echo sequences being described as the reference standard.[20,58] If the first MR image is negative, it would be wise to wait 3 or 4 weeks before doing another MR imaging study.

In the event of a negative CT angiography or negative MR angiography and a considerable suspicion of vascu-

lar abnormalities, the patient should be examined further with DS angiography, especially young patients.

Intracerebral hemorrhage is a dynamic process, and early clinical deterioration might occur due to hematoma expansion.[18] Hematoma growth is an independent predictor of death and outcome.[27] Intraventricular hemorrhage is also an independent predictor of death and poor outcomes.[14,30,42,84] It is estimated to be present in 45% of patients with ICH and is related to ICH volume and location.[43]

Medical Management Trials

In emergency departments, treatment commonly includes airway support, blood pressure control, intracranial pressure monitoring and management, and, if necessary, anticoagulation reversal. To date, no trials have completely assessed the definitive benefits of tested therapies.

Blood Pressure Management

Early elevation of blood pressure is common after ICH,[76] and there is a strong correlation between increasing blood pressure and poor outcomes.[38,59,71,85] Several nonrandomized studies[72,74] have suggested that an early reduction in blood pressure is associated with better outcomes.

To date, the largest trial concerning blood pressure reduction management in ICH is INTERACT (intensive blood pressure reduction in acute cerebral haemorrhage trial).[3] In that study, adults were enrolled if they had an ICH confirmed by CT within 6 hours of onset and an elevated systolic blood pressure (150–220 mm Hg). Eligible patients were randomized in 2 groups: guideline-based treatment to lower blood pressure (201 patients) and intensive treatment to lower blood pressure (203 patients).[3] From 1 to 24 hours after treatment, the mean systolic blood pressure was significantly different between the 2 groups. The risk of severe adverse events was not altered by an intensive reduction in blood pressure. At 90 days after treatment, there was no significant difference in outcomes between the 2 groups.[3] The mean hematoma expansion was significantly greater in the guideline treatment group at 24 hours after treatment. However, after adjusting for the initial hematoma volume and the time from ICH onset to CT, the median hematoma growth differed between the groups ($p = 0.06$).[3] Anderson et al.[2] provided more information about hematoma growth in the INTERACT. The adjusted mean absolute increases in hematoma growth were significantly different between the 2 groups over 72 hours.[2]

At present, INTERACT2[29] is an ongoing trial aimed to confirm these results and to establish whether early intensive treatment to lower blood pressure is associated with better outcomes.

The ATACH (Antihypertensive Treatment of Acute Cerebral Hemorrhage) trial[4] was a phase I multicenter prospective study assessing the feasibility and safety of a reduction in blood pressure by intravenous nicardipine in patients with a systolic blood pressure superior or equal to 170 mm Hg (target blood pressure level of 170–200 mm Hg in the first group, 140–170 mm Hg in the second group, and 110–140 mm Hg in the third group).[4]

Hemostatic Therapy

More than 33% of ICHs enlarge from 3 to 24 hours after onset, and there is a strong correlation between volume hematoma and outcomes.[18,27] Thus, therapies to avoid hematoma expansion might improve outcomes.

Two large trials have been focused on the rFVIIa,[62,63] an agent aimed to promote hemostasis to limit hematoma enlargement.

A phase IIb, international, multicenter, randomized placebo-controlled trial has evaluated escalating doses of rFVIIa administered within 4 hours of ICH onset.[63] Adults with ICH confirmed by CT within 3 hours after onset were randomized in 4 groups to receive placebo (96 patients), 40 μg of rFVIIa per kilogram of body weight (108 patients), 80 μg of rFVIIa per kilogram of body weight (92 patients), or 160 μg of rFVIIa per kilogram of body weight (103 patients) within 1 hour after the baseline CT. Hematoma volume increased significantly more in the placebo group than in the 3 treatment groups. The mortality rate at 90 days after treatment was significantly higher in the placebo group. The authors concluded that treatment with rFVIIa within 4 hours after ICH onset limits hematoma growth, reduces the mortality rate, and improves functional outcomes at 90 days after treatment.

The FAST (Factor Seven for Acute Hemorrhagic Stroke) trial[62] is a phase III clinical trial on the safety and efficacy of rFVIIa in ICH. Adults with ICH were randomized in 3 groups to receive placebo (268 patients), 20 μg of rFVIIa per kilogram of body weight (276 patients), or 80 μg of rFVIIa per kilogram of body weight (297 patients) within 4 hours after ICH onset. Treatment with 80 μg of rFVIIa per kilogram of body weight significantly reduced hematoma growth. The authors of this study concluded that hemostatic therapy with rFVIIa reduced hematoma growth but did not improve survival or functional outcomes after ICH.

The results of these 2 large trials[62,63] are concordant in terms of the reduction of hematoma growth thanks to rFVIIa. However, the results are discordant regarding outcomes, perhaps because of the more elevated frequency of arterial events in the group treated with 80 μg of rFVIIa per kilogram of body weight.

Anticoagulant-Associated ICH

Anticoagulant-associated ICH is linked to a higher risk of hematoma expansion and a higher mortality rate.[36] Patients with this ICH subtype should receive anticoagulation reversal such as fresh-frozen plasma or prothrombin-complex concentrate[61,92] and vitamin K.[47] If rapid normalization of the INR to below 1.4 is not achieved, the risk of death increases.[40] However, these protocols often require a long time before obtaining a normalized INR. The use of rFVIIa to correct the INR has been described in healthy volunteers,[32] and its administration can normalize INR within minutes. Recombinant FVIIa has been used in patients with ICH before their needed neurosurgical procedures with good clinical results.[41,80]

Protamine sulfate should be used in patients treated with unfractionated or low-molecular-weight heparin.[88]

Surgical Management Trials

The surgical management of ICH is one of the most controversial issues in neurosurgery. The management method is different based on the hematoma location. Although surgical treatment is still under debate, it is well codified regarding an infratentorial hematoma location.

Supratentorial Hematoma

Different surgical options have been evaluated and considered as safe: open craniotomy,[54] frameless stereotactic aspiration,[9] or endoscopic evacuation[8] with or without thrombolysis. A randomized study[25] compared these 3 techniques for basal ganglia hemorrhage. Ninety patients were randomly assessed in 3 groups: 30 patients underwent endoscopic surgery, 30 underwent stereotactic aspiration, and 30 underwent craniotomy. Stereotactic aspiration needed a significantly greater time delay before surgery than the other techniques ($p < 0.001$). The craniotomy group had the longest operation time ($p < 0.001$) and more blood loss ($p < 0.001$). Endoscopic surgery had the highest hematoma evacuation rate ($p < 0.01$). The mortality rate at 3 months after treatment among the techniques was not significantly different; it was 0% in the endoscopic surgery group, 6.7% in the stereotactic aspiration group, and 13.3% in the craniotomy group. However, the functional independence mean and the Barthel Index scores were significantly better in the endoscopic surgery group than in the craniotomy group.

Prasad et al.[73] performed a meta-analysis to assess whether surgical treatment (craniotomy, stereotactic aspiration, and endoscopic evacuation) plus routine medical management was effective as compared with routine medical treatment alone. They included 10 clinical trials[7,11,23,46,50,52,65,66,82,94] in the meta-analysis. The primary outcome was death or dependence at the end of the follow-up. This meta-analysis was the first to demonstrate that surgery is more effective in reducing the odds of death than is medical management. Indeed, the odds ratio for death at the end of the follow-up was 0.74 (95% CI 0.61–0.90). However, in a subgroup analysis, a difference was found among the surgeries. Stereotactic aspiration or endoscopic evacuation significantly reduced the odds of death (OR 0.66 [95% CI 0.46–0.95]), whereas craniotomy did not reduce the odds of death (OR 0.82 [95% CI 0.59–1.15]).

The largest study comparing surgery versus medical treatment for ICH is STICH (Surgical Trial in Intracerebral Haemorrhage).[65] This trial did not show an overall benefit from surgery as compared with medical management.

An ongoing controlled trial, STICH II is focused on spontaneous lobar ICH of ≤ 1 cm from the cortex surface of the brain. Its authors aim to assess whether early surgery plus appropriate medical treatment is effective as compared with the best medical treatment combined with delayed surgery only if it becomes necessary.

Another large Chinese study[89] has investigated the benefits of surgery as compared with medical treatment. Three hundred seventy-seven patients with basal ganglia ICH were randomly assessed in a minimally invasive craniopuncture group (195 patients) and in a conservative control treatment group (182 patients). There was no difference in cumulative fatality rates at 3 months after treatment between the 2 groups. However, the proportion of dependent survival patients in the craniopuncture group (40.9%) was significantly lower than in the conservative treatment group (63%).

The MISTIE (Minimally Invasive Surgery plus Tissue Plasminogen Activator for Intracerebral Hemorrhage Evacuation) trial is an ongoing trial designed to find the best dose of thrombolytic agent to reduce hematoma volume via stereotactic aspiration.

Many questions persist. Actually, despite the existence of several trials, there are no guidelines on the best management for supratentorial ICH. Subgroup analyses (ICH location, Glasgow Coma Scale score, clinical evolution, and so forth) are necessary to know for whom a surgical treatment is beneficial. It also seems interesting to differentiate the subtypes of surgery in terms of each subtype of hematoma location or population characteristic.

Cerebellar Hemorrhage

There are guidelines for the treatment of these subtypes of ICH, which comprise around 10% of all ICH cases.[16] Surgery is a Class I recommendation in patients with a cerebellar hemorrhage larger than 3 cm who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from a ventricular obstruction.[16] In these conditions, hematoma evacuation should be performed as soon as possible.

Conclusions

Some surgical trials on ICH tend to show a benefit from surgery in reducing the mortality rate and the proportion of dependent patients. However, larger trials focusing on subgroup analyses are required to know who surgery could really benefit. The ongoing STICH II should be able to reveal whether craniotomy for lobar ICH is beneficial. Further multidisciplinary and multicenter studies are required to establish clear guidelines on the management of ICH.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: both authors. Acquisition of data: Dubourg. Analysis and interpretation of data: Dubourg. Drafting the article: Dubourg. Study supervision: Messerer.

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Manuscript submitted February 15, 2011.
Accepted March 9, 2011.

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