

## Treatment of Acute Intracerebral Hemorrhage

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Although hemorrhagic stroke occurs less frequently than ischemic stroke and accounts for only about 15% of stroke cases in Europe and the United States, it is less conducive to treatment and is associated with higher morbidity and mortality [1]. In a national survey conducted in all 28 Israeli hospitals, 7% of the 2174 patients who had been admitted with acute cerebrovascular disease had intracerebral hemorrhage [2]. Several studies have indicated that the mortality rate of patients with this condition exceeds 40% [3].

Hemorrhagic stroke consists of several subtypes: subarachnoid hemorrhage, subdural hemorrhage, and intracerebral hemorrhage. ICH accounts for about 60% of all hemorrhagic strokes. This is a review of what is currently known about the treatment of acute ICH.

Primary intracerebral hemorrhage is commonly attributed to uncontrolled hypertension, “hypertensive ICH,” which increases the risk of ICH by about fourfold. Other risk factors include age, male gender, vascular anomalies, hematologic disorders, anticoagulation therapy, history of excessive alcohol consumption and substance abuse [4]. The anatomic sites most commonly involved, especially in “hypertensive hemorrhage,” are the basal ganglia, thalamus, cerebellum and pons [5]. Lobar hemorrhage accounts for one-third of patients with PICH, and amyloid angiopathy in which the cortical vessels are infiltrated with amyloid beta protein is a frequent cause of lobar ICH, such as that in the frontal, parietal, temporal or occipital cortex for which there is no other definite cause [6]. Affected patients are usually older than 60 and the incidence increases markedly with advanced age. There are no specific treatments for the prevention of hemorrhage in patients with cerebral amyloid angiopathy. Patients with PICH due to amyloid angiopathy have a lower mortality rate and a higher risk of recurrence than patients with ICH due to hypertension. Microbleeds that are visible as low intensity spots on T2\* magnetic resonance imaging are associated with amyloid angiopathy and increased risk for lobar PICH [7].

The most important predictor for outcome in patients with PICH is the size of the hematoma. For example, the mortality risk in a patient with a PICH whose hematoma is the size of a ping-pong ball is approximately 40%, compared to 70% in a patient with a hematoma the size of a golf ball. Other prognostic

factors include age, state of consciousness, infratentorial location and intraventricular hemorrhage [8], and recent reports have also included hyperglycemia [9].

In the past, deterioration in the neurologic status of a patient with PICH during the first 24 hours was explained by a mass effect of the hemorrhage and the edema surrounding it, causing increased intracranial pressure and subsequent brain herniation. Recent studies have afforded a better understanding of the pathophysiology of PICH, revealing it as a dynamic process and not a static phenomenon [10]. As many as one-third of the patients with ICH develop a substantial increase in the volume of the parenchymal hemorrhage during the first day, especially within the first 3–4 hours. Since this ongoing bleeding is associated with neurologic deterioration, the growth of the hematoma is an independent determinant of both mortality and functional outcome after PICH. One recent study demonstrated that the hazard ratio of dying increased by 1% for each 1 ml increase in baseline PICH volume [11].

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*Administration of rFVIIa appears to be safe in patients with anticoagulant-related intracranial hemorrhage, rapidly lowering the INR, but it does not completely restore hemostasis*

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Another proposed mechanism for the deterioration that takes place after PICH is the secondary neuronal damage that is due to peri-hemorrhagic hypoperfusion. This phenomenon is observed around the hematoma and is referred to as a “penumbra.” Based on positron emission tomographic studies, it is now believed to be due to reduced metabolic demand and not to ischemia [12]. Therefore, although there is no evidence for treatable ischemic penumbra in PICH, it is still a dynamic process in which the main goal of treatment is to limit the volume of the hemorrhage.

The past few years have witnessed a better understanding of PICH in terms of its pathophysiology, risk factors, imaging and new modes of treatment. The main goals of management of

ICH = intracerebral hemorrhage  
 PICH = primary intracerebral hemorrhage

acute ICH are to control the hypertension, prevent death from herniation due to increased intracranial pressure, limit the damage caused by bleeding, prevent secondary complications, and provide rehabilitation. Physician awareness of the condition and early symptom recognition is of major importance for optimizing medical management. A patient diagnosed in the emergency room as having PICH should be admitted to the stroke unit or to an intensive care unit if he/she is comatose or in need of mechanical ventilation [5].

Although elevation in blood pressure is sometimes secondary to the increased intracranial pressure, it may promote hematoma enlargement and even rebleeding. Paradoxically, treating blood pressure aggressively may increase the hypoperfusion and ischemia surrounding the hematoma. Although the manner of appropriate control of blood pressure is still a controversial issue, blood pressure should be monitored and kept below 180 mmHg systole and 105 mmHg diastole [13]. A recent retrospective study even suggested that lowering systolic blood pressure below 150 mm Hg may prevent the risk of hematoma enlargement [14]. Intravenous labetalol and enalapril, which are used for this purpose, do not cause cerebral vasodilatation and potential "steal syndrome" [5]. A large randomized controlled trial is needed to confirm those results and to establish an evidence-based medication policy.

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*In anticoagulant-related intracranial hemorrhage, a combination of activated prothrombin complex and rFVIIa might be the best therapeutic approach.*

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No medical treatment for the mass effect caused by ICH has been found by randomized trials to be beneficial. Mannitol, an osmotic diuretic that lowers intracranial pressure, was not found effective for improving outcome in PICH and may even cause complications, such as acute renal failure and electrolyte disturbances [15]. Treatments with intravenous glycerol (another osmotic agent that lowers intracranial pressure by decreasing water content), steroids and epsilon aminocaproic acid (a pro-coagulative drug) were also not found to be effective [16-18].

Two important milestones in the treatment of PICH are the STICH trial (Surgical Trial in Intracerebral Hemorrhage) [19], and the administration of recombinant activated factor 7 (NOVO 7) given during the 3-4 hours after the initiation of symptoms [20]. The recently published STICH trial [19] is the first powered large prospective randomized clinical trial to compare early open surgical evacuation with medical treatment in patients with spontaneous supratentorial PICH. Previous small trials that tested the efficacy of surgical procedures in patients with PICH failed to show any beneficial efficacy, and so the role of surgery remains

controversial [21]. The results of the STICH trial were similar to those of earlier small studies. The mortality rate in the early surgery group and the conservative treatment group was 36% and 37%, respectively. In addition, 33% had a favorable outcome (based on the Rankin scale) in the surgical group compared with 28% in the medical group ( $P = \text{NS}$ ). The results of surgery were better for superficial PICH, i.e., hematomas  $\leq 1$  cm from the cortical surface, but they were not significantly better than medical treatment. Thus, the STICH trial provided no convincing evidence to support the policy of early surgery in patients with spontaneous supratentorial PICH.

Understanding the dynamic nature of PICH provides us with the rationale for attempting to accelerate the formation of the clot and prevent the expansion of the hematoma. It is now understood that early treatment (i.e., given within 3 to 4 hours of onset) may potentially arrest ongoing bleeding and minimize hematoma growth after an intracerebral hemorrhage. NOVO 7 has been approved to treat bleeding with hemophilia and other coagulopathies, such as Glanzmann's thromboasthenia and factor 7 deficiency. It was also found to be effective in treating bleeding in patients with no coagulopathy. In a randomized placebo-controlled study of 400 patients with PICH, NOVO 7 given in three different doses within 4 hours after the onset of PICH significantly reduced growth of the hematoma, compared with placebo, by approximately 5 ml at 24 hours [20]. Mortality at 90 days was 29% for patients who received placebo compared with 18% in the three NOVO 7 groups ( $P = 0.02$ ). There was a small increase in the frequency of thromboembolic events, especially myocardial infarctions and ischemic strokes. The overall frequency of fatal or disabling adverse events was not significantly higher in the NOVO 7 group compared to the placebo group. These initial data suggest that NOVO 7 is an effective, safe and well-tolerated treatment for spontaneous PICH and that it has the potential to be used as the counterpart of tissue plasminogen activator for the treatment of acute ischemic stroke. A large randomized clinical trial is currently underway for confirming the results of the first study.

In conclusion, although PICH is still the deadliest and most disabling form of stroke, a better understanding of the disease, the completion of large clinical trials, and new treatment modalities hold some promise for a better outcome of this devastating condition in the future.

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