Until the present, intracerebral hemorrhage (ICH) has been the stroke subtype that has defied attempts to find a scientifically proven effective therapy. Possible treatments of acute ICH include: (1) slowing or stopping of the bleeding during the first several hours after onset or (2) removal of the accumulated hematoma to prevent the mechanical complications of mass effect as well as the toxic effects of blood on the surrounding brain parenchyma. Critical care management of the complications of ICH is clearly important. The evolution of lesions and the pathophysiology of intracerebral hemorrhage, like that of ischemic stroke, are time-dependent, but only the recently published trials of Novo VII have tried to intervene during the first hours after onset of ICH. The recent publication of the Novo VII phase II trial also provides hope that an effective treatment for acute ICH is within reach.

The STICH Trial represents an important milestone in the role of surgical treatment for ICH. The relative paucity of data from randomized trials has severely limited progress in the surgical treatment of ICH and has led to substantial variability in the management of ICH throughout the world. Dr Mendelow, collaborators, and the Medical Research Council (MRC) are to be congratulated for completing the largest ever randomized treatment trial of ICH. This trial adds substantially to what we know about surgical management of ICH and will have an impact on current treatment as well as design of future trials.

The goal of the STICH Trial was to investigate the effectiveness of early surgery (within 24 hours of randomization) as compared with initial conservative medical treatment with later evacuation if deemed necessary by the treating neurosurgeon. The STICH Trial showed no significant difference in outcome between the early surgical and initial conservative management groups. Of the prespecified subgroups that were examined, patients with an ICH within a centimeter of the cortical surface showed a benefit for early surgery and there was a significant treatment interaction between treatment assignment and depth of the ICH from the cortical surface. However, statistical testing of this subgroup was not adjusted for the multiple subgroup comparisons as the investigators note. The STICH investigators concluded that “patients with spontaneous supratentorial ICH in neurosurgical units show no overall benefit for early surgery when compared with initial conservative management.”

The design and conduct of the STICH Trial are keys to interpretation of the STICH Trial. Inclusion criteria for STICH included computed tomographic evidence of a spontaneous supratentorial ICH that had arisen within 72 hours, uncertainty concerning the benefits of either treatment by the treating neurosurgeon, and a recommendation for a minimum hematoma diameter of 2 cm and a Glasgow Coma Score of 5 or more. Exclusion criteria included ICHs likely caused by an aneurysm or an angiographically proven arteriovenous malformation, tumor, or trauma; cerebellar or brain stem ICH; and inability to perform surgery within 24 hours of randomization. An important characteristic of the care plan was that patients randomized initially to conservative management could undergo evacuation of the ICH if clinically indicated in the judgment of the treating physicians. This latter design feature reflects the clinical reality that ICH patients, on average, the most gravely ill of all stroke patients, frequently die despite the best efforts of physicians, nurses, and other health care personnel. In the face of marked deterioration and imminent death, holding to a course of medical management may be challenging.

The surgical approach was left to the choice of the treating neurosurgeons. In 77% of cases, craniotomy was the surgical procedure and the remainder of cases had hematoma removal by burr hole, endoscopy, or stereotaxy in similar numbers. Thus, the STICH Trial is primarily a trial of craniotomy for ICH removal. Interestingly, there was a borderline statistical interaction ($P=0.07$) between surgical method and outcome.

Timing of surgery in the STICH Trial, even in the “early surgery group,” was relatively long after onset of symptoms. The median time from onset to treatment for early surgery group was 30 hours (interquartile range, 16 to 49 hours); thus, this trial cannot speak to the effectiveness of surgery within
the first 12 hours after onset (only 16% of patients in the surgical group). Twenty-six percent of the initial conservative group underwent subsequent evacuation at a mean of 60 hours (interquartile range, 27 to 99 hours). Thus, the trial is better described as a trial of surgical removal of ICH at $\approx 30$ hours from onset on average versus initial medical treatment with or without delayed surgical removal for those that “subsequently required” surgery in the judgment of the treating investigator.

The fact that the investigators noted a benefit for surgical removal of superficial hematomas but saw no benefit overall demonstrates that STICH patients with deep ICHs randomized to earlier surgery tended to do more poorly. This observation likely reflects that most patients with a deep ICH had a craniotomy rather than a less invasive approach such as endoscopy or stereotaxy. The overall result of the trial may have been different if less invasive approaches had been used uniformly in patients with deep ICHs with subsequent minimization of brain injury from the surgical procedure itself.

What does the STICH tell us about the role of surgical removal of ICH? A fair summary is that except for possibly those with superficial ICHs, craniotomy at 1 day or longer after onset is not better than initial conservative medical treatment with or without later craniotomy for patients who have deterioration. A nonsignificant absolute benefit of 5% in favor of early surgery ($P = 0.116$) in the prognosis-based Rankin Scale at 6 months is a hopeful finding for future surgical trials. It also illustrates the importance of adequate sample size in detecting smaller absolute clinical benefits.

What STICH leaves unanswered is the role of less invasive surgery to remove ICH, particularly at earlier time windows. Several small randomized trials of less invasive surgical approaches, particularly using stereotactic localization, have reported positive outcomes for surgical removal as compared with medical management.6–8 These favorable results have stimulated pilot randomized studies of stereotactic removal of ICH using tissue plasminogen activator and drainage of blood via catheter, such as the National Institute of Neurological Disorders and Stroke-funded Minimally Invasive (stereotactic) Surgery Plus rtPA for ICH Evaluation (MISTIE) Study (personal communication, Dr Mario Zuccarello and Dr Daniel Hanley; 2005). In the randomized, dose-finding, pilot MISTIE Study, patients have to have placement of the catheter into the hematoma and instillation of the first dose of recombinant tissue plasminogen activator within 24 hours of symptom onset. The MISTIE study also requires a second computed tomographic scan to document stabilization in the volume of ICH before placement of the catheter. This design feature addresses the frequent growth of ICH during the first hours after ICH.

However, because the pathophysiology of ICH is time-dependent, removal of blood from the brain should be ideally accomplished as soon as possible. Removal should occur with minimal damage to the overlying normal brain parenchyma and without increasing the risk of further growth of hemorrhage. The challenge of very early surgical removal, in addition to the logistical challenges of rapid mobilization of surgical teams,7 is that ongoing bleeding may not be completed and could potentially be exacerbated by the surgical procedure and instillation of lytic therapy. A possible solution to improve the effectiveness of very early surgical removal and to prevent ongoing bleeding would be to initiate Novo VII within the first several hours after onset, followed by a stereotactic surgical procedure to remove the accumulated hematoma. Timing of surgery soon after Novo VII could theoretically minimize bleeding in the operative field. Such an approach may be the next step in surgical trials of ICH if the benefit of Novo VII is confirmed in the planned Phase III Trial, and the results of MISTIE and other less-invasive pilot surgical studies merit further study. The time is nearing when ICH will join ischemic stroke and subarachnoid hemorrhage as a cerebrovascular disease with scientifically proven therapies.

References

The STICH Trial: What Does It Tell Us and Where Do We Go From Here?
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