Emerging Therapy Critiques

Section Editors: Sean I. Savitz, MD, and Heinrich P. Mattle, MD

Surgery for Intracerebral Hemorrhage
Moving Forward or Making Circles?

Matthew L. Flaherty, MD; Jürgen Beck, MD

Intracerebral hemorrhage (ICH) is the deadliest stroke subtype, with 30-day mortality rates of \( \approx 40\% \) and significant morbidity among survivors. Progress has proven difficult for this disease state. Unlike ischemic stroke, where incidence seems to be declining in high-wealth countries, and subarachnoid hemorrhage, where case fatality has improved, there is little evidence that ICH has become less common or less morbid.

Fortunately, many clinicians and researchers have been unwilling to accept a nihilistic attitude toward parenchymal brain hemorrhage. In the past decade, large trials have tested a variety of treatment approaches for ICH, including neuroprotection, blood pressure control, hemostatic therapy, and surgery. Recently, results of the second International Surgical Trial in Intracerebral Hemorrhage (STICH II) were published.

STICH I and STICH II

There are 2 basic rationales for surgical removal of blood after ICH. The first is mechanical: to reduce mass effect, to improve intracranial pressure and brain perfusion, and to prevent dangerous compartment shifts and herniation. The second is chemical: removal of blood products may reduce secondary injury caused by blood breakdown and adverse biochemical or inflammatory processes. Blood removal, however, comes with a price, which typically involves general anesthesia and (in most centers) craniotomy followed by dissection through viable brain to reach the hematoma.

This invasive approach to the hematoma is often considered the reason for failure of surgical trials. The concept may be challenged when one considers carefully planned elective procedures such as brain tumor resection, and it may not apply to STICH II, which was limited to superficial hematomas. The urgent removal of a brain hematoma is not a simple matter and requires study on several levels. During this procedure, the extent of damage to or removal of still viable brain may be hard to quantify. There is no standard technique for hematoma removal, and the quantification of the extent of evacuation that will lead to best results remains to be determined.

Thus, randomized trials are necessary to demonstrate that surgery improves outcome beyond medical management and before such a strategy can be advocated for the majority of patients. STICH I, published in 2005, remains the largest trial (with a sample size of 1033 subjects) to test this hypothesis. Subjects were randomized to early surgery (within 96 hours of ictus) versus medical management with delayed surgery, if deemed necessary, by the attending surgeon. The trial was powered to show a 10% absolute increase in good outcomes among patients in the surgical arm. Both lobar and deep hemisphere ICHs were included. The results showed no benefit in 6-month favorable outcome in the surgical group (26%) compared with the medical group (24%, \( P=0.41 \)), as measured by the Glasgow Outcome Scale. However, in a prespecified subgroup analysis, subjects with lobar ICH \( \leq 1 \) cm from the brain surface who underwent surgery had an 8% absolute increase in good outcomes compared with similar subjects in the medical arm (\( P=0.02 \) for interaction between depth from the cortical surface and treatment effect). The results seemed plausible if one assumes that lobar ICH can be more safely evacuated than deep-seated hemorrhages that can be reached only via traversal of significant intact brain.

STICH II was designed to confirm the signal found in STICH I. Subjects with lobar hematomas of 10 to 100 mL located \( \leq 1 \) cm from the brain surface and without intraventricular hemorrhage or coma were randomized to surgery versus initial medical management. Among 607 subjects, 307 were assigned to surgery, the vast majority done via craniotomy (98%), a median of 26 hours after stroke onset.

Disappointingly, the primary outcome of the trial, measured as favorable outcome on the Extended Glasgow Outcome Scale, did not reach statistical significance. Among patients with available data, 41% of early surgery subjects had a favorable outcome at 6 months compared with 38% of subjects in the medical arm (odds ratio, 0.86; \( P=0.37 \)). There was a trend toward lower 6-month mortality in the surgical group (18% versus 24%, \( P=0.095 \)). The definition of favorable outcome in STICH II was based on expected prognosis at enrollment. Prognosis was predicted by a formula that includes baseline Glasgow Coma Scale (GCS) score, age, and hemorrhage volume (10×GCS−age−0.64×volume), with a predefined...
cut point of 27.672. Thus, patients with lower GCS scores, greater age, and larger ICH volumes were expected to fair less well, and the definition of favorable outcome on the Extended Glasgow Outcome Scale was adjusted accordingly. Notably, a subgroup analysis on the effect of baseline prognosis (poor versus good) identified an interaction, such that subjects in the poor prognosis group randomized to surgery were more likely to have a favorable outcome than those randomized to medical care (odds ratio, 0.49; \( P=0.02 \)). There was no advantage with surgery for subjects predicted to have a good outcome. Not surprisingly, among subjects in the medical arm, those with a predicted poor prognosis were more likely to cross over to surgery than those with a predicted good prognosis.

**Patient Selection**
When considering STICH I and STICH II, it is important to consider which patients were included and excluded. Randomization in both studies depended on clinical equipoise of the enrolling surgeons. Subjects who were judged in need of surgery were not enrolled. This may have preferentially applied to healthier subjects with large lobar hemorrhages. Many clinicians would view operation in these cases as life saving and worth pursuing. The results of STICH II may support this contention. The strongest signal for benefit came among patients with poor predicted prognosis, the patients for whom a clinician might instinctively feel more aggressive treatment is necessary.

Surgical trials must also deal with crossovers. In STICH I, 26% of subjects randomized to medical management ultimately crossed over to surgery. In STICH II, 21% of subjects crossed over to surgery. These subjects were typically sicker, with lower GCS scores and larger hematomas. If none of these patients had undergone surgery, the rates of poor outcome and death in the medical group may have been higher.

**New Approaches**
STICH I and II are the most important surgical trials for ICH to date. However, they are not the last word on surgery for this condition. Other approaches are being tested, most notably minimally invasive hematoma drainage assisted by tissue plasminogen activator infusion; the Minimally Invasive Surgery plus rtPA for Intracerebral Hemorrhage Evacuation (MISTIE) I and MISTIE II trials have been completed, and a phase III trial is being organized.9

Decompressive hemicraniectomy for malignant middle cerebral artery infarction has been shown to reduce mortality. Hemicraniectomy without concomitant hematoma drainage is also being explored for ICH although randomized trials have not been completed.10

**Continuing Efforts**
STICH II will not change management for the majority of patients with ICH. Most deep hemorrhages do not benefit from surgery, at least as currently undertaken. Patients with small lobar hemorrhages and good level of consciousness can also be observed without surgery. However, for patients with a large lobar ICH that is producing mass effect and impairing consciousness, STICH II may move the needle. When a surgeon is faced with such a patient and uncertain whether surgery is necessary, STICH II may provide the assurance that surgery is a reasonable and probably useful undertaking. Caution is always necessary when analyzing subgroups in neutral or negative trials. However, ICH will continue to occur, and decisions will need to be made for individual patients, regardless of whether definitive evidence is available.

So, have these efforts led us forward or simply back to our starting point? We think the field is moving forward. As with research efforts for ischemic stroke and subarachnoid hemorrhage, progress in treating ICH will consist of incremental gains; we should expect single base hits rather than home runs and a few strikeouts along the way. Conducting large stroke trials is difficult, especially for ICH. STICH II refines our knowledge of craniotomy and its role in the treatment of ICH. The STICH investigators are to be congratulated for their efforts and the information they have provided us. Now is the time to test new approaches.

**Disclosures**
Dr Flaherty is Principal Investigator of a phase II National Institute of Neurological Disorders and Stroke–funded treatment trial for ICH. Study drug is provided by Novo Nordisk. Dr Flaherty has served on an advisory board and as a consultant for CSL Behring.

**References**

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