Surgery versus conservative treatment for intracerebral haemorrhage—is there an end to the long controversy?

The International STICH trial, reported by David Mendelow and colleagues in today’s Lancet, is a long-awaited study. The results of STICH have already attracted the attention of physicians engaged in stroke medicine. Is surgery for spontaneous intracerebral haemorrhage beneficial compared with conservative treatment? Since the trial by McKissock et al, in 1961,1 seven randomised trials have been reported,2–7 and there have been three meta-analyses of these trials.8–10 Yet conclusions of whether surgery is beneficial over conservative treatment remain controversial. The reason is that these studies had only weak analytical power because they were small and limited to local areas. STICH is the first large multicentre randomised trial, and recruited 1033 patients from 83 centres in 27 countries.

Mendelow and colleagues included some new features in STICH. The first was adoption of prognosis-based outcome for evaluation of patients’ outcome. This method first divides patients into groups by good and poor prognosis based on their clinical status at randomisation, and assesses outcomes of these groups by a different outcome threshold. Prognosis for patients with spontaneous intracerebral haemorrhage is correlated with age and the volume and location of haematomas before treatment. If groups of patients with differences in clinical condition are assessed on the basis of the same criteria, the interpretation of results will lack precision. Adoption of prognosis-based outcome solves this problem and makes results of the STICH study pragmatic.

Second, the surgery group was limited to patients who had early surgery, on the basis that many neurosurgeons believe early clot-removal is effective in rescuing the penumbra surrounding the haematoma, and on experimental study.11 However, as in conventional trials, there was no evidence of overall benefit with a policy of early surgery compared with initial conservative treatment in STICH. We do not believe, however, that this result directly challenges the usefulness of surgery for spontaneous intracerebral haemorrhage. We consider it important that of the patients randomised to initial conservative treatment, 26% needed surgery a few days after randomisation. Because the most common reason they required surgery was neurological or clinical deterioration and they were more likely to have haematomas with a volume greater than 50 mL, subsequent brain oedema must have increased compression of the surrounding normal tissues in those patients. These crossovers should be regarded as candidates for surgery, although they were randomised to initial conservative treatment. Surgery in the early stage might have prevented subsequent brain oedema associated with neurological deterioration in these patients.

Besides appropriate selection of subgroups of patients for surgery, it is important to improve operative techniques to obtain good surgical results. The results of STICH show that there is more likely to be a favourable outcome of surgery, mainly craniotomy, if the haematoma is 1 cm or less from the cortical surface, and significant interaction was shown between depth from the cortical surface and efficacy of treatment. The reason is that if the haematoma is near the cortical surface, surgical destruction of brain tissue in reaching the haematoma is minimal. For deep haematomas, such as those in the basal ganglia or thalamus, benefits like those of craniotomy for subcortical haematoma will be obtained if a less invasive, safe, and effective method of clot evacuation exists. Endoscopic surgery is one of the methods expected to be effective for treatment of deep haematoma.7–9 From a similar point of view, we have developed endoscopy for surgery for intracerebral haemorrhage, have treated patients with it, and now are making an effort to improve it (figure).12 We expect that such technical progress will open new possibilities for treatment of intracerebral haemorrhage, and, in the future, yield results different from that of International STICH.

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Figure: Endoscopic system specialised for intracerebral haemorrhage surgery
New steerable endoscope for intracerebral haemorrhage surgery to obtain manoeuvrability needed for effective evacuation of clot.
Smallpox vaccines: from first to second to third generation

In this issue of The Lancet, Richard Greenberg and colleagues report a trial that compared a new smallpox vaccine derived from cell culture with a vaccine derived from calf lymph. Their report is timely, given current concerns over biological weapons.

The smallpox vaccines currently licensed in the USA and UK are live, attenuated vaccinia virus derived from calf lymph. Although this type of vaccine was used to eradicate smallpox worldwide, well-documented safety limitations prevent its widespread use in a civilian population without an outbreak. Historically, out of every million people vaccinated for smallpox, 14–52 people had serious or life-threatening adverse reactions to the vaccine, and one to two people per million primary vaccinees died because of the vaccine.1 Serious side-effects include eczema vaccinatum, progressive vaccinia, postvaccinal encephalitis, fetal vaccinia, vaccinia keratitis, and myopericarditis. There were also cases of inadvertent self-inoculation and vaccinated people transmitting vaccinia vaccine virus to others.2 Also, smallpox vaccine is contraindicated in up to 30% or more of the population, including infants, pregnant women or women who are breastfeeding infants, the immunocompromised, those with vaccinia or exfoliative skin disorders, people who live in the same house or are in intimate contact with people with the above conditions, and people with cardiovascular conditions (such as a history of myocardial infarction, angina, congestive heart failure, cardiomyopathy, stroke or transient ischaemic attack, chest pain or shortness of breath with activity, or any cardiac condition under the care of a physician).3,4

In their trial, Greenberg and colleagues randomly allocated 350 healthy adults to receive cell-cultured smallpox vaccine (CCSV) or calf-lymph-derived vaccine (Dryvax). Participants included 150 vaccinia-naive people 18–30 years of age and 100 participants who were not naive to vaccinia and 32–65 years of age. A further 100 vaccinia-naive people 18–30 years of age received one of five CCSV doses of various dilutions in a single-blind manner. To assess safety and immunogenicity, researchers made physical examinations, recorded adverse events and take-rates, and performed neutralisation antibody titres, T-cell proliferative-response assays, and interferon-γ Elispot. The last two assays were designed to measure cell-mediated immunity.

All but one participant developed pock lesions. Vaccine-associated adverse reactions were similar between the CCSV and Dryvax recipients. Although none of the participants had serious vaccine-related adverse events, the vaccinia-naive recipients had the expected side-effects: erythema, axillary adenopathy, swelling, pain, and lymphangitis. The number of participants who became immune to the virus was high, although antibody seroconversion rates were lower in CCSV recipients, while measures of cell-mediated immunity were similar. The researchers concluded that the vaccine was safe and effective.5


