Surgical Trial In Traumatic intraCerebral Haemorrhage (STITCH): a randomised controlled trial of Early Surgery compared with Initial Conservative Treatment

Barbara A Gregson,[1]* Elise N Rowan,[1] Richard Francis,[1] Paul McNamee,[2] Dwayne Boyers,[2] Patrick Mitchell,[1] Elaine McColl,[3] Iain R Chambers,[4] Andreas Unterberg[5] and A David Mendelow[1] on behalf of the STITCH(TRAUMA) investigators

[1]Neurosurgical Trials Group, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK
[2]Health Economics Research Unit, University of Aberdeen, Aberdeen, UK
[3]Newcastle Clinical Trials Unit, Newcastle University, Newcastle upon Tyne, UK
[4]South Tees Hospitals Foundation Trust, James Cook University Hospital, Middlesbrough, UK
[5]Department of Neurosurgery, University of Heidelberg, D-69120 Heidelberg, Germany

*Corresponding author

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Scientific summary

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Background

In the UK there are 1.4 million presentations of head injury at emergency departments each year. The mortality rate for severe isolated traumatic brain injury varies between 16% and 40%. More than 150,000 of those who present to emergency departments with head injury are admitted to hospital each year. Of these, about 20,000 injuries are serious. One year after a serious head injury, 35% of patients are dead or severely disabled. Intracranial haemorrhage occurs in more than 60% of serious head injuries in one or more of three types: extradural haematoma (EDH), subdural haematoma (SDH) and intracerebral haemorrhage (ICH). Prompt surgical removal of significant SDH and EDH is of established and widely accepted value. ICH is more common and is associated with a worse outcome but the role of surgical removal of the clot remains undefined.

Surgical practice in the treatment of traumatic ICH (TICH) differs widely. Several issues inform the debate:

(a) Contused brain does not recover but appears as encephalomalacic brain tissue loss on convalescent phase imaging. This suggests that removing TICH does not increase tissue loss.
(b) Extravasated blood is believed to be neurotoxic, leading to secondary injury that may be avoided by surgical removal.
(c) Larger TICHs may be associated with an ischaemic penumbra of brain tissue that could be salvaged.
(d) Some TICHs expand to the point at which they cause mass effect with high intracranial pressure (ICP), resulting in secondary brain injury.

The aim of early surgical TICH removal is to prevent secondary brain injury from these mechanisms. Use of the operation varies around the world. It is more frequently done in the Far East than in Europe or the USA.

Traditional neurosurgical care of patients with severe head injury is frequently based on ICP measurement. Patients with high ICP (> 30 mmHg) and TICH would undergo craniotomy and those with low ICP (< 20 mmHg) would be managed conservatively. Patients with ICP between 20 and 30 mmHg would be observed with ongoing ICP monitoring and undergo craniotomy if the ICP rises. This ICP-based approach has been recommended by the Brain Trauma Foundation, but has recently been challenged in the Trial of Intracranial Pressure Monitoring in Traumatic Brain Injury (BEST TRIP) from Latin America. In the light of this controversy, the early management of patients with TICH needs evaluation to determine if Early Surgery should become part of the standard of care in the same way it is for significant EDH and SDH.

There have been trials of surgery for spontaneous intracerebral haemorrhage (SICH) but none so far of surgery for TICH. The Cochrane Review (2nd edition) has shown benefit from surgical evacuation for SICH (Prasad K, Mendelow AD, Gregson B. Surgery for primary supratentorial intracerebral haemorrhage. *Cochrane Database Syst Rev* 2008;**4**:CD000200). There are differences in the pathogenesis, clinical behaviour and outcome of the two conditions (SICH and TICH). Patients suffering a TICH tend to be younger and, therefore, their level of disability may have a larger effect on their ability to return to work and their economic output. TICHs are more likely to be lobar, to be superficial and to have a medium-sized volume (25–65 cc). These differences between the conditions mean that we cannot derive the role of surgery for TICH from SICH trials.

We already know that surgery is effective in patients with traumatic EDH and SDH and that Early Surgery results in improved outcomes compared with delayed surgery. This is not known for TICH. If Early Surgery is of benefit to these patients, then implementation of early referral and diagnosis with immediate treatment may reduce death and disability in this specific group of head-injured patients.

Several authors have compared surgery with conservative treatment in single-centre retrospective series and recommended surgery for larger TICHs even if patients were in an apparently good clinical state initially. None of these studies involved randomisation into surgical and non-surgical groups. They also differed in the characteristics of the parenchymal blood. Such uncontrolled observational studies may be potentially misleading and a randomised controlled trial was needed.

Guidelines for the surgical management of traumatic brain injury were published in 2006 in *Neurosurgery* (Bullock M, Chesnut R, Ghajar J, Gordon D, Hartl R, Newell D, *et al.* Surgical management of traumatic parenchymal lesions. *Neurosurgery* 2006;**58**:S25–46; discussion Si–iv). These confirmed that studies in this area have been observational and that there is a lack of evidence from well-designed randomised controlled trials. Those studies that attempt to compare outcome between surgical and non-surgical groups cannot adequately control for unknown prognostic variables.

The National Institute for Health and Care Excellence (NICE) recommended in the Head Injury Update Full Guideline (2007) (NICE. *Clinical Guidelines CG56 Head Injury: Triage, Assessment, Investigation and Early Management of Head Injury in Infants, Children and Adults*. London: NICE; 2007.) that research is needed to develop a consensus on criteria for lesions not currently considered to be surgically significant, namely TICH. This trial, Surgical Trial in Traumatic intraCerebral Haemorrhage [STITCH(TRAUMA)], was recommended by that NICE Head Injury Guideline Development Group.

Objectives

To determine whether or not a policy of Early Surgery in patients with TICH improved outcome compared with a policy of Initial Conservative Treatment.

To assess the relative costs and consequences of Early Surgery versus Initial Conservative Treatment.

To investigate the use of ICP monitoring for clinical management of head-injured patients with TICH and its effect on treatment decisions.

Methods

STITCH(TRAUMA) was an international, multicentre, pragmatic, randomised, parallel-group trial comparing early surgical evacuation of TICH with Initial Conservative Treatment. Only adult patients for whom the treating neurosurgeon was in equipoise about the benefits of early surgical evacuation compared with Initial Conservative Treatment were eligible for the trial. Patients had to be within 48 hours of head injury and to have no more than two TICHs larger than 10 ml. They were ineligible if they had a significant EDH or SDH that required surgery, if a haematoma was located in the cerebellum or if they had a severe pre-existing physical or mental disability or severe comorbidity that would lead to a poor outcome even if they made a full recovery from their head injury. An independent 24-hour telephone- and web-based randomisation service was used. Stratification by country was used together with minimisation by age and severity with a random component to ensure that the two groups were balanced. Patients were randomised to Early Surgery (within 12 hours) or to Initial Conservative Treatment. Delayed evacuation of the haematoma was permitted for patients in the Initial Conservative Treatment group if it became clinically appropriate. Outcome was measured at 6 months via a postal questionnaire using the Extended Glasgow Outcome Scale (GOSE).

Additional data were collected in those centres that practised invasive brain monitoring to see if there was evidence that such monitoring techniques would add value to clinical decision-making. Such monitoring was not mandatory.

The costing analysis was undertaken on the intention-to-treat basis from an international health services perspective. Resource-use requirements to deliver the interventions (e.g. staff time, overheads) and time spent on hospital wards were collected using site-specific questionnaires and case report forms. Hospital readmissions were reported on participant outcome questionnaires. Costing followed recommended procedures for international studies applying country-specific unit costs (sourced from site-specific questionnaires) to resource use data to generate total costs. Costs were transformed into 2013 international dollars.

Results

Between December 2009 and September 2012, 170 patients were recruited from 31 centres in 13 countries and randomly assigned to treatment groups: 83 to Early Surgery and 87 to Initial Conservative Treatment. The study was halted by the funding agency after the recruitment of 170 of the planned 840 patients because of low recruitment in the UK; only six patients had been recruited in the UK. The study was halted without the funding agency or the study team knowing the outcome despite the Data Monitoring Committee recommending that it should continue. This study reports results for 82 eligible patients assigned to Early Surgery and 86 eligible patients assigned to Initial Conservative Treatment.

The distribution of baseline variables between the two treatment groups was very similar. Patients ranged in age from 16 to 83 years with a median age of 50 years, and 122 (73%) were male. Prior to the head injury, 164 (98%) had a score on the Rankin Scale of 0 or 1, and 22 (13%) had a medical history of cardiovascular disease. The main causes of the head injury were road traffic accidents 113 (67%) and falls 47 (28%). Sixty-eight patients (40%) were admitted to another hospital prior to their transfer to the neurosurgical unit. At the time of randomisation, 70 (42%) patients had a Glasgow Coma Score (GCS) of 13–15, 78 (46%) a GCS of 8–12 and 20 (12%) a GCS of < 8. The volume of the largest haematoma varied between 10 and 97 ml with a median of 23 ml, and 61 (36%) patients had a second haematoma between 0 and 26 ml with a median of 3 ml.

Of the 82 patients in the Early Surgery group, only 61 (74%) had surgery, 57 (93%) of these within 12 hours of randomisation. The reasons for not having surgery were patient or relative refusal (15) or change in medical status (6). Of the 86 patients randomised to Initial Conservative Treatment, 31 (36%) had surgery within 14 days of randomisation, 10 (32%) of these within 12 hours. The reasons for having surgery were neurological deterioration (29) or other (2).

Surgical patients in the Early Surgery group were more likely to have craniotomy than surgical patients in the Initial Conservative Treatment group (97% vs. 81%; Fisher's exact test, $p = 0.016$). Surgical patients in the Early Surgery group had significantly higher pre-operative GCSs than those requiring surgery in the Initial Conservative Treatment group. Comparison of the baseline characteristics of patients in the Initial Conservative Treatment group who had surgery with those who did not showed that patients who deteriorated and went on to have surgery had larger haematomas initially (Mann–Whitney *U*-test, $p = 0.010$) and were more likely to have at least one pupil unreactive (Fisher's exact test, $p = 0.0005$) but did not differ on age, GCS at the time of randomisation or presence of a second haematoma.

At some point in the first 2 weeks, seven (9%) Early Surgery patients were ICP monitored, compared with 16 (19%) Initial Conservative Treatment patients ($p = 0.073$), and this affected management decisions in one Early Surgery patient compared with 10 Initial Conservative Treatment patients ($p = 0.069$).

Six-month outcome was available for 82 Early Surgery patients and 85 Initial Conservative Treatment patients; one patient from the Initial Conservative Treatment group was lost to follow-up. Fifty-two (63%) Early Surgery patients had a favourable outcome on the dichotomised Glasgow Outcome Scale (GOS), compared with 45 (53%) Initial Conservative Treatment patients [odds ratio (OR) 0.65, 95% confidence interval (CI) 0.35 to 1.21; $p = 0.171$], an absolute difference of 10.5% (95% CI –4.4% to 25.3%). Adjusting for age, volume and GCS gives an OR of 0.58 (95% CI 0.29 to 1.16; $p = 0.122$). However, there was a highly significant difference in mortality at 6 months, with 12 (15%) Early Surgery patients dying, compared with 28 (33%) Initial Conservative Treatment patients (OR 0.35, 97% CI 0.16 to 0.75; $p = 0.007$), and absolute difference of 18.3% (95% CI 5.7% to 30.9%). The Kaplan–Meier plot of survival for the two groups of patients illustrated the significant advantage of Early Surgery compared with Initial Conservative Treatment ($p = 0.008$). The main causes of death were the initial head injury (Early Surgery 5 vs. Initial Conservative Treatment 14) and pneumonia (Early Surgery 4 vs. two Initial Conservative Treatment 2). This reduction in mortality was not associated with an increase in lower severe dependency and there were no vegetative survivors in either group.

For each of GOS, GOSE and Rankin Scale at 6 months there was a significant trend in improved outcomes in the Early Surgery group using the chi-squared trend analysis ($p = 0.047$, $p = 0.052$ and $p = 0.043$ respectively), although the proportional odds models did not reach statistical significance (OR 0.67, 95% CI 0.39 to 1.16, $p = 0.153$; OR 0.66, 95% CI 0.38 to 1.13, $p = 0.127$; OR 0.67, 95% CI 0.39 to 1.15, $p = 0.147$).

None of the pre-specified subgroups displayed any significant heterogeneity of treatment response, although patients with a GCS of 9–12 exhibited the best response to Early Surgery.

Considering outcome by allocated and received treatment, 33% (20 out of 61) of patients who were allocated to Early Surgery and had surgery died or were severely disabled at 6 months. However, 65% (20 out of 31) of patients who were allocated to Initial Conservative Treatment and had delayed surgery had died or were severely disabled at 6 months, compared with 37% (20 out of 54) of the conservatively treated patients who did not have surgery.

Patients randomised to the Early Surgery group had an average gain of 0.019 quality-adjusted life-years (QALYs) over a 6-month period (95% bootstrapped CI –0.004 to 0.043 QALYs), when compared with those randomised to the Initial Conservative Treatment. This is equivalent to an incremental QALY gain of 3.5 days over a 6-month period. The broad QALY gains are driven primarily by the increased chance of survival in the Early Surgery group.

Conclusions

The STITCH(TRAUMA) trial has demonstrated a large reduction in mortality associated with Early Surgery for parenchymal TICH ($p = 0.007$) and there were no vegetative survivors. There was not a statistically significant effect on the pre-specified primary outcome in this reduced sample. However, the observed 10.5% advantage in favourable outcome for the Early Surgery group would have been statistically significant if it had been maintained for the trial sample size as originally planned. Nevertheless, this was a very strong signal that Early Surgery will indeed prevent deterioration. This is seen in the improvement in better outcomes in the ordinal analysis of the GOS and Rankin Scale. A larger trial is urgently needed to confirm or refute this finding.

Implications for health care

1. There is a strong case for operating on patients with TICH who have a GCS of 9–12. Those who are alert or just confused (GCS of 13–15) can probably be watched carefully for any deterioration because there is a safety margin which diminishes the lower down the GCS the patient descends. Once the GCS has dropped below 8, surgical intervention appears to be less effective.
2. Based on the results of the study, and the World Health Organization guidelines for cost-effectiveness, the Early Surgery intervention could be interpreted as offering a high probability of cost-effectiveness in both high- and upper middle-income countries. There may also be a high probability of cost-effectiveness in lower middle-income countries, but, based on the cost-effectiveness acceptability curve analysis, this conclusion would be more sensitive to the threshold value of cost-effectiveness imposed by decision-makers.

Recommendations for research

This trial has given a very strong signal that Early Surgery is superior to Initial Conservative Treatment for patients with TICH. This signal was evident despite the sample size being only 20% of that originally planned. Given that there are 800,000 such injuries each year in the world (8000 per year in the UK because the UK accounts for 1% of the world's population of 7 billion), the 10.5% absolute improvement in favourable outcome represents 84,000 patients every year that could have a better outcome. If this is true, then the trial needs to be repeated with the utmost urgency to avoid this enormous annual excess death and disability rate that currently prevails for these patients.

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