Analysis plan for STITCH(Trauma) after funding withdrawn

Introduction

STITCH(Trauma) was halted early by the funding agency for "failure to recruit in the UK". The planned sample size was 840 patients with about 10% from the UK. This sample size was planned to provide 80% power to observe a 10% difference in a two-sided test with significance level set at 5% and allowed for some loss to follow-up. The achieved sample size, at the point that recruitment was halted on instruction from the funding agency, was 170 patients with 4% from the UK. This analysis plan has therefore been adapted from the original analysis statement published in the protocol (*Trials* 2012: 13,293) in the light of this much reduced sample size. This plan has been developed without access to treatment allocation.

Objectives of the reduced trial

To determine whether a policy of early surgery in patients with traumatic intracerebral haemorrhage (TICH) improves outcome compared to a policy of initial conservative treatment.

To assess the relative costs and consequences of early surgery versus conservative management for TICH in a subgroup of countries covering the highest recruiting centres.

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

Study design

This is an international multicentre parallel group trial with patients randomised to receive either "Early Surgery" or "Initial Conservative Treatment". Outcome is measured at six and twelve months by postal questionnaire to the patients. Primary outcome point is at 6 months.

Study population

All appropriate patients who are considered for STITCH (TRAUMA) must have a CT scan to confirm the diagnosis and the size and location of the hematoma. Any clotting or coagulation problems must be corrected prior to randomization in line with standard clinical practice.

Inclusion criteria

- Adults aged 14 years or over
- Evidence of a TICH on CT with a confluent volume of attenuation significantly raised above that of the background white and grey matter that has a total volume >10 mL calculated by (width × height ×length)/2 in cm
- Within 48 h of head injury
- Clinical equipoise: only patients for whom the responsible neurosurgeon is uncertain about the benefits of either treatment are eligible

All patients who are randomised and have outcome measured will be included in the analysis. Patients who withdraw from the study will not be included.

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The primary analysis will be "Intention to treat" with data analysed according to the treatment group to which the patient was randomised. Since there are a significant proportion of crossovers secondary exploratory analyses will include 'per protocol' analysis, 'per-treatment' analysis and analysis considering crossovers to surgery from the conservative group as failed medical treatment that is "poor outcome". Further exploratory analyses of factors that drive crossovers will be conducted to investigate their effect on the outcome in the study.

The power of the trial as a result of halting the trial

Using the uncorrected chi-squared test and assuming equal sample sizes in the two groups, and given an average favourable outcome of 60% (as observed after the recruitment and follow-up of 96 patients), we would have 26.4% power to detect a 10% difference. The sample size of 170 will mean that we will have 80% power to detect a 21.0% difference.

Randomisation Procedures

Allocation is stratified by geographic region, with a minimization algorithm based on age group (<50, 50 - <70, 70 or more) and severity (as measured by whether the pupils are equal and reacting or not) and with a random component (that is, with probability of 80%).

Analysis statement given early stopping of the trial

Analysis will be on an 'intention-to-treat' basis. The primary analysis will be a simple categorical frequency comparison using the uncorrected chi-squared test for favourable and unfavourable outcomes at 6 months. Patients will be categorized as having a favourable outcome if they achieve good recovery or moderate disability on the Glasgow Outcome Scale. Patients will be categorized as having an unfavourable outcome if they have severe disability on the Glasgow Outcome Scale, are vegetative or have died. A sensitivity analysis using logistic regression will be undertaken to adjust for age, volume of haematoma and GCS.

Secondary outcome analysis will include proportional odds model analysis of GOS, GOSE and Rankin at 6 and 12 months, Kaplan-Meier survival curve with log-rank test, mortality at six months and 12 months, dichotomised Rankin score (0-2,3-6) at 6 and 12 months (comparing patients able to look after their own affairs with patients who need help) and dichotomised GOS (as described above) at 12 months. For dichotomised outcomes absolute differences and 95% CIs will be reported.

Minimal subgroup analysis will be undertaken and regarded as exploratory. Odds ratios and 95% confidence intervals will be reported for the following subgroups: age (2 bands using randomisation strata: <50, 50 or more – since there are very few patients aged over 70 we will combine the two upper age bands), volume of haematoma (using median split <= 23ml, >23ml), GCS (using standard classification of head injury severe, moderate, minor: 3 – 8, 9 – 12, 13 – 15), time from ictus to randomisation (using median split <21 hours, >=21hrs), geographic region (4 bands: Europe, India, China, Other). Interaction tests (chi-squared test for heterogeneity) will be undertaken and relevant p-values will be reported.

Problems: There have been a large number of crossovers. Patients will be classified according to the reason for crossover: change in clinical status or change in patient preference. Sensitivity analyses will be conducted including and excluding these patients, including per protocol and per treatment analyses. There have also been two cases of major protocol violation in that the treatment decision was taken prior to randomisation. One patient randomised to surgery had already had a decision

made for no surgery to take place and one case randomised to initial conservative treatment had already had surgery. These two cases will be excluded from all analyses.

ICP analysis: ICP monitoring has only been undertaken in 24 patients. We will investigate whether this had any effect on treatment decisions particularly for crossover patients.

Health economics analysis: A cost-utility analysis will be conducted from a health service perspective and will be based on an intention to treat principle.

Costs: Health care resource use data will be sourced from individual case report forms, participant questionnaires and supplemented using additional questionnaires administered to a sample of trial recruiting centres. Standard unit costs estimates will be applied to resource use data for intervention delivery, hospital length of stay and rehospitalisation. Where standard unit costs are not available, these will be supplemented with information collected from the additional questionnaire (e.g. cost of an hour of a surgeons time) and WHO choice data for the cost per night in hospital. Intervention and follow up costs will be summed to generate total costs to the health services for each individual within the trial. Standard general linear regression methods will be used to estimate the impact of treatment group (conservative or early surgery) on costs. The treatment group co-efficient will represent a measure of incremental costs. The models used will be estimated following adjustment for key minimisation and baseline covariates, in order to develop unbiased estimates of the effect of treatment on costs. Estimation will be presented for all countries as well as country sub-groups classified according to Gross National Product per capita (low and lower middle; upper middle and high income).

QALYs: The EQ-5D generic quality of life measure is administered to all trial participants, regardless of country of recruitment. EQ-5D responses will be valued using national tariffs to generate a utility measure for quality of life. These data will be combined with mortality data from the trial (EQ-5D = 0). Length of life and quality of life data will be combined to generate QALY estimates for each individual trial participant. Difference in QALY estimates across groups will be adjusted for baseline EQ-5D score and analysed using standard linear regression modelling similar to those described for cost data. Valuations will use UK specific data for the base case analysis, and sensitivity analysis will explore using alternative country specific valuation for the EQ-5D where such data are available.

Cost-effectiveness: Non-parametric bootstrapping techniques will be used to account for the likely skewed nature of the data on costs and QALYs. The primary health economic outcome will be presented as incremental cost per QALY gained by adopting either treatment approach. This will be calculated using the incremental cost-effectiveness ratio (ICER), calculated as the co-efficient of treatment effect on costs divided by the co-efficient of treatment effect on QALYs from the respective linear regression models. Costs and QALY differences will be presented on the cost-effectiveness plane and cost-effectiveness acceptability curves will be derived from the net benefit statistic to illustrate the probability of early surgery being the most cost-effective option. Missing cost and QALY data will be reported. A sensitivity analysis will explore the impact of multiple imputation techniques on cost-effectiveness outcomes. Further deterministic sensitivity analyses will be conducted to account for uncertainty in key assumptions and data sources used.

Statistics that will be reported

For categorical variables the number and percentage in each group will be reported. Percentages will be reported to no decimal places. For continuous variables the median, quartiles, maximum and

minimum will be reported. Where p values are reported these will be to 3 decimal places or at P<0.0001. The presence of missing data will be reported. Outcomes will be reported as odds ratios with 95% confidence interval reported to two decimal places and p values to 3 decimal places. Absolute benefits with 95% confidence intervals to 1 decimal place will also be reported.

Evaluation of demographics and baseline characteristics

Baseline characteristics will be reported broken down by treatment. Pre-treatment information will include gender, age, pre-ICH mobility, pre-ICH Rankin, time between ictus and randomisation, Glasgow Coma Score, pupillary reaction, handedness, whether receiving any anticoagulation or thrombolytic treatment prior to ictus, past medical history, cause of injury, mechanism of injury, whether the patient had suffered an initial loss of consciousness or any amnesia.

We will include details of site of haematoma, volume and depth from the site assessments plus those and other measures from the central assessment.

Evaluation of treatment compliance and exposure

Crossovers will be reported. We will include details of surgery for both groups including time from ictus to surgery and number and percentage operated within 12 hours of ictus, time from randomisation to surgery, method of surgery, any additional procedures, and status prior to evacuation , whether sedated, GCS, and neurological status of worst arm, leg and speech. Reasons for crossover will be reported. Amount of blood removed during operation will be reported (as assessed by differences in blood volume on randomisation scan and on the five day CT scan).

Outcome analysis

The primary outcome analysis will be a simple categorical frequency comparison using the chi-squared test for favourable and unfavourable outcomes on the 8 point Glasgow Outcome Scale (GOSE) at six months. Glasgow Outcome Scale will be computed from the answers to the 14 questions as per the paper of Wilson, Pettigrew et al. Where a response to a question is missing and that response is required to assign an appropriate category an assignment will be made using the responses to all assessment scales in the outcome questionnaire. The allocation of outcome assignment will be made prior to unblinding the treatment assignment.

Planned papers

The primary paper will include the evaluation of demographic and baseline characteristics, and evaluation of treatment compliance and exposure as described above. It will report the primary outcome and secondary outcomes at six months and the EQ-5D.

Further papers will explore the economic analysis in more detail, CT analysis in more detail, the effect of crossovers, per protocol and per treatment analyses.

Gregson BA, Rowan EN, Mitchell PM, Unterberg A, McColl EM, Chambers IR, McNamee P, Mendelow AD. (2012) Surgical trial in traumatic intracerebral hemorrhage (STITCH(Trauma)): study protocol for a randomized controlled trial. *Trials* 13(1), 193.

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