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Central assessment of Computed Tomography (CT) brain scans for international stroke trials

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EDITORIAL

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Introduction

Development of multislice CT (MSCT) scanners since 1998 has resulted in submillimetre thick slices being able to be acquired, without increasing the radiation dose to the patient. Although the incident x-ray beam is widened in the slice thickness direction (Z-direction), the emergent x-rays fall upon multiple rows of small detectors. This means data can be collected simultaneously for more than one slice per rotation of the x-ray tube. For example, the dose received by the patient will be the same for four thin slices of 2.5 mm, as for one slice of 10 mm thickness. A 64-slice MSCT can create 0.625 mm thick slices. This leads to high diagnostic value in the detection of small abnormalities in stroke patients and in the reconstruction of data from CT angiography (CTA) of the brain.

Experience with five stroke trials has highlighted the value of central adjudication of computed tomography (CT) and magnetic resonance imaging (MRI) brain scans. The original approach for the CT scan reading came from The University of Edinburgh[1] and was expanded and adapted to four other trials, which involve the Universities of Nottingham and Edinburgh, and with the inclusion of MRI scans. This has generated a reliable and clinically informative large dataset from which numerous additional questions can be answered from the data being returned by the adjudicators.

Experience with five trials - International Stroke Trial-3 (IST-3), Efficacy of Nitric Oxide in Stroke(ENOS), Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS), Tranexamic acid for acute Intracerebral Haemorrhage (TICH-2) and Rapid Intervention with Glyceryl trinitrate in Hypertensive Stroke Trial (RIGHT-2) - will be discussed, together with the method for undertaking the central adjudication.

Informed consent was obtained from all patients in the five studies.

All procedures were in accordance with the ethical standards of Good Clinical Practice, the EU Clinical Trials Directive and the Helsinki Declaration of 1975, as revised in 2008.

Both Edinburgh and Nottingham are co-ordinating international trials aimed at improving the outcome for the stroke patient.

The author's task in all five trials has been to adjudicate de-identified brain CT scans for a patient; before treatment, and 24 to 168 hours later. Sometimes the CT is repeated three, six and eighteen months following treatment. Outcome data in ENOS, TARDIS, TICH, TICH2 and RIGHT1/2 is collected at 90 days and 365 days.

In each trial, the CT findings were assessed as part of patient characterisation at baseline and also to try to improve prediction of outcome after stroke.

Work in preparation for IST-3 included a large observer reliability study. This showed that more experienced readers could detect very subtle changes in tissue attenuation whereas the less experienced could still identify hyperattenuated arteries, established ischaemia and pre-existing structural changes with good reliability.[1]

Methods

Referring centres in each country de-identify the scans at source and send these electronically over the Internet to the Trial Co-ordinating Centres, accompanied by the Trial Number their patient has been allocated at the time of randomisation into the trial.

Staff in the university centres designed a structured reporting form,[2] originally for IST-3 but then adapted to other trials, with questions to be answered by the Adjudicator who was blind to treatment assignment. Some trials' forms provide no information at all (RIGHT 1/2) and others provide only the age and gender of the patient, as well as the dates of onset of the stroke and performance of the scan.

The form can accommodate questions for both ischaemic and haemorrhagic strokes, as well as providing for the recording of conditions that can mimic stroke such as tumours and infection, plus complications of stroke (haemorrhagic transformation, lesion swelling, infarct expansion) and pre-stroke changes (old infarcts/haemorrhages, atrophy, leukoaraiosis).

Upon locating a scan, the adjudicator works through the form and enters any comments at the end; for example the presence of a congenital abnormality and signs off with an identifiable pin number.

Even in patients who have had a haemorrhage, the presence of pre-existing abnormalities can be important when attempting to predict which patients will do better than others.

The aim of adjudication was to ensure the diagnosis was correct and to allow secondary hypothesis generating analysis based on radiological features that may relate to outcome, such as leukoariosis.

IST-3 (International Stroke Trial-3)[3–6]

Trial registration number: ISRCTN25765518

The author collaborated with the University of Edinburgh during this trial which ran from 2000- 2011, her involvement being only 2005 – 2011, when it was completed.[3]

Data for 3,035 patients from 12 countries were randomised. Patients were given alteplase intravenously (IV) within six hours of having an ischaemic stroke to dissolve the clot. Fifty per cent of patients were assigned to receive alteplase and 50 per cent were controls.[4]

Brain scans were essential prior to treatment to exclude haemorrhage or mimics of stroke. Adjudicators recorded the presence of stroke, haemorrhage, occluded arteries, Alberta Stroke Program early CT Score (ASPECTS), mass effect, white matter disease, atrophy and any other visible focal lesion.

Each patient had two or three scans, so 7,000 scans were read by expert readers from eight countries. Agreement for the presence of early acute ischaemic signs and pre-existing signs was required with no more than one category difference between readers.

Results

CT brain scan findings were normal in nine per cent. Forty one per cent had early ischaemic signs; namely visible infarct, tissue hypoattenuation, hyper-attenuated artery and whether or not pre-existing signs were also present. Fifty one per cent had pre-existing signs; old infarct, periventricular hypoattenuation (leukoaraiosis) and atrophy but no early ischaemic signs.

Clinical Outcome

In analysis adjusted for the main clinical predictors (age, stroke severity, time to treatment)[2] a reduction in independence at six and 18 months was predicted by the baseline CT showing:- tissue hypoattenuation, a large lesion, swelling, hyperattenuated artery, atrophy, or leukoaraiosis.

Similarly, symptomatic intracranial haemorrhage was independently predicted by the CT showing: - old infarct, tissue hypoattenuation or hyperattenuated artery.

The absolute risk of symptomatic intracranial haemorrhage was increased if more than one of these signs was present, for example an old infarct and also a hyperattenuated artery. However, these signs should be considered in light of the clinical features, not in isolation.

CT scanning in acute stroke was of value to safely initiate and monitor the administration of intravenous (IV) alteplase. At 18 months, patients receiving alteplase were associated with fewer events and less likely to need help with everyday activities.[4]

It was concluded that IV alteplase for thrombolysis does not affect patient survival but does lead to statistically significant, clinically relevant improvements in functional outcome and health-related quality of life.[4]

Prognostic assessment in patients with acute ischaemic stroke should take into account CT evidence of pre-existing signs, as well as acute ischaemic signs.

ENOS trial (Efficacy of Nitric Oxide in Stroke)[7–10]
This ran between 2001 and 2014.
Trial registration number: ISRCTN99414122
The author participated in this trial from 2012–2014 which collected data for 4,011 patients from 23 countries and was co-ordinated by Professor Philip Bath at The University of Nottingham. The Neuroradiology Lead was Clinical Associate Professor Robert Dineen.

Clinical problem being addressed was the known fact that high blood pressure is associated with poor outcome after stroke. It is not known whether blood pressure should be lowered early after stroke or whether to continue or temporarily withdraw existing antihypertensive drugs.

Procedure
Patients with an acute ischaemic or haemorrhagic stroke and raised systolic blood pressure (SBP) 140-220mm Hg were randomly assigned to seven days of transdermal glyceryl trinitrate started within 48 hours of stroke onset, or to a control group. A subset of patients who were taking antihypertensive drugs before their stroke was also randomly assigned to continue or stop taking these drugs.

Primary outcome at 90 days was function, assessed by observers masked to treatment assignment. The scan reading was adapted from IST-3 to include presentation with primary haemorrhage but was otherwise the same.

Results
It was concluded that there was no benefit in lowering blood pressure with glyceryl trinitrate in patients with acute stroke and raised blood pressure, when started at an average of 26 hours after stroke onset. However, as glyceryl trinitrate had acceptable safety, including in patients with carotid stenosis, it might have benefits when started within six hours of stroke onset.

In the subset of patients taking anti-hypertensive drugs prior to the stroke, there was no difference in functional outcome measured with the groups who continued their pre-stroke anti-hypertensive drugs versus those who stopped. Many stroke patients have a difficulty with swallowing, so to continue oral drugs could have a deleterious effect. It seems reasonable to withhold blood pressure-lowering drugs until patients are medically and neurologically stable and have suitable oral or enteral access to allow safe drug reintroduction.

However, post-acute blood pressure control is important to reduce the risk of subsequent vascular events. Analysis of the independent contribution of CT findings to clinical outcomes is ongoing.

In parallel with the ENOS study, the University of Nottingham ran a pilot study, RIGHT-1. The Principal Investigator was Professor Philip Bath based in Nottingham.

RIGHT-1 (Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial)[11] was a local ambulance based study, with 41 patients, using a transdermal patch of glyceryl trinitrate (GTN). No ill effects were identified in either ischaemic or haemorrhagic stroke patients. Refer to http://www.right-trial.org/.

Trial registration number: ISRCTN 66434824
Paramedics could successfully enroll patients with ultra-acute stroke into an ambulance-based trial. GTN reduces systolic blood pressure at two hours and seemed to be safe in ultra-acute stroke. A larger trial was needed to assess whether GTN improves functional outcome which is RIGHT-2.

RIGHT-2 (Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial – 2) is to assess the safety and efficacy of transdermal glyceryl trinitrate, a nitric oxide donor, in hyper-acute ischaemic or haemorrhagic stroke in the context of a multicentre ambulance-based trial. The Principal Investigator is Professor Philip Bath and the Neuroradiology Lead is Professor Joanna Wardlaw.

This trial commenced in 2015, funded by the British Heart Foundation and is to run until 2018 so no results are yet available.

Trial registration number: ISRCTN 6986053.
The scan rating in RIGHT-1 and 2 uses the IST-3/ENOS form, with rating angiographic findings added for those patients having Computed Tomography Angiography (CTA).

TARDIS (Triple Antiplatelets for Reducing Dependency in Stroke) trial
Co-ordinated by the University of Nottingham with the Principal Investigator being Professor Philip Bath and the Neuroradiology Lead is Clinical Associate Professor Robert Dineen. The trial was initially funded by the British Heart Foundation (BHF) and is now being funded by the National Institute for Health Research – Health Technology Assessment Program (NIHR HTA).The author has been involved since 2012. The trial closed to

recruitment in March 2016 and the follow up data is still being obtained. Results have therefore yet to be analysed and published.

Trial registration number: ISRCTN 47823388
For this trial 3,096 patients were recruited, comprised of 2,155 with an ischaemic stroke and 941 who had suffered a transient ischaemic attack (TIA).

Aim was to test safety, tolerability and effectiveness of an intensive blood thinning therapy involving a combination of three drugs – aspirin, clopidogrel and dipyridamole. It was hypothesised this combination would reduce the effects of the stroke and the chances of recurrence.

Stroke patients, and most with TIA had a baseline CT or MRI scan; a post-treatment scan could be performed if a recurrent event of bleed occurred.
TARDIS uses an adapted scan rating from IST-3/ENOS.

TICH-1 trial - (Tranexamic acid for acute Intracerebral Haemorrhage)[12]
Co-ordinated by the University of Nottingham with the Principal Investigator being Associate Professor Nikola Sprigg and the Neuroradiology Lead is Clinical Associate Professor Rob Dineen. This was a randomised double-blind placebo-controlled trial to test the feasibility, tolerability and acceptability (adverse events) of tranexamic acid in haemorrhagic stroke. A secondary aim was to test the effects of tranexamic acid on haematoma expansion and death and dependency in haemorrhagic stroke. The trial commenced in March 2011 and ended in March 2012.
Trial registration number ISRCTN50867461

Intravenous tranexamic acid (Cyklokapron®) or 0.9 per cent normal saline was administered as 1 g loading dose infusion over 10 minutes followed by 1 g infusion over eight hours, given within 24 hours of the stroke. The drug was given to 16 patients and eight received the placebo.

No adverse effects were observed, so a larger trial, TICH-2, was started to assess the safety and efficacy of tranexamic acid in intracerebral haemorrhage.

TICH-2 (Tranexamic acid for acute Intracerebral Haemorrhage) trial
The start-up phase commenced in 2013, the main phase in 2014 and the trial will continue until March 2018, with the target being 2,000 patients.

Trial registration number: ISRCTN93732214
Over 1,600 have been recruited to date. The trial is being funded by the National Institute for Health Research - Health Technology Assessment Program (NIHR HTA).

Clinical problem
No effective treatment for intracerebral haemorrhage is available. Tranexamic acid is an anti-fibrinolytic drug that has been found to reduce mortality in patients bleeding following trauma in the CRASH-2 trial (Clinical Randomisation of an Antifibrinolytic in Significant Head Injury).[13]

The main phase of TICH-2 is to confirm safety and assess efficacy of tranexamic acid in spontaneous intracerebral haemorrhage patients.

Associate Professor Nikola Sprigg is Chief Investigator and Clinical Associate Professor Robert Dineen is the Neuroradiology Lead. The author commenced as an adjudicator in July 2015.

In the same manner, as in all the previously discussed studies, a record is made on a standardised questionnaire of any pre-existing signs of old infarcts, atrophy and leukoaraiosis. The contribution of these factors, if any, will not be known for some time, as the trial will continue for a further 20 months.
TICH1 and 2 use the adapted scan rating from IST-3/ENOS.

It is noted that the IST-3 parent questionnaire, with modifications, is in use in several other trials in which the author is not involved, namely European Stroke Research Network for Hypothermia (EUROHYPE), Promoting Acute Thrombolysis in Ischaemic Stroke (PRACTISE), Restart or Stop Antithrombotics Randomised Trial (RESTART), Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE), Enhanced Control of Hypertension and Thrombolysis (ENCHANTED) and Lacunar Intervention Trial (LACI 1 and 2)

Conclusion

World-wide collaborative efforts are being made to improve outcome following stroke and the useful foundation stone for the trials is obtaining a good quality CT brain scan at the time of the stroke and having it interpreted by an expert reader. Apart from the human factor, economic considerations are very large, as it costs a great deal to care for a dependent survivor of a stroke; about AUS$ 20,000 per year but only eight per cent of that figure to care for an independent survivor. The CT findings may assist in predicting outcome in individual

cases and thus assist with planning of rehabilitation.

Physicians wishing to have patients enrolled in the two ongoing studies can contact: Associate Professor Nikola Sprigg: TICH-2 <tich-2@nottingham.ac.uk> and refer to http://tich-2.org.
Professor Philip Bath :RIGHT-2 trial@right2trial and refer to http://right-2.ac.uk/

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The author declares that she has no competing interests.

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