Commentary

Acute stroke: we have the treatments and we have the evidence - we need to use them

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Abstract

Despite huge global burden, stroke disease has traditionally received little attention in the general medical press. We review a series of four acute stroke research articles published in a themed issue of the *Lancet*. Claiborne-Johnston and coworkers presented a scoring system to stratify risk of stroke following transient ischaemic attack. Chalela and colleagues demonstrated that magnetic resonance imaging is superior to computed tomography in detecting acute ischaemic stroke and that fears of missing intracranial haemorrhage are unfounded. The SITS-MOST (Safe Implementation of Thrombolysis in Stroke - Monitoring Study) group reported positive experience of translating acute stroke thrombolysis trials into routine clinical practice in Europe, and the PROSIT (Project on Stroke Services in Italy) group studied acute effects of admission to a dedicated stroke unit. The message from all of these reports is that evidence-based, successful management of acute stroke is possible, and that investment in health infrastructure and changing mind sets of health practitioners to improve stroke care will deliver benefits.

The global burden of stroke is immense. Six million people will die from stroke this year, with millions more left disabled. Despite these alarming figures, we under-utilize proven acute stroke treatments. As such, we welcome the recent stroke themed issue of the *Lancet*. The research articles presented in the journal mirror the stroke patient journey - from transient ischaemic attack (TIA) [1] through acute stroke requiring imaging [2] and therapy [3], to care within a dedicated stroke ward [4].

We are all aware that TIA predicts stroke, but the magnitude of risk has until recently been underestimated. In fact, stroke risk during first week following TIA exceeds 30% in certain groups [1]. Scoring systems have been developed to allow risk stratification. Collaboration between UK and North American centres produced the ABCD^2 score [1]. (The abbreviation ABCD^2 is derived from the measures of age, blood pressure, clinical signs, duration and diabetes, on which the score is based.) This simple five-item instrument identifies high (8.1%), medium (4.1%) and low (1%) 48-hour stroke risk. The score was robustly developed and validated in over 4,800 patients across diverse ethnic and socio-economic groups.

Given the high initial risk for stroke, the best use of the score may be to identify patients who require immediate in-patient assessment. At the very least, by providing an assessment framework it should improve detection of the highest risk individuals but maybe improve diagnostic accuracy in suspected TIA; at present approximately 50% of referrals to diagnostic accuracy in TIA referrals is only 50% [5]. Although the evidence base for hyper-early intervention in TIA is limited, we know that prompt carotid endarterectomy is effective [6], and acute stroke trials report reduced recurrence with antiplatelet treatment [7]. We assume that early initiation of secondary prevention in TIA will have similar effects, but we await the results of ongoing trials to address this definitively.

We should treat stroke with at least the same urgency as myocardial infarction; in fact, the time window for intervention is shorter. All patients with stroke symptoms require brain imaging to assist in diagnosis and to exclude treatable stroke mimics. We have suspected for many years that magnetic resonance imaging (MRI) is superior to computed tomography (CT) in this regard; Chalela and colleagues [2] have reported definitive proof. In a pragmatic trial of all referrals to an acute stroke service, initial MRI had a sensitivity of 83% in detecting acute ischaemic stroke; in contrast, the sensitivity with CT was only 16%.

Traditionally, CT has been preferred because of perceived superior sensitivity in detecting intracerebral haemorrhage

CT = computed tomography; ICH = intracerebral haemorrhage; MRI = magnetic resonance imaging; rt-PA = recombinant tissue-plasminogen activator; TIA = transient ischaemic attack.

Table 1

Summary of outcomes from SITS-MOST, meta-analysis of previous rt-PA trials and placebo arm

	Mortality (at 3/12)	Independence (at 3/12)	Symptomatic ICH (per SITS-MOST)[a]	Symptomatic ICH (per previous trials)[b]
Trials	17.3%	49%	N/A	8.6%
SITS-MOST	11.3%	54.8%	1.7%	7.3%
Placebo	18.4%	30.2%	N/A	1.9%

[a]Bleed large enough to cause symptoms and accompanying neurological deterioration. [b]Any bleed with any alteration in neurological status, regardless of severity. rt-PA, recombinant tissue-plasminogen activator; SITS-MOST, Safe Implementation of Thrombolysis in Stroke Monitoring Study.

(ICH), better (but by no means acceptable) availability and concerns regarding practicalities of emergency MRI scanning. In their study, Chalela and coworkers [2] demonstrated equal ability of MRI to detect ICH in a real-time acute setting. A strong case can now be made for 24-hour access to MRI in all stroke centres. This requires investment; we note with pessimism that many UK centres still struggle to achieve national targets of CT scanning within 24 hours of ictus [8].

Consider the following scenario. sing MRI, a diagnosis of ischaemic stroke has been made for your patient. If this were myocardial infarct, thrombolytic therapy - with a number needed to treat of approximately 30 to avoid one death [9] - would be instituted. Imagine if a similar treatment were available for acute ischaemic stroke but that the number needed to treat to reduce disability was only three. Such a treatment is available. We have known for more than a decade that intravenous recombinant tissue-plasminogen activator (rt-PA) is effective if administered within 3 hours of stroke onset [10] and a recent meta-analysis has confirmed efficacy [11] (Table 1).

There is of course a real and important risk for ICH with rt-PA. As such it was a condition of the European licence that a comprehensive monitoring study be performed (the SITS-MOST [Safe Implementation of Thrombolysis in Stroke-Monitoring Study]) [3]. This multicentre international study, including 6,483 patients across 285 centres, confirmed a high rate of good outcomes and allayed fears of frequent ICH (Table 1).

The SITS-MOST population and definition of haemorrhage demand some consideration. Only patients treated within the strict terms of the European licence were studied, and so patients with any of the following were excluded: age greater than 80 years, severe stroke, anticoagulation, history of diabetes and previous stroke. A substantial number of patients treated with rt-PA do not satisfy these criteria, and similar data on their outcomes would be of value. Symptomatic ICH was defined as haemorrhage involving 30% or more of infarct volume with objective clinical deterioration [3]. Although this is a different definition to that used in the original trials, it is arguably more meaningful. Previous definitions of symptomatic ICH included patients with minor bleeds or no measurable neurological sequelea. However, even these generously defined events were less common in routine practice than in the previous trials (Table 1).

An important finding in SITS-MOST [3] is that outcomes were similar regardless of the experience of the centre (although all were designated acute stroke centres), implying that thrombolytic therapy should now be more widely used. There is a long way to go; currently fewer than 5% of eligible patients in Europe receive thrombolytic therapy.

All stroke patients, whether they are treated with rt-PA or not, should be offered a further evidence-based intervention, namely specialist stroke unit admission. A systematic review has demonstrated consistent survival advantages of stroke units in addition to their rehabilitation role [12]. To date, studies provide little guidance on timing of admission and long-term benefits. The PROSIT (Project on Stroke Services in Italy) [4] observational study goes some way to addressing this shortfall. Acute (within 48 hours) admission to a dedicated stroke unit was associated with improved survival and functional outcome; benefits persisted at long-term follow up.

In the PROSIT study [4] a loose definition of stroke unit care was used. In extensive subgroup analysis, no single element of stroke unit care was convincingly linked to improved outcomes. The study was underpowered to address this issue, but it remains likely that a stroke unit is 'greater than the sum of its parts', with the individual components of care working synergistically. Our limited understanding of why stroke units work should not defer us from making use of this evidence-based intervention. The number of hospitals in PROSIT that offered dedicated stroke unit care is disappointing (30 out of 260 hospitals) and emphasizes how much further we have to go to improve stroke patient care in Europe. Surprisingly, patients admitted to centres with stroke units did better even if they were not admitted to the specialist ward. Perhaps simply having an enthusiastic stroke team within a centre has knock-on effects on other staff and practices.

A theme across all of the reports in this *Lancet* collection is that evidence-based effective management of acute stroke is possible but implementation will require changes in attitudes and infrastructures. Our challenge is to promote utilization of proven therapies while developing novel ones. We encourage future generations of enthusiasts to help us take on this challenge.

Competing interests

The authors declare no relevant competing interests in relation to this work. KRL is a named author on the SITS-MOST paper, and chaired the independent data monitoring committees for the ECASS III and DIAS trials of thrombolysis in stroke.

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