Thrombolysis for acute ischaemic stroke: a new challenge for emergency medicine

J Kendall

Correspondence to:
Dr J Kendall, Department of Emergency Medicine, Frenchay Hospital, North Bristol NHS Trust, Frenchay Park Road, Bristol BS16 1LE, UK;
jason.kendall@nbt.nhs.uk

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ABSTRACT

Introduction: Acute ischaemic stroke (AIS) is a leading cause of death and disability within the United Kingdom. Despite evidence of the benefit of thrombolysis for appropriately selected patients with AIS, this intervention remains markedly underutilised in this country when compared with other developed countries. The delivery of thrombolysis for AIS has become a political, as well as a clinical, priority in the United Kingdom.

Discussion: Research has shown that, althongh thrombolysis for AIS is associated with increased shout-term mortality, this is offset by a signficant benefit in terms of reduced long-term death and disability. Recent observational data have shown that it can be safely and effectively delivered in the "normal" clinical setting (ie, a non-research environment). Furthermore, thrombolysis for AIS is supported by the Royal College of Physicians and the National Insititute for Health and Clinical Excellence. Emergency physicians are trained to receive and assess patients with possible stroke. The emergency department (ED) is an ideal location in which to perform these clinical duties and to communicate and coordinate the necessary tasks required for the delivery of thrombolysis. All of the skills and resources are already available within the ED, with the exception of a single training requirement: certification in the National Institute for Health Stroke Scale scoring system, which can be acquired following limited Internet-based traning.

Results: Emergency physicians should be integrally involved in the development of protocols for the delivery of thrombolysis to patients with AIS. This will require communication and collaboration locally with stroke physicians and radiologists, a process that should be facilitated by the newly emerging Stroke Networks.

Stroke is the next leading cause of death after coronary artery disease and all cancers combined. There are 110 000 new strokes per year in England and Wales; two thirds will survive of which half will be left with a permanent disability. The United Kingdom has a 100% higher mortality rate for stroke than the United States, Canada and Australia, and is the only country not to demonstrate an improvement in the fatality rate over recent years.

THE CHALLENGE

How often, and until how recently, have we thought that there is no viable acute intervention for patients with a stroke? There is (and has been for several years) evidence that early thrombolysis reduces the combined endpoint of death and long-term disability in acute ischaemic stroke (AIS). Despite this, only 0.2% of patients with AIS received thrombolysis in the United Kingdom in 2006 compared with 10% in Australia. The National Audit Office has estimated the cost of thrombolysis for 9% of patients with AIS to be £9.9 million and the saving in care costs to be £26.4 million.[1]

The Department of Health (DoH) have moved the political focus onto the management of AIS; in recent publications "Mending hearts and brains",[2] "Delivering quality and value—focus on acute stroke"[3] and "A new ambition for stroke"[4] parallels are drawn with successful strategies in the management of acute myocardial infarction (AMI). Appropriate focus is brought to bear on the aggressive early management of AIS and, in particular, thrombolysis for selected patients. Stroke networks are emerging to develop local strategies to implement DoH policy.

This presents an excellent opportunity for emergency medicine. However, with this opportunity also comes a potential threat; DoH strategy hints at delivering patients directly to stroke units for "hyperacute" assessment and management (including thrombolysis). There is an argument that a logical and cost-effective place for the initial treatment of a patient with a stroke is the emergency department (ED). In order to administer thrombolysis robustly, safely and expediently to a patient with AIS the following are required: a 24 h service, immediate availability of experienced clinicians, rapid access to computed tomography (CT) scanning, the ability to manipulate haemodynamic parameters (eg, control hypertension) and competence in the delivery of thrombolysis—sound familiar? Any modern UK ED should already be able to fulfil these criteria.

There is, however, one specific area for additional training that will be required for emergency physicians—certification in the National Institute for Health Stroke Scale (NIHSS). This is a clinical stroke scoring system that contributes to eligibility for thrombolysis, which is discussed further below. This training is relatively straightforward, takes little time and is available on the Internet at no cost.

Given these arguments, it would seem illogical and expensive to try and re-create this environment in a different part of the hospital. Certainly, once initial assessments, investigations and interventions (including, when appropriate, thrombolysis) have been performed, the patient should be transferred directly to a stroke unit for further care and rehabilitation. Our challenge within emergency medicine is to make the case that we are the most appropriate specialty to receive, triage, investigate and, when appropriate and with collaboration, thrombolyse patients with AIS, so

that Stroke Networks do not overlook ED for the hyperacute care of patients with AIS.

In order to achieve this, emergency physicians need to be familiar with the evidence base, get involved with strategic planning regionally (ie, have representation within local Stroke Networks), develop appropriate protocols in collaboration with other stakeholders (eg, pre-hospital care, radiology and stroke physicians) and get certified in NIHSS scoring.

THE EVIDENCE

Approximately 6000 patients have been recruited into 18 placebo-controlled randomised trials (RCT) over the past 15 years that have, to varying degrees, addressed the issues of efficacy and safety, different thrombolytic agents, adjuvant therapy, time window and patient-related factors such as age, stroke severity and CT findings. There is significant heterogeneity between these trials, as one might expect, related to the thrombolytic agents used, the protocols used, the age ranges recruited, the time window from symptom onset, CT exclusion criteria and scales used for disability measurement. A Cochrane Review published in 2003 of the pooled data from these trials was, however, able to report some important findings.[5]

One of the main findings of the meta-analysis is that, across all trials, there appears to be no doubt that short-term mortality (7–10 days) is increased by thrombolysis (15% versus 10%, thrombolysis versus placebo, odds ratio (OR) 1.81, 95% CI 1.46 to 2.24) and that this is driven by fatal intracranial haemorrhage (ICH) (5% versus 1%, OR 4.34, 95% CI 3.14 to 5.99). By the end of follow-up (90 days), however, the excess mortality associated with thrombolysis is still significant but markedly reduced (18% versus 15%, OR 1.33, 95% CI 1.15 to 1.53). Despite the increased mortality, the combined endpoint of death or dependency by the end of follow-up associated with thrombolysis was significantly less (53% versus 58%, OR 0.84, 95% CI 0.75 to 0.95). This is the equivalent of 43 fewer patients dead or dependent for every 1000 treated, or a number needed to treat of 23. This compares favourably with other interventions such as thrombolysis or primary percutaneous coronary intervention for AMI.

The findings also indicate a significant heterogeneity in outcome between the thrombolytic agents studied (streptokinase,[6–9] recombinant tissue plasminogen activator (rt-PA),[10–16] and urokinase)[17–20] with a significantly worse outcome associated with streptokinase compared, in particular, with rt-PA; indeed three of the streptokinase trials were prematurely discontinued because of excess early mortality.[6–8] A further two trials evaluated local (intra-arterial) pro-urokinase.[21 22]

The findings of the pooled data from the trials that evaluated rt-PA[10–16] indicate significantly superior benefit/risk outcomes than the pooled data across all trials and the pooled data from any other specific agent. There is still excess short-term mortality associated with rt-PA, but this is no longer significant (OR 1.24, 95% CI 0.85 to 1.81); it is driven by a reduced but significant increase in fatal ICH (OR 3.6, 95% CI 2.26 to 5.68). Increased mortality by the end of follow-up is also no longer significant (OR 1.17, 95% CI 0.95 to 1.45). The combined endpoint of death and disability is even lower (OR 0.80, 95% CI 0.69 to 0.93) with 55 fewer dead or dependent for 1000 patients treated with rt-PA (number needed to treat 18).

Time to treatment is an important factor, with a more favourable outcome associated with a shorter time from the onset of symptoms to thrombolysis. Across all trials, which treated patients up to 6 h post-onset of symptoms, the OR for death or dependency was 0.84 in favour of thrombolysis (see above). The trials that reported data for patients who were randomly assigned within 3 h of the onset of symptoms showed superior outcomes, with an OR of 0.66 (95% CI 0.53 to 0.83) for death or dependency in favour of thrombolysis.

There are few data to indicate an upper age limit for thrombolysis. Most trials of thrombolysis for AIS have an upper age limit of 80 years and, in those that did not, there are not enough data to draw conclusions about the safety or efficacy in this age group. This is clearly an area for further research because there are large numbers of elderly patients who have AIS.

Only one trial evaluated concomitant antithrombotic therapy (aspirin) a priori as part of the trial design and reported significantly worse outcomes.[8] A post hoc analysis of the trials in the Cochrane dataset based on their adjuvant antithrombotic regimes indicates that aspirin should be delayed and certainly should not be administered within 24 h of thrombolysis.[5]

All trials of thrombolysis in AIS to date clearly define the presence of ICH on the CT scan as a contraindication to thrombolysis. A post hoc analysis in one trial reported that the presence of early ischaemic change visible on the CT scan was associated with a worse outcome.[23] The evidence is, however, inconsistent; in one analysis, early ischaemic change involving more than one third of the territory of the middle cerebral artery was associated with an increased risk of ICH following thrombolysis,[24] but another study reported that these radiological findings were not independently associated with adverse outcomes.[25] Furthermore, the radiological appearance of early ischaemic change is subtle and its reporting seems to be subject to significant interobserver variability.[26] Other CT changes associated with early infarction (oedema or mass effect) have been associated with haemorrhagic transformation and worse outcomes.[10] The most recent recommendation of the American Stroke Association (July 2007) is that, with the exception of haemorrhage, there are no specific CT findings that should preclude treatment with rt-PA.[27]

A final factor that is of importance is the severity of the stroke; there appears to be a worse outcome associated with thrombolysis in more severe AIS. The NIHSS is a clinical stroke scale that ensures that the major components of the neurological examination are performed expediently (see below). It quantifies the neurological deficit, facilitates communication between healthcare professionals, provides early prognosis and contributes to eligibility criteria for thrombolysis.[28 29] Emergency physicians can correctly identify and safely treat stroke patients using a standardised scale such as this.[30] The likelihood of a favourable outcome has been reported to be related to the severity of the stroke; patients with mild to moderate AIS (NIHSS <20) have the greatest potential for positive response to treatment.[31] Conversely, patients with an NIHSS greater than 22 have a very poor prognosis; because the risk of haemorrhage is considerable among patients with severe deficits, the decision to treat with rt-PA should be made with caution.[32]

The Cochrane Review in 2003 concluded that "thrombolytic therapy appears to result in a significant net reduction in the proportion of patients dead or dependent in activities of daily living" and that "the data are promising and may justify the use of thrombolytic therapy with intravenous rt-PA in experienced centres in highly selected patients where a licence exists".[5]

The licence for rt-PA for AIS was granted in the United States in 1996, in Canada in 1999 and in Europe in 2002. The licence conditions are that it be given within 3 h of the onset of AIS, to patients between the ages of 18 and 80 years, with a blood

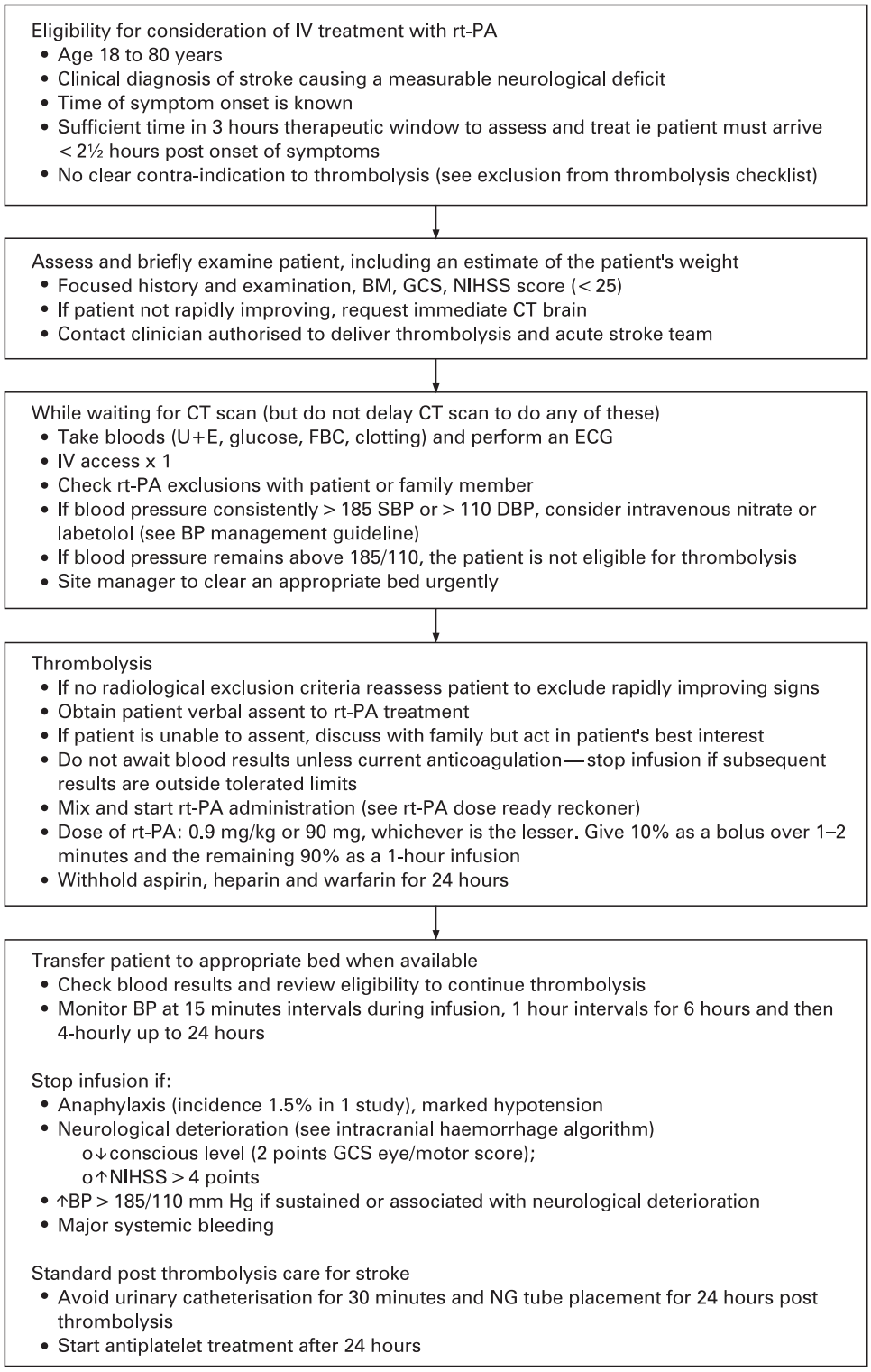

Figure 1 Acute ischaemic stroke thrombolysis guideline.
BM, blood glucose test; BP, blood pressure; CT, computed tomography; DBP, diastolic blood pressure; FBC, full blood count; GCS, Glasgow coma score; IV, intravenous; NG, nasogastric; NIHSS, National Institute for Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; SBP, systolic blood pressure; U + E, urea, creatinine and electrolytes.

pressure of less than 185/110 mm Hg, with an NIHSS score of less than 25 and with no concomitant antithrombotic therapy. Despite this, there has been virtually no impact on public health within the United Kingdom, with only 0.2% of patients receiving thrombolysis in 2006. This is undoubtedly due to a combination of factors including continued fear or doubt related to benefit and risk in the "real world" rather than a research environment, disorganisation of acute stroke management, delays in neuro-imaging, resource limitation and delay in presentation (even in countries where thrombolysis is well established, intervention rates are limited to 10%). The recent publication of the SITS–MOST Registry should allay fears relating to the feasibility of thrombolysis for AIS outside the setting of an RCT[33] and the recent political prioritisation of AIS should improve the process issues and resource environment.

The SITS–MOST observational study assessed the safety and efficacy of thrombolysis with rt-PA for AIS in 14 countries between 2002 and 2006. A total of 6483 patients were thrombolysed in 285 centres (half of which had little previous experience of thrombolysis for AIS). Mortality, symptomatic

ICH and functional outcomes were measured at 3 months. The observed incidence of symptomatic ICH at 7 days in SITS–MOST was 7.3% (versus 8.6% in RCT), the 3-month mortality was 11.3% (versus 17.3% in RCT) and complete recovery at 3 months occurred in 38.9% (versus 42.3% in RCT).

The authors concluded that "intravenous rt-PA is safe and effective in routine clinical use when used within three hours of onset of stroke, even by centres with little experience of thrombolytic therapy for acute stroke" and that "the findings should encourage wider use of thrombolytic therapy for suitable patients". These statements are supported by the Royal College of Physicians (Guidance on the Recognition and Early Management of Suspected Stroke and TIA)[34] and by the National Institute for Health and Clinical Excellence (Guidance on Alteplase for the Treatment of AIS).[35]

In summary, therefore, there should no longer be any doubt about the benefit of thrombolysis in selected patients with AIS and, furthermore, it should be part of routine clinical practice within emergency medicine in the United Kingdom. There is a sound evidence base, plenty of international precedent regarding feasibility, it is a licensed treatment and it is recommended by authoritative UK clinical bodies.

THE POLITICS

Thrombolysis for AIS is currently high on the political agenda of the DoH.[2–4] Given the evidence of benefit, the lack of progress with the implementation of this intervention within the United Kingdom and the potential cost savings, this is entirely appropriate. Implementation will be steered by health authority groups similar to the equivalent Cardiac Networks that have achieved significant progress in the setting of AMI in the recent past. Indeed, in the Avon, Gloucestershire and Wiltshire (AGW) region, the newly formed Stroke Clinical Reference Group is an offshoot of the Cardiac Network.

It is vital, as it was within the Cardiac Networks, for there to be representation of emergency medicine within these newly forming stroke groups. The main priorities are (1) to promote the ED as the location, and emergency medicine as the specialty, initially to receive patients with possible AIS, evaluate and resuscitate when needed, organise appropriate urgent investigations (including CT scanning) and (2) to encourage a collaborative approach (ie, following communication with the relevant local clinicians—stroke physicians/radiologists) for ED-based thrombolysis. Given the relevant roles and skills within emergency medicine, this would seem a logical and cost-effective argument when compared with creating, equipping and staffing another 24 h critical care environment within the hospital.

Every hospital should have a stroke unit responsible for the continued management and subsequent rehabilitation of stroke patients, but this does not need to be a "hyperacute" unit with all of the resources entailed therein. These arguments were made at our regional Stroke Clinical Reference Group and it was agreed that initial management and thrombolysis for AIS throughout the AGW region would be ED based. The discussion was not controversial and it appeared that the main issue was raising awareness of the existing skills and resources within emergency medicine and ED.

COLLABORATION AND EDUCATION

There is no doubt that thrombolysis for AIS is more complex than for AMI. Given the novelty of the intervention, the need for a CT scan and the strict patient-related eligibility criteria, the decision should be made by experienced clinicians and with the collaboration of the other immediately involved specialties (eg, stroke medicine, radiology/neuroradiology). The screening process to ensure that the patient is clinically (time window, NIHSS score, contra-indications, etc) and radiologically suitable needs to be robust and rapidly accessible.

Most of the clinical and organisational aspects of the process can be performed by an experienced emergency physician. The only clinical educational requirement that is not currently within the emergency medicine syllabus is the ability to perform an NIHSS score, which is one of the factors required to determine suitability for thrombolysis. This score is essentially a comprehensive but rapid (with experience, it takes approximately 5 minutes) neurological examination for which a score is attributed to each of 11 domains (eg, consciousness level, visual deficit, motor deficit, speech deficit, etc). The scores are summed to give a final score (between 0 and 42), which must be below 25 for thrombolysis to be indicated (see above). The training to become certified in NIHSS scoring is available on the Web via the American Stroke Association (www.nihstrokescale.org/), is free of charge and takes approximately half a day to complete. It consists of various practice and testing modules, following successful completion of which you are awarded a certificate valid for one year.

Although the whole process can be organised from the ED, communication with other specialties will almost certainly be required, particularly for a confident interpretation of the CT scan. This will require a local solution that will vary from hospital to hospital and from region to region. In the AGW network we are planning to provide a regional rota of "stroke experts" drawn from the specialties of stroke medicine, emergency medicine and neuroradiology (mostly clinicians from within the Clinical Reference Group) who will be available to discuss cases over the telephone and who will have access to the digital radiology systems of the hospitals within the network so that they can review CT scans. The local emergency physician will, following clinical evaluation and with the results of the CT scan, be able to discuss their case with the "stroke expert" for that day. In order for emergency physicians within the network to be authorised to administer thrombolysis, they will be certified in NIHSS scoring and will have attended a training day organised by the Stroke Network Clinical Reference Group where the clinical, radiological and process issues are all discussed.

Professor Roger Boyle (the National Director for Heart Disease and Stroke) recently stated that: "With appropriate training, emergency physicians could be deemed sufficiently trained and experienced in the use of thrombolytic treatments and trained and experienced in neurological care" and that "…it would be important for there to be local agreement between stoke and emergency physicians and provision of appropriate training for non-stroke specialist physicians who want to provide this treatment". Furthermore, he states "…within such a governance agreement, it would be possible to provide a 24/7 thrombolytic treatment service with emergency physicians taking the lead…"(personal communication, January 2008).

AN EXAMPLE PROTOCOL

Part of the protocol that has been developed by the AGW Clinical Reference Group is shown in fig 1. This is the "frontsheet" for which there are various supporting documents (eg, the FAST pre-hospital protocol, screening eligibility criteria, algorithm for blood pressure management, rt-PA dosage chart, and algorithm for ICH management). It is based on a protocol

developed collaboratively (ie, emergency physicians, stroke physicians and neuroradiologists) that was already in place at one of the participating institutions (Frenchay Hospital), where small numbers of patients with AIS have been successfully thrombolysed over the past few years (ie, this process can and does already work within a UK ED). The challenge for us as a region is to implement this protocol into the other ED of the network, modified to take into account local factors and incorporating a regional telephone rota of expert support.

CONCLUSION

Thrombolysis for appropriately selected patients with AIS is an evidence-based intervention that should be part of routine emergency medicine practice; it improves outcome and has the potential to save the costs of long-term care. It is a major political priority for the DoH and this represents a great opportunity for emergency medicine. With our clinical, organisational and communication skills, we are ideally placed to be at the centre of the development of ED-based protocols for the assessment and initial management of patients presenting with possible stroke and the subsequent thrombolysis of those considered eligible to benefit from this intervention.

Emergency physicians need to have a working knowledge of the evidence for our credibility, to be represented within the various developing Stroke Networks to promote the skills available within our specialty and need to get involved with the development of relevant protocols.

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