Thrombolysis in acute stroke

Cerebrovascular disease has a major impact on people's physical, social and mental well-being, and is a major financial burden on the NHS. In recent times, the management of acute stroke has changed significantly. Thrombolysis is being used to reduce the disability from stroke and to avoid other devastating complications. In this article,we review the need and evidence for thrombolysis in acute stroke.

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Cerebrovascular disease, or stroke, is the second most common cause of death and is a leading cause of disability.[1,2] It has a devastating impact on people's lives worldwide. The World Health Organization (WHO) estimates that 5·5 million people died of stroke in 2001 and that 15·5 million people were left with a permanent residual deficit, which affected them physically and mentally, leading to a major burden on their family and society.

More than 110,000 people in England suffer from stroke every year, costing the health service over £2·8 billion in direct or indirect costs.[3] The National Service Framework (NSF) for Older People recommends early identification of people at risk of stroke.[4]

Cerebral ischaemia accounts for 73% to 86% of presentations and intracerebral haemorrhage, accounts for 8% to 18%.[5]

Thrombolysis in stroke patients is still the biggest challenge. Cerebral angiography after acute cerebral infarction demonstrates arterial occlusion in up to 80% of cases of cerebral ischaemia.[6] Thrombolytic therapy after acute stroke results in better recovery of function.

The first thrombolytic therapy for stroke was reported in 1958[7] followed by a small trial guided by angiography in the absence of brain imaging in 1963.[8]

Initial trials, involving streptokinase as the thrombolytic agent, showed an increased risk of cerebral haemorrhage and death with no overall benefit.[9–11] Recombinant tissue plasminogen activator (rt-PA) is the agent currently used for thrombolysis after acute ischaemic stroke.[12,13]

The National Institute of Neurological Disorders and Stroke (NINDS) was the first landmark trial to provide good evidence for the safe implementation of thrombosis in stroke patients with excellent clinical outcome.[14] Despite this evidence, thrombolysis in stroke is not always practised because of apprehension about the risk of symptomatic intracerebral haemorrhage (SICH) and delayed admission to a stroke centre. In most countries, it is estimated that fewer than 2% of patients with acute ischaemic stroke receive rt-PA. This is primarily due to delayed admission to a stroke centre.[15]

Thrombolysis without stroke

Thrombolytic therapy restores circulation to the ischaemic area. This is accompanied by clot lysis and results in reperfusion. Early treatment is the key to achieving better results.

In a typical middle cerebral artery stroke, the number of nerve cells lost per minute is 2 million if reperfusion is not achieved.[16] The efficacy of thrombolysis is time dependent.

In a pooled analysis, treatment with rt-PA was almost twice as efficacious when administered within the first 1·5 hours as when administered 1·5–3 hours after the onset of stroke symptoms, compared with placebo.

Table 1: Criteria for stroke thrombolysis

Age ≤ 80 years
Presentation to the hospital within 3 hours of onset of symptoms and sign*
Intracranial haemorrhage excluded by CT head scan
Onset of symptoms less than 3 hours before (may extend to 4·5 hours*)
Previously independent
Verbal or written informed consent or assent

*Up to 4·5 hours based on ECASS III (off-license)

The odds ratio (OR) of a favourable outcome three months post stroke was 2·81 for thrombolysis administration 0–90 minutes after onset, 1·55 for 91–180 minutes afterwards, and 1·40 for 181–270 minutes, compared with placebo.[17]

The initial trials with a six-hour time window were conducted in Europe. The European Cooperative Acute Stroke Study (ECASS I) and ECASS II failed to show the benefits of thrombolysis.[18,19] The potential explanation for this was the choice of endpoints and time window.

Other randomised controlled trials have shown the benefits of thrombolysis when performed within three hours of the onset of stroke symptoms.[20–21] Further supporting studies include randomised controlled trials of large numbers of patients using other agents, doses, time windows and intravenous or intra-arterial administration.[22]

Not all patients presenting with stroke symptoms receive thrombolysis. This is mainly due to a lack of proper facilities and/or awareness amongst people. The number needed to treat (NNT) in the NINDS trial was 1:8 for complete resolution and 1:3 for any improvement.[23] These figures were 1:14 and 1:8 respectively in the ECASS III trial.

Treatment

Treatments assessed for thrombolysis include streptokinase, urokinase, desmoteplase and alteplase. The rt-PA became a focus of interest because it is associated with a lower risk of SICH compared with streptokinase. A trial comparing streptokinase with aspirin and a combination of the two treatments found that streptokinase was associated with an increased risk of SICH.[10]

Pharmacotherapy for rt-PA

Tissue plasminogen activator is produced endogenously by endothelial cells and converts the proenzyme plasminogen to its activated enzyme, plasmin. Activated plasmin dissolves fibrin clots, releasing fibrin degradation products and aiding clot dispersal within occluded vessels; hence ischaemic damage is limited.

For clinical use, rt-PA is produced by recombinant DNA techniques. The serum half-life of rt-PA is four to six minutes and can be lengthened when it is bound to a fibrin clot. If the residual amount is located in a deep compartment, it has a tissue half-life of 40 minutes. Post thrombosis, other coagulation inhibitory agents should consequently be avoided for 24 hours to reduce the risk of haemorrhage.

Suitability scale

Pre- and post-thrombolysis assessments are needed to establish suitability for thrombolysis and its effectiveness. Two commonly used scores are the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin score (mRS). The NIHSS is a standardised reproducible scale with scores from 0 to 42 based on neurological signs. This is easily adequate if the health professional has received appropriate training. Patients with an NIHSS score >22 are at an increased risk of SICH if they receive rt-PA. The mRS is based on symptoms and helps assess independence with respect to daily activities.

Thrombosis risks

A systematic review of randomised trials comparing thrombolysis with placebo for treatment of acute ischaemic stroke showed that rt-PA given up to 6 hours after the onset of stroke symptoms increased the risk of SICH by about three fold (OR = 3·28; 95% confidence interval 2·48–4·33; p=0·00001) compared with placebo.[24]

Table 2: Contraindications for thrombolysis in stroke

Uncontrolled hypertension (systolic >185 mmHg or diastolic >100 mmHg)
Blood glucose <3 mmol/l or >22 mmol/l
Coma
Seizure at stroke onset
Rapidly resolving symptoms
Head injury at the time of stroke or within the preceding three months
H/O intracranial haemorrhage (eg, any previous intracranial haemorrhage any time in the past)
Symptoms suggestive of SAH even if CT normal
Non-ischaemic pathology (eg, functional, migraine, brain tumour, septic embolus etc. probable)
Any history of CNS damage (arteriovenous malformation, neoplasm, intracranial or spinal surgery)
Potential source of GI bleed (colitis, liver disease, pancreatitis, oesophageal varices, active peptic ulcer disease)
Endocarditis, pericarditis, recent MI, aortic aneurysm or ventricular aneurysm
Trauma with fracture or internal injuries within previous four weeks
Surgery or visceral biopsy, cardiopulmonary resuscitation within previous four weeks or arterial or lumbar puncture within seven days
Pregnancy or childbirth within the previous four weeks
Haemorrhagic retinopathy (eg, untreated proliferative diabetic retinopathy)
On warfarin, heparin or equivalent anticoagulation (unless INR <1·5 / APTT normal)
History of recent bleeding or any bleeding problem/blood disorder
Platelet count <100
Haematocrit <25%, abnormal INR
History of any past stroke or diabetes mellitus
Hypodensity or sulcal effacement in 1/3 of middle cerebral artery occlusion territory (relative contraindication)

Within 3 hours of symptoms, the treatment was associated with a similar increase in SICH, no clear effect on mortality but a greater reduction in poor outcome.

The evidence base

Within 3 hours

Thrombolysis is most effective when given within 3 hours of symptom onset. The NINDS rt-PA Stroke Study was the first double-blind, randomised study of thrombolysis in ischaemic stroke.[14] It demonstrated the benefit of intravenous rt-PA when given within 3 hours of ischaemic stroke onset. All subsequent trials have taken this as the measure trial for implementing thrombolysis.

The NINDS trial had two parts. Part 1 monitored the clinical activity of 291 patients, and part 2 assessed the clinical outcome of 333 patients using a global test, based on the Barthel index, mRS, NIHSS and Glasgow outcome scale, at three months.

In part 1, there was no significant difference in NIHSS score improvement within 24 hours of symptom onset between the groups given rt-PA and placebo. However, in part 2, benefits were observed for the rt-PA group at three months for all four outcome measures. It showed that patients treated with rt-PA had gross advantage over those given placebo, with at least 30% having minimal or no disability at three months. This benefit was observed with no increase in mortality.

SICH was more common with rt-PA treatment than placebo within 36 hours of stroke onset (6·4% versus 0·6%), particularly in patients with severe baseline deficits (median NIHSS score = 20). Seventeen of the 28 patients with SICH had died by three months. Overall, mortality at three months was 17% in the rt-PA group compared with 21% in the placebo group (p = 0·30). Overall, for every

100 patients treated with rt-PA within three hours, 32 will have a better outcome and three will have a worse prognosis.

The Canadian Alteplase for Stroke Effectiveness Study (CASES) was a prospective observational study of all patients at 60 centres in Canada given alteplase for acute ischaemic stroke between February 1999 and June 2001.[25] Its results are comparable to those for the NINDS rt-PA Stroke Study.[26] Serious adverse events occurred in 6·6% of patients. SICH occurred in 4·6% of the patients, of whom 3·45% died in hospital. Stroke severity was high, with a median NIHSS score of 14. The pre-stroke function level returned in more than one third of the patients and was comparable to that in the NINDS rt-PA Stroke Study. The incidence of SICH was lower than that in any other major trial of thrombolysis. This study provided adequate evidence for the development of acute stroke protocols across Canada.

The Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) was a prospective, observational study that assessed the safety and efficacy of intravenous alteplase as a thrombolytic agent when administered within 3 hours of onset of acute ischaemic stroke.

In all, 6483 patients were recruited from 285 centres in 14 countries affiliated with the European Medicines Agency from 2002 to 2006. Half of the centres had little experience of thrombolysis in ischaemic stroke. Study patients, aged 18–80 years, presented within three hours of onset of ischaemic stroke.

The incidence of SICH was 7·3% compared with 8·6% in the pooled, randomised controlled trials (with the Cochrane review). In addition, the three-month mortality rate was 11·3%, compared with 17·3% in the pooled analysis.[14] Complete recovery at three months in SITS-MOST was 39% compared with 42% in the review of pooled randomised controlled trials and 32% in the CASES trial.

The appropriate selection of patients is essential by taking into account strict inclusion and exclusion criteria to prevent adverse outcomes with alteplase.

Within 3–4·5 hours

Thrombolysis administered within 3–4·5 hours, though not as beneficial as that within three hours, still shows benefits. In addition, mortality from SICH is not increased.

ECASS III was a double blind study that randomly assigned 821 patients to alteplase or placebo between 3 and 4·5 hours after stroke onset.[22] The rt-PA was given at a dosage of 0·9 mg/kg weight up to a maximum of 90 mg. The primary outcome was considered favourable if the mRS score was 0 or 1. More patients had a favourable outcome with alteplase than placebo (52·4% vs. 45·2%; OR = 1·34: 95% confidence interval, 1·02–1.76; p=0·04). The incidence of SICH was higher with rt-PA than placebo (2·4% vs. 0·2%; p = 0·008). The mortality rate did not differ significantly between rt-PA and placebo groups (7·7% and 8·4%, respectively; p = 0·68).

The incidence of SICH was increased with rt-PA compared with placebo, but mortality was not affected — as seen in related randomised controlled trials.[13, 16, 27]

The overall significance of ECASS III was that there is still significant improvement in the clinical outcome with no increase in mortality despite increasing the time window to 4·5 hours.

We need more randomised trials showing better outcome of thrombolysis in ischaemic stroke with an increased timeframe window before it could be adopted as a standard practice.

Within 3–9 hours

The Desmoteplase in Acute Ischaemic Trial (DIAS) was the first prospective, placebo-controlled randomised acute stroke thrombolysis trial to use MRI for selection of patients and for assessing primary outcome.[28] The timeframe window was 3–9 hours after the onset of acute ischaemic stroke symptoms. The patients were selected on the basis of perfusion/diffusion mismatch. This trial showed a higher rate of reperfusion and better clinical outcome with desmoteplase compared with placebo. The SICH was low if the maximum dose used was 125 µg/kg.

Within 6 hours

Due to lack of awareness and other issues, many patients do not reach the hospital in time to be considered for thrombolysis.

The ongoing IST-3 trial is a randomised trial comparing rt-PA with placebo for ischaemic stroke.[29] It aims to establish the balance of risk and benefit more precisely for thrombotic therapy with rt-PA, especially along patients who do not meet the current license criteria in a wide variety of emergency hospitals settings. IST-3 trial is specifically looking at the effect of thrombolysis on the incidence of SICH and mortality. The researchers will also do subgroup analysis to see the effect of "door to needle time", especially in patients thrombolysed for 3–6 hours. Further analysis

to see the effect of age, severity of stroke, risk factor for SICH and severity of grading based on the appearance of CT scan will also be undertaken.

Intra-arterial infusion

The reported experience using intra-arterial infusion agents in a limited number of patients suggests that direct intra-arterial delivery of thrombolytic agent within 6 hours of stroke can work better than intravenous delivery.[30–32] The Prolyse in Acute Cerebral Thromboembolism (PROACT) trial was the first randomised, double-blind, multicentre trial to use an intra-arterial agent for stroke thrombolysis.[33] Its aim was to compare the safety, recanalisation frequency and clinical efficacy of direct intra-arterial infusion of recombinant pro-urokinase (rpro-UK) with placebo in patients with symptomatic middle cerebral artery occlusion (MCA) of less than 6 hours duration.

The eligible patients in PROACT received either rpro-UK (6 mg) or placebo over 120 minutes into the proximal thrombus face. The 40 patients were randomised to receive rpro-UK (n=26) or placebo (n=14). Recanalisation was significantly associated with rpro-UK. The incidence of partial or complete recanalisation two hours after rpro-UK treatment was 5·7% compared with 14·3% with placebo.

Haemorrhagic transfusion causing neurological deterioration within 24 hours of rpro-UK treatment was observed in 15·4% of patients compared with 7% in the placebo group. There was a 10–12% absolute increase in excellent neurological outcomes in the rpro-UK group over placebo, at 90 days. Concomitant heparin was associated with clinically significant brain haemorrhage.

NICE recommendations

The National Institute for Health and Clinical Excellence (NICE)[34] recommends alteplase (rt-PA) for treating acute ischaemic stroke (when used by appropriately trained physicians) in accordance with its current marketing authorisation (within 3 hours of onset of symptoms). It should be administered only in a well-organised stroke service with facilities that enable its use in accordance with the marketing authorisation.

Appropriately trained and supported staff can administer rt-PA provided that patients can be managed in an acute stroke service with appropriate support from a radiology department and a stroke physician. Local protocols should be in place for the delivery and management of thrombolysis, including post-thrombolysis complications.

Post-thrombolysis management

After thrombolysis, the main aim is to maintain haemodynamic stability through neurological assessment and optimising the patient's biochemical environment. This protects against ischaemic penumbra and hastens recovery. Patients are monitored in a stroke unit and assessed at regular intervals. Assessment scores (NIHSS, mRS) are calculated so that they can be compared with the baseline level and general deterioration can be noticed at an early stage.

Early mobilisation helps enhance recovery and reduce complications.[35] It does this by improving circulation, respiratory function and oxygenation, as well as providing a positive psychological influence on the patient. The early mobilisation and rehabilitation appear to be very important aspects of effective stroke unit care.[35,36]

Conclusion

Thrombolysis makes a significant difference in the acute care of stroke patients. It resolves the symptoms with minimal disability in up to one third of appropriately selected patients. Ongoing trials are assessing the benefits of thrombolysis when timeframe windows are extended beyond 3 hours, when different thrombolytic agents are used and also via different routes of administration (eg. intra-arterial).

Dr Agarwal has no conflict of interest to declare

References

1. Bonita R, Mendis S, Truelsen T, et al. The global stroke initiative. *Lancet Neurol* 2004; **3**: 391–393
2. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997; **349**: 1436–42
3. The Department of Health. Stroke. www.dh.gov.uk/stroke (accessed 8 July 2010)
4. Department of Health. The National Service Framework for Older People. http://tiny.cc/ce5n4 (accessed 8 July 2010)
5. Shiber J, Fontane E, Adewale A. Stroke registry: haemorrhagic vs ischaemic strokes. *Am J Emerg Med* 2010; **28**: 331–3
6. Fieschi C, Argentino C, Lenzi GL, et al. Clinical and instrumental evaluation of patients with ischemic stroke within the first six hours.

Neurol Sci 1989; **91**:311–21
7. Sussman B, Fitch T. Thrombolysis with fibrinolysin in cerebral arterial occlusion. *J Am Med Assoc* 1958; **167**:1705–09
8. Meyer J, Gilroy J, Barnhart M, Johnson J. Therapeutic Thrombolysis in Cerebral Thromboembolism. Double-Blind Evaluation of Intravenous Plasmin Therapy in Carotid and Middle Cerebral Arterial Occlusion. *Neurology* 1963; **13**: 927–37
9. Lees KR. Thrombolysis. *Br Med Bull* 2000; **56**: 389–400
10. Multicentre Acute Stroke Trial--Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. *Lancet* 1995; **346**: 1509–14
11. Thrombolytic therapy with streptokinase in acute ischemic stroke. The Multicenter Acute Stroke Trial--Europe Study Group. *N Eng J Med* 1996; **335**: 145–50
12. Adams HP,Jr, Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the American Stroke Association. *Stroke* 2003; **34**: 1056–83
13. European Stroke Initiative Executive Committee, EUSI Writing Committee, Olsen TS, Langhorne P, Diener HC, et al. European Stroke Initiative Recommendations for Stroke Management-update 2003. *Cerebrovasc Dis* 2003; **16**: 311–37
14. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; **333**: 1581–87
15. Albers GW, Olivot JM. Intravenous alteplase for ischaemic stroke. *Lancet* 2007; **369**: 249–50
16. Saver JL. Time is brain-quantified. *Stroke* 2006; **37**: 263–66
17. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004; **363**: 768–74
18. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995; **274**: 1017–25
19. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet* 1998; **352**: 1245–51
20. Clark WM, Wissman S, Albers GW, et al. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. *JAMA* 1999; **282**: 2019–26
21. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g) : results of a double-blind, placebo-controlled, multicenter study. Thromblytic therapy in acute ischemic stroke study investigators. *Stroke* 2000; **31**: 811–16
22. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; **359**:1317–29
23. Saver JL. Number needed to treat estimates incorporating effects over the entire range of clinical outcomes: novel derivation method and application to thrombolytic therapy for acute stroke. *Arch Neurol* 2004; **61**: 1066–70
24. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2009; **7** (4): CD000213
25. Hill MD, Buchan AM, Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. *CMAJ* 2005; **172**: 1307–12
26. Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA Stroke Trial. *Stroke* 1997; **28**: 2119–25
27. Lansberg MG, Albers GW, Wijman CA. Symptomatic intracerebral hemorrhage following thrombolytic therapy for acute ischemic stroke: a review of the risk factors. *Cerebrovasc Dis* 2007; **24**:1-10.
28. Hacke W, Albers G, Al-Rawi Y, et al. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 2005; **36**: 66–73
29. Sandercock P, Lindley R, Wardlaw J, et al. Third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke. *Trials* 2008; **9**: 37
30. del Zoppo GJ, Ferbert A, Otis S, et al. Local intra-arterial fibrinolytic therapy in acute carotid territory stroke. A pilot study. *Stroke* 1988; **19**: 307–13
31. Mori E, Tabuchi M, Yoshida T, Yamadori A. Intracarotid urokinase with thromboembolic occlusion of the middle cerebral artery. *Stroke* 1988; **19**: 802–12
32. Zeumer H, Freitag HJ, Zanella F, Thie A, Arning C. Local intra-arterial fibrinolytic therapy in patients with stroke: urokinase versus recombinant tissue plasminogen activator (r-TPA). *Neuroradiology* 1993; **35**: 159–62
33. del Zoppo GJ, Higashida RT, Furlan AJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. *Stroke* 1998; **29**:4–11
34. TA122 Alteplase for the treatment of acute ischaemic stroke: guidance http://guidance.nice.org.uk/TA122/Guidance/pdf/English (accessed 18 March 2011)
35. Indredavik B, Bakke F, Slordahl SA, et al. Treatment in a combined acute and rehabilitation stroke unit: which aspects are most important? *Stroke* 1999; **30**: 917–23
36. Langhorne P, Pollock A, Stroke Unit Trialists' Collaboration. What are components of effective stroke unit care? *Age Ageing* 2002; **31**: 365–71