THEME

Stroke

Time is brain

Acute stroke management

Rajinder K Dhamija

MD, FRCP, is Stroke Fellow, National Stroke Research Institute, Austin Health, University of Melbourne, Victoria.

Geoffrey A Donnan

MD, FRACP, is Director, National Stroke Research Institute, Austin Health, University of Melbourne, Victoria. gdonnan@unimelb.edu.au

BACKGROUND

In recent years, four specific strategies have emerged which have proven clinical benefit in treating acute stroke. These are the administration of tissue plasminogen activator (tPA), aspirin, management in a stroke care unit (SCU) and the use of hemicraniectomy in patients with severe cerebral oedema.

OBJECTIVE

This article discusses current management strategies and evidence with emphasis on the role of the general practitioner in initial diagnosis and hospitalisation.

DISCUSSION

Although tPA has been shown to be remarkably clinically effective, less than 5% of eligible stroke patients receive this therapy. The main obstacle is its very narrow therapeutic time window of 3 hours. This necessitates the immediate recognition of stroke and rapid transfer to hospital. Computerised tomography is mandatory to rule out cerebral haemorrhage. Starting aspirin within 48 hours of stroke onset in patients with ischaemic stroke results in a significant reduction in mortality and morbidity. Management in a SCU is the most useful intervention with significant reductions in mortality and morbidity for all stroke subtypes. The management of stroke is changing, and the role of the GP is crucial in facilitating the rapid transfer of patients to a SCU together with subsequent risk factor control and community support.

Stroke is one of the most common neurological disorders in clinical practice, with over 50 000 incident strokes in Australia each year. It is the second leading cause of death in people over 60 years of age and is the major cause of adult disability.[1] This poses serious medical, socioeconomic and rehabilitation challenges.[2] While stroke may affect anyone from childhood through to the elderly, its major impact is in the sixth to eighth decades. With the prevalence and disability from stroke expected to rise in coming decades, it is a challenging task for stroke physicians and general practitioners to provide effective stroke care; to attempt to reduce the mortality, disability and dependency of stroke survivors.

The management of stroke has been revolutionised in recent years and is a multifaceted continuum of care from onset of symptoms to rehabilitation and community management. Proven therapeutic interventions, including the administration of tissue plasminogen activator (tPA), are outlined in *Table 1*. However, due to the short therapeutic window for therapies, particularly tPA, early recognition of stroke and urgent transfer to a specialised stroke unit is of paramount importance in order to salvage ischaemic brain tissue.[3]

Prehospital management

Stroke is a medical emergency. It is crucial for the attending GP to recognise the symptoms and signs of a transient ischaemic attack (TIA) and stroke (*Table 2*). Although stroke and TIA are recognised as medical emergencies by most GPs, this does not always translate into appropriate action. In one German study using standardised questionnaires and case vignettes, only two-thirds of primary care physicians immediately 'transferred' patients with clear stroke symptoms to a hospital emergency department.[4] Rapid recognition and transfer are the first and one of the most important key components of the acute stroke survival chain. In order to make a rapid diagnosis of stroke in the field by paramedical staff or medical practitioners by telephone, simplified algorithms have been developed. One of the most useful is FAST (**F**ace, **A**rm, **S**peech, **T**ime) which should facilitate rapid stroke recognition and referral to the nearest SCU[5] (see *Resource*).

It is equally important to educate high risk patients on how to recognise warning signs of TIA and stroke and to call an ambulance immediately they note these symptoms. A based controlled trial demonstrated that community and GP educational interventions on early identification and

management of stroke led to a significantly increased use of thrombolytic therapy in ischaemic stroke.[6]

Factors shown to be associated with delayed hospital admission include:

- uncertain time of symptom onset[7]
- contact with a GP
- transportation by means other than an ambulance, and
- patient failure to perceive danger.[8]

The fact that GP contact delays transfer to a hospital may seem paradoxical. However, GPs cannot always immediately attend the home to establish a diagnosis, or patients may attend the GP's rooms without prior phone contact.[9] One study found that admission by emergency medical services was the fastest, and patients who had contacted their family physician arrived last.[10] Hence, there is now overwhelming evidence that rapid transfer by calling an ambulance in suspected stroke cases with notification to the nearest hospital with a SCU is the optimal management strategy. This allows patients to gain access to thrombolytic therapy within the therapeutic time window and emphasises the importance of 'time is brain'.

Brain imaging

Once the patient has been transferred to the nearest hospital with a SCU, evaluation and assessment of suspected stroke patients in the emergency department should continue with the same level of urgency. The first and foremost task is to differentiate ischaemic from haemorrhagic stroke. Noncontrast computerised tomography (NCCT) is the basic imaging modality of choice and is now widely available. It is used before reperfusion therapy is instituted to:

- exclude cerebral haemorrhage
- diagnose 'stroke mimics', and
- assess for extensive early ischaemic changes (a relative contraindication to thrombolytic therapy as it reflects a large area of irreversibility).

Limitations of brain imaging

The interobserver reliability in NCCT assessment of early ischaemic changes is relatively low, so quantitative approaches to scoring changes have been developed, eg. the Alberta Stroke Programme Early CT Score (ASPECTS). Although this approach has probably improved the reliability of determining the extent of these signs, it is still unclear how accurately the baseline ASPECTS on NCCT identifies the entire extent of irreversible ischaemic tissue. Computerised tomography perfusion (CTP), which has become possible since the advent of spiral CT, has the potential to provide additional information on the presence of potentially salvageable tissue (ischaemic penumbra) and the irreversible infarct core. Using the same principle, a concurrent CT angiogram may provide additional information about the patency of cerebral vessels. Magnetic resonance imaging (MRI) with perfusion and diffusion weighted imaging (PWI/DWI) may also provide similar information about infarct penumbra and core together with MR angiography (MRA) to document the extent of arterial patency. However, MRA takes longer (up to 40 minutes), is not universally available, and not all patients may be scanned because of the presence of a pacemaker, claustrophobia or because they are medically unstable. The ultimate role of both CTP and MRA in acute stroke assessment is still being evaluated.[11–13]

Table 1. Proven interventions for acute stroke

- tPA within 3 hours
- Aspirin within 48 hours
- Stroke care units
- Hemicraniectomy for severe cerebral oedema

Table 2. Symptoms of stroke and TIA

- Sudden onset of weakness of face, arm, hand or leg
- Sudden onset of sensory symptoms on one side of the body
- Sudden onset of vertigo or ataxia
- Sudden loss or difficulty in speech
- Sudden loss of vision or diplopia

Proven interventions

Aspirin

Two large studies involving over 40 000 patients showed a modest but significant beneficial effect when treatment with aspirin was initiated within 48 hours of stroke onset.[14,15] For every 100 patients treated, about one patient is saved from death or significant disability (*Table 3*). The primary effect may be very early secondary prevention, although there is some evidence from experimental studies in animal models that aspirin may reduce infarct volumes when given hyperacutely.

Aspirin is recommended at 325 mg orally within 48 hours and then continued daily in most patients. It is advisable not to give aspirin until brain imaging is performed to exclude intracerebral haemorrhage.

Thrombolysis

The main aim in acute stroke therapy is to salvage the ischaemic penumbra and to improve functional outcome. Ischaemic penumbra usually surrounds the infarct core and although it is nonfunctional physiologically, it is still is viable and potentially salvageable. Thrombolytic therapy is effective because it enhances recanalisation of major intracranial arteries and reperfusion of tissue, thereby

allowing penumbral salvage to occur. As the majority of the penumbra has a narrow time window of survival of only a few hours, thrombolytic therapy given in the first 3 hours has shown to be most effective with better outcomes than when given later.

The agent of choice is tPA, which is given intravenously at a dose of 0.9 mg/kg. Tissue plasminogen activator is the most potent therapy in stroke management, with a conservative estimate of the number of patients needed to treat (NNT) being 18 to achieve benefit.[16] The pooled analysis of four large placebo controlled trials (NINDS, ECASS, ECASSII, ATLANTIS) involving 3000 patients showed intravenous tPA (when given within the 3 hour window) resulted in improved clinical outcomes with a relative risk reduction of about 9.8% for achieving minimal or no disability at 3 months (*Table 3*).[17–20] In the National Institute of Neurological Disorders and Stroke trial (NINDS), treatment with tPA led to complete or near complete recovery at 3 months in 38% of patients compared with 21% who received placebo. Three month mortality was not significantly different between the two groups.[19] In the other studies there was no significant improvement in 3 month mortality rates or favourable neurologic outcomes in patients treated with tPA after 3 hours.[17,18,20]

There is a small risk of haemorrhage in 6–7% of cases, which can be minimised by refining selection of eligible patients. A follow up CT scan within 24 hours is advised to detect the presence of haemorrhagic transformation. A less common adverse event is angio-oedema.

Intravenous tPA for the management of acute ischaemic stroke in eligible patients was approved by the USA Federal Drug Administration in 1996 and licensed for use in managing stroke in appropriate centres in Australia in 2003. However, only 5% of patients with acute ischaemic stroke presenting to most treating hospitals receive tPA, mainly because of the narrow therapeutic time window. With collaborative effort throughout the stroke survival chain to enable improved organisation of health services, this figure has been shown to increase to 15% in some centres.[16]

Although not routinely used, intra-arterial thrombolysis using pro-urokinase is also a recognised modality for selected patients of acute ischaemic stroke who arrive at an emergency department within 6 hours and are otherwise ineligible for intravenous tPA therapy.[21]

Table 3. Acute stroke treatment effects

Intervention	RRR (95% CI)	ARR %	NNT %
Stroke care unit[22]	6.5	3.8	26
Aspirin[15]	2.6	1.2	83
Thrombolysis[19]	9.8	5.5	18
Hemicraniectomy[26]	48.8	23	4

RRR = relative risk reduction, ARR = absolute risk reduction, NNT = number needed to treat to achieve desired outcome or significant benefit in one patient

Stroke care units

There is Level I evidence that the management of stroke patients in a SCU improves outcomes (death and institutionalisation) by approximately 20%; an effect which persists for up to 10 years.[22,23] Because all patients are potentially eligible for SCU management, more patients benefit than for any other intervention (*Table 3*).[23] This emphasises the need for all stroke patients to be managed within a geographically defined SCU staffed by expert health care professionals. Most SCUs have stroke physicians, stroke nurses, a speech pathologist, physiotherapist, occupational therapist, dietician, rehabilitation specialist and medical social worker working as a well co-ordinated team. Apart from general care, emphasis is on speech and swallowing problems, nutrition and hydration, early mobilisation, prevention of deep vein thrombosis, early treatment of infections, and postdischarge planning. Currently SCUs are being established in Australia in an attempt to raise the number of patients getting access to care from a baseline of only about 25%.[24,25]

Hemicraniectomy

In a limited number of patients, the rapid development of cerebral oedema and raised intracranial pressure at about 24–72 hours poststroke may be alleviated by ipsilateral hemicraniectomy. Until recently this was a rarely performed and an unproven form of intervention, although more commonly carried out in the posterior fossa for cerebellar infarction where this causes raised intracranial pressure. Recent evidence has changed with the publication of a meta-analysis of three RCTs that clearly demonstrated that this was a highly effective intervention with a NNT of four to obtain significant benefit (*Table 2*). Importantly, the patients had improved outcomes across the entire range of disability scores. In other words, patients were not being saved from death merely to exist in a grossly disabled state. While most SCUs may only perform this procedure on a few patients each year, the impressive outcomes further emphasise the need to have patients managed in an SCU to recognise the predictors of this so called 'malignant infarction' so that rapid neurosurgical intervention can be arranged.[26,27]

Conclusion

Despite the availability of newer modalities for stroke intervention, the number of patients who have access to them is few. In some leading hospitals in Australia up to 5% of stroke patients are thrombolysed and more than

40% of these patients then fully recover.[28] The main barrier to wider use of these interventions are nonrecognition of symptoms by patients and/or their families, failure to seek urgent help, calling the GP rather than an ambulance, nonurgent triage of stroke patients, delays in obtaining CT scans, difficulty in obtaining consent for thrombolysis and its short therapeutic time window of 3 hours. Timely referral of patients eligible for thrombolysis to specialised centres and access to dedicated SCUs may be particularly difficult in rural or remote settings. Rapid transfer by ambulance together with an acute stroke triage pathway within hospitals is the key to maximising the obvious benefits of these newer interventions in both urban and rural settings. General practitioners have an important role in patient and community education on symptoms of stroke and the importance of immediate hospital transport. Once patients are discharged from hospital, GPs play a critical role in the co-ordination of community care of stroke survivors and management of risk factors to prevent recurrence.

Summary of important points

- Stroke is a medical emergency.
- Stroke patients need to be urgently transferred to a SCU for comprehensive care.
- Thrombolytic therapy with tPA given within 3 hours can result in better outcomes with less disability.
- Aspirin given up to 48 hours of stroke onset has proven to be effective in acute ischaemic stroke.
- Education of patients at high risk of stroke (and other members of the community) in recognising stroke signs and calling an ambulance is vital.
- GPs have an important role in the rapid diagnosis and quick referral to a SCU, as well as for managing risk factors in secondary prevention of stroke.

Resource

The National Stroke Foundation: FAST test and warning signs of stroke. Available at www.strokefoundation.com.au/signs-of-stroke.

Conflict of interest: none declared.

References

1. Thrift AG, Dewey HM, MacDonnell RAL, et al. Stroke incidence on the east coast of Australia: the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke 2000;31:2087–92.
2. Murray C, Lopez A. Global mortality, disability, and the distribution of risk factors: global burden of disease study. Lancet 1997;349:1436–42.
3. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. Neurology 2000;55:1649–55.
4. Roebers S, Wagner M, Ritter MA, Dornbach F, Wahle K, Heuschmann PU. Attitudes and current practice of primary care physicians in acute stroke management. Stroke 2007;38:1298–303.
5. Morganstem LB, Bartholomew LK, Grotta JC, Staub L, King M, Chan W. Sustained benefit of community and professional interventions to increase acute stroke therapy. Arch Intern Med 2003;163:2198–202.
6. Smith M, Doliszny K, Shahar E, et al. Delayed hospital arrival for acute ischaemic stroke: the Minnesota Stroke Survey. Ann Intern Med 1998;129:190–6.
7. Lacy C, Suh D, Bueno M, Kostis J. Delay in presentation and evaluation for acute stroke: Stroke Time Registry for Outcomes Knowledge and Epidemiology (STROKE). Stroke 2001;32:63–9.
8. Ma H, Ly J, Donnan G. TIA and stroke: a management guide for GPs. Medicine Today 2007;7:26–33.
9. Agyeman O, Nedeltchev K, Arnold M, et al. Time to admission in acute ischemic stroke and transient ischemic attack. Stroke 2006;37:963–6.
10. Schramm P, Schellinger PD, Fiebach JB, et al. Comparison of CT and CT angiographic source images with diffusion weighted images in patients with acute stroke within 6 hours after onset. Stroke 2002;33:2426–32.
11. Wintermark M, Meuli R, Browaeys, et al. Comparison of CT perfusion and angiography and MRI in selecting stroke patients with acute treatment. Neurology 2007;68:694–7.
12. Tan J, Dillon WP, Liu S, et al. Systematic comparison of perfusion CT and CT angiography in acute stroke patients. Ann Neurol 2007;61:533–43.
13. Parsons MW, Pepper EM Chan V, et al. Perfusion computed topography: prediction of final infarct extent and stroke outcome. Ann Neurol 2005;58:672–9.
14. CAST (Chinese Acute Stroke Trial) Collaborative group. CAST: randomised placebo controlled trial of early aspirin use in 20000 patients with acute stroke. Lancet 1997;349:1641–9.
15. International Stroke Trial Collaborative Group. The International Stroke Trial(IST): a randomised trial of aspirin, subcutaneous heparin, both or neither among 19435 patients with acute ischemic stroke. Lancet 1997;349:1569–81.
16. Grotta JC, Burgin WS, El-Mitwalli A, et al. Intravenous tissue-type plasminogen activator therapy for ischaemic stroke: Houston experience 1996 to 2000. Arch Neurol 2001;58:2009–13.
17. Kaste M, Hacke W, Fieschi C, et al. Results of European Cooperative Acute Stroke Study (ECASS). Cerebrovasc Dis 1995;5:225.
18. Hacke W, Kaste M, Fieschi C, et al. Second European Australasian Cooperative Acute Stroke Study Investigators. Randomised double blind placebo controlled trial of thrombolytic therapy with intravenous ateplase in acute ischemic stroke (ECASSII). Lancet 1998;352:1245–51.
19. Hacke W, Donnan G, Fieschi C, et al. ATLANTIS Trial Investigators, ECASS Trial Investigators, NINDS rt-PA Study Group Investigators, Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS and NINDS rp-PA stroke trials. Lancet 2004;363:768–74.
20. Levi CR, Australasian Stroke Unit Network, New South Wales Greater Metropolitan Transition Taskforce Stroke Initiative, Towards A Safer Culture Stroke Expert Working Group. Tissue plasminogen activator (tPA) in acute ischaemic stroke: time for collegiate communication and consensus. Med J Aust 2004;180:634–6.
21. DelZappo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomised trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. Stroke 1998;1:4–11.
22. Langhorne P, Williams BO, Gilchrist W, Howie K. Do stroke units save lives? Lancet 1993;342:395–8.
23. Dhamija RK .Comprehensive management of stroke: 'the concept of stroke units'. J Assoc Physicians India 1997;45:902–3.
24. Gilligan AK, Thrift AG, Sturm JW, Dewey HM, MacDonell RAL, Donnan GA. Stroke units, tissue plasminogen activator, aspirin and neuroprotection: which stroke intervention could provide the greatest community benefit. Cerebrovasc Dis 2005;20:239–44.
25. Cadilhac DA, Lalor EE, Pearce DC, Levi CR, Donnan GA. Access to stroke care units in Australian public hospitals: facts and temporal progress: Intern Med J 2006;36:700–4.
26. Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol 2007;6:215–22.
27. Hofmeijer J, Amelink GJ, Algra A, et al. Hemicraniectomy After Middle Cerebral Artery Infarction with Life Threatening Edema Trial (HAMLET). Protocol for a randomised controlled trial of decompressive surgery in space occupying hemispheric infarction. Trials 2006;7:29.
28. Donnan GA, Davis SM, Levi CR. Strategies to improve outcomes after stroke. Med J Aust 2003;178:309–10.

afp **CORRESPONDENCE** email: afp@racgp.org.au