A protocol-driven model for the rapid initiation of stroke thrombolysis in the emergency department

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ABSTRACT

Objective: To assess efficacy and safety of a 24-hour comprehensive protocol-driven model for rapid assessment and thrombolysis of stroke patients in the emergency department.

Design: Prospective open observational study.

Participants and setting: All patients with acute stroke presenting within 3 hours to the St Vincent's Hospital (Sydney) emergency department between 1 December 2004 and 30 July 2005.

Main outcome measures: Proportion of patients treated, patient demographics, clinical outcome, adverse events and time to treatment parameters.

Results: 134 patients (100 stroke; 34 transient ischaemic attack) were admitted to the stroke unit during the study period. Of the 100 stroke patients, 40 presented within 3 hours of symptom onset. Fifteen patients had no contraindications and received intravenous thrombolysis. At 3 months, 10 patients (67%) were independent (modified Rankin score [mRS], 0–2) and seven (47%) had an excellent functional outcome (mRS ≤ 1). Symptomatic intracranial haemorrhage was not observed. The median time from symptom onset to tissue plasminogen activator treatment was 155 minutes (range, 105–197 min). Median onset-to-door, door-to-computed tomography, and door-to-needle times were 48, 25, and 87 minutes, respectively.

Conclusion: Rapid assessment of stroke in the emergency department according to a comprehensive protocol allows identification and treatment of acute ischaemic stroke patients eligible for thrombolysis.

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For editorial comment, see page 548

Stroke is the third commonest cause of death and a major cause of disability in Australia.[1] Intravenous therapy with tissue plasminogen activator (tPA) is currently the only approved medical therapy for patients with acute ischaemic stroke. Patients who receive tPA within 3 hours of ischaemic stroke onset are at least 30% more likely to have little or no disability compared with those who do not,[2] with a number needed to treat to obtain a clinical benefit as low as three.[3]

Even in international centres, however, only a small proportion of patients (2%–10%) with ischaemic stroke receive thrombolytic therapy.[4] In Australia, the proportion is lower; an audit of eight metropolitan tertiary referral hospitals from five Australian states found that < 1% of ischaemic stroke patients received thrombolytic therapy.[5]

The major reason for the small numbers receiving thrombolysis is delayed presentation of stroke patients to hospitals. However, even in stroke patients who present to hospital within the 3-hour timeframe, the use of thrombolysis has remained controversial, with questions about whether this treatment can be broadly and safely administered in the emergency department (ED).[6] Hence, thrombolysis for ischaemic stroke has been limited to a few centres in Australia with a "stroke team", usually comprising stroke neurologists, stroke fellows, registrars and nurses who assess and administer therapy.[7]

A stroke-team model is labour- and cost-intensive, and not applicable to most hospitals. Therefore, we prospectively evaluated the safety and efficacy of a comprehensive protocol-driven model for the assessment and thrombolysis of eligible stroke patients in the ED. Specifically, we assessed:

- identification of stroke patients eligible for thrombolysis;
- safety and clinical outcomes of stroke patients receiving thrombolysis following this protocol; and
- time parameters for initiation of thrombolytic therapy.

METHODS

The acute stroke care protocol (Box 1) was initiated in the ED at St Vincent's Hospital (SVH), Sydney, in October 2004, and extended to 24-hour, 7-days-a-week coverage in December 2004. The protocol was developed jointly by neurology, emergency and intensive care unit physicians and nurses. The working party provided education to staff in the ED, including triage nurses, radiology and acute stroke unit staff, before implementing the protocol and quarterly thereafter.

This was a prospective, open, observational study with subjects comprising all patients presenting to the ED within 3 hours of stroke onset between 1 December 2004 and 30 July 2005. All eligible patients received tPA.

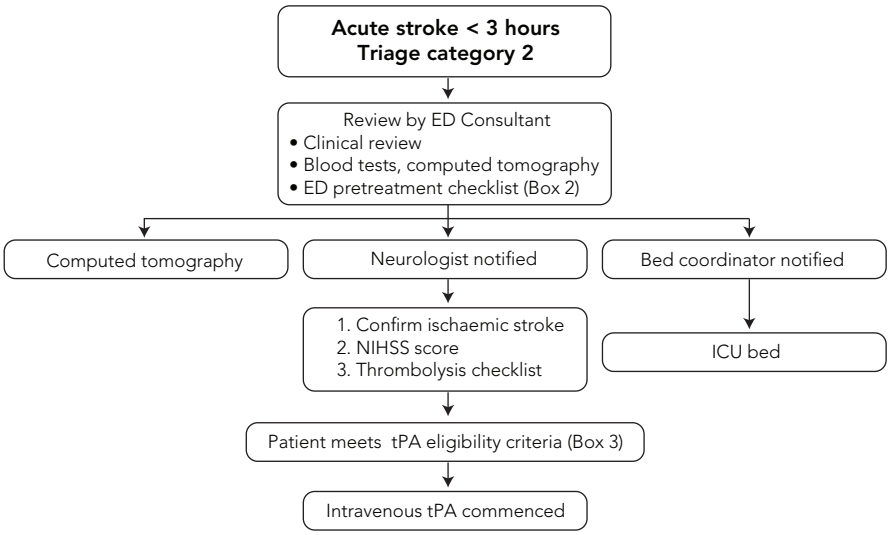
All patients admitted to the stroke unit at SVH are prospectively entered into the SVH stroke database, which records stroke onset and arrival times, demographics, and vascular risk factors, and is used to generate a discharge summary.[8] In addition, stroke subtype according to the Oxfordshire Classification and stroke mechanism according to the modified TOAST criteria are recorded for each patient.[9] Patients with ischaemic stroke receiving thrombolytic therapy were also entered into the Safe Implementation of Thrombolysis in Stroke (SITS) International Registry (http://www.acutestroke.org), an Internet-based, data-entry monitoring system designed for auditing the efficacy and safety of routine thrombolytic therapy in acute ischaemic stroke.

Treatment protocol

All patients presenting to the ED within 3 hours of stroke onset were triaged as category 2 and underwent rapid assessment (within 10 minutes) by a senior emergency physician (Box 1). Initial assessment included a brief history and examination focused on time of onset of symptoms and identifying major contraindications to thrombolysis. Monitoring of vital signs, intravenous cannulation, and investigations, including blood tests and urgent computed tomography (CT) brain scans, were initiated according to a standing order (Box 2).

The decision to treat with tPA was made by the attending neurologist after reviewing

1 Acute stroke assessment protocol



ED = emergency department. ICU = intensive care unit. NIHSS = National Institutes of Health Stroke Scale. tPA = tissue plasminogen activator. ◆

the patient and CT scan, documenting the severity of stroke according to the National Institutes of Health Stroke Scale (NIHSS), and completing a thrombolysis inclusion/exclusion criteria checklist (Box 3). The presence of early ischaemic changes on CT was not considered a contraindication. The patient and/or next of kin were informed about the risks and benefits of thrombolysis.

Eligible patients without contraindications were treated with intravenous tPA (0.9 mg/kg) in the ED, with 10% of the dose given as a bolus over 1 minute, followed by a 1-hour infusion. The protocol mandated a 1 : 2 nursing ratio to monitor haemodynamic parameters for 24 hours after thrombolysis. Because of staffing logistics, all patients were monitored in the intensive care unit for up to 24 hours before being transferred to the acute stroke unit. A CT brain scan was obtained 24–48 hours after treatment, and subsequently if clinically indicated.

Outcome measures and analysis

Clinical outcomes measured were: NIHSS scores at baseline, 2 and 24 hours, 7 days, and 3 months after thrombolysis; and modified Rankin scores (mRS) at baseline, 7 days, and 3 months after thrombolysis. Intracerebral haemorrhage (ICH) was defined as any parenchymal haematoma on follow-up CT scan at 24–48 hours, and classified as symptomatic if there was associated clinical deterioration with NIHSS score worsening by ⩾ 4.

Significant early improvement was defined as NIHSS score improvement of ⩾ 4 at 24 hours or full recovery (end state NIHSS score = 0). Independence at 3 months was defined as an mRS of 0–2. An excellent functional outcome was defined as an mRS of 0–1. The proportion and 95% confidence intervals for clinical outcome measures were compared with data from the SITS registry.

Statistical analysis was performed with InStat version 3 (GraphPad Inc, San Diego, Calif, USA). Quality parameters measured were onset-to-door, door-to-CT, door-to-needle, and onset-to-needle times.

RESULTS

One hundred and thirty-four patients (100 stroke; 34 transient ischaemic attack) were admitted to the Acute Stroke Care Unit between 1 December 2004 and 30 July 2005. Forty (40%) of the stroke patients presented within 3 hours of onset of stroke symptoms. Four patients, all with posterior circulation infarcts, were given incorrect non-stroke diagnoses initially and missed rapid assessment. One patient who would have fulfilled the eligibility criteria for thrombolysis was incorrectly triaged and did not receive treatment.

Of the 35 stroke patients assessed according to the protocol, 14 patients (14% of all

2 Emergency department (ED) pretreatment checklist for acute stroke patients presenting within 3 hours of onset

				Signature of ED physician
1	Initiate monitoring and record data every 5 minutes until stable, then every 15 minutes. Monitoring will include cardiac, non-invasive BP, and pulse oximetry			
2	Record time of stroke onset (last time that the patient was seen without stroke symptoms)			
3	Insert two 18 G IV access lines (in the cubital fossa) and attach 500 mL normal saline to IV cannula at KVO rate			
4	Collect bloods for (mark urgent on request form)			
	Full blood count	Glucose	PT/INR	
	Electrolytes	Platelets	APTT	
5	Urgent CT brain scan			
6	Electrocardiogram			
7	Obtain urine for pregnancy test (if applicable)			
8	BP control to bring BP < 185 mmHg systolic and/or < 110 mmHg diastolic			
	(a) Consider IV metoprolol up to 5 mg at 1–2 mg/min			
	(b) If SBP > 185 mmHg and/or DBP > 110 mmHg after 10 minutes, may repeat once			
	If BP is not reduced and maintained at desired level (SBP ⩽ 185 mmHg and DBP ⩽ 110 mmHg), do not administer tPA			
9	NO antiplatelet or anticoagulants to be given			
10	Avoid the use of indwelling urinary catheters and nasogastric tubes			

APTT = activated partial thromboplastin time. BP = blood pressure. CT = computed tomography. DBP = diastolic blood pressure. INR = international normalised ratio. IV = intravenous. KVO = keep vein open. PT = prothombin time. SBP = systolic blood pressure. tPA = tissue plasminogen activator. ◆

3 Thrombolysis inclusion and exclusion criteria checklist

Inclusion criteria (must be positive)	Yes	No
Age ⩾ 18 years (should be used with caution in people ⩾ 80 years)		
Clinical diagnosis of ischaemic stroke causing measurable neurological deficits (defined as impairment of language, motor function, cognition, and/or gaze, vision, or neglect)		
Onset of ischaemic stroke symptoms within 0–3 hours		
Non-contrast CT head scan that does not demonstrate any haemorrhage, tumour, or mass effect		
Exclusion criteria (must answer NO to all to be eligible for thrombolysis)	**Yes**	**No**
History		
History of intracranial haemorrhage		
Known arteriovenous malformation or aneurysm		
Any intracranial surgery, serious head trauma or previous stroke within 3 months		
Myocardial infarction in the previous 3 months		
Any gastrointestinal or urinary tract haemorrhage within the previous 21 days		
Major surgery or serious trauma within the previous 14 days		
Arterial puncture at a non-compressible site or lumbar puncture within the previous 7 days		
Clinical		
Symptoms rapidly improving or minor symptoms (NIHSS = 0)		
SBP > 185 mmHg or DBP > 110 mmHg despite simple measures		
Clinical presentation suggestive of subarachnoid haemorrhage even with normal CT		
Evidence of active bleeding or acute trauma (fracture)		
Seizure at onset		
Coma or severe obtundation		
Laboratory		
Patient taking anticoagulants and INR ⩾ 1.5		
Patients receiving heparin within 48 hours and with an elevated APTT		
Platelet count < 100 000 per mm^3		
Blood glucose level < 2.8 mmol/L or > 22.2 mmol/L		

APTT = activated partial thromboplastin time. CT = computed tomography. DBP = diastolic blood pressure. INR = international normalised ratio. NIHSS = National Institutes of Health Stroke Scale. SBP = systolic blood pressure. ◆

4 Baseline details for 15 ischaemic stroke patients treated with thrombolysis

	Number of patients
Modified Rankin score before stroke onset	
No symptoms (mRS = 0)	11
No significant disability (mRS = 1)	4
Slight to severe disability (mRS = 2–6)	0
Risk factors	
Hypertension	8
Diabetes	3
Hyperlipidemia	4
Current smoker	3
Previous smoker	5
Previous ischaemic stroke	3
Atrial fibrillation	3
NIHSS score	
NIHSS score < 7	4
NIHSS score 8–14	6
NIHSS score ⩾ 15	5
Stroke subtypes	
Total anterior circulation infarct	4
Partial anterior circulation infarct	10
Lacunar infarct	1
Posterior circulation infarct	0

mRS = modified Rankin score. NIHSS = National Institutes of Health Stroke Scale. ◆

stroke admissions) fulfilled the eligibility criteria for thrombolysis and received intravenous tPA. The overall rate of tPA use in patients presenting within 3 hours was 35%. The rate of use among eligible patients was 95%. One further patient who presented in October 2004 received thrombolysis before the protocol was expanded to 24-hour, 7-days-a-week coverage.

Twenty-one patients were not treated because they did not meet clinical eligibility criteria. Nine patients had rapidly improving symptoms, four had ICH on CT, four were on anticoagulants with coagulation parameters above the guideline, one had a known intracerebral aneurysm, and in another a large aneurysm was seen on initial non-contrast CT scan. One older patient with a severe neurological deficit (NIHSS > 22) who died within a few hours of presentation to ED and a 95-year-old woman were not considered suitable.

Baseline characteristics for the 15 patients receiving thrombolytic therapy are shown in Box 4. The mean age was 67 years, 53% were male, and the median baseline NIHSS score was 11 (range, 5–18). The mean systolic blood pressure was 144 mmHg, and mean diastolic blood pressure was 81 mmHg. The baseline stroke severity was similar to that in the SITS registry.[10]

Clinical outcomes

Significant early improvement at 24 hours was observed in seven (47%; 95% CI, 21%–73%) of 15 stroke patients receiving thrombolysis. Independence at 3 months (mRS, 0–2) was seen in 67% (10/15; 95% CI, 38%–88%) of treated patients, compared with 54.8% (95% CI, 53.5%–56%) in the SITS registry data.[10] Of this group, five improved completely (mRS = 0), two had no significant disability (mRS = 1) and three had slight disability (mRS = 2). Thus, seven of 15 patients (47%; 95% CI, 21%–73%) achieved an excellent functional outcome (mRS, 0–1) at 3 months.

In the 15 patients receiving thrombolysis, no ICH (0/15; 95% CI, 0–22%) was observed. One patient developed orolingual angio-oedema and was managed medically without an adverse outcome.[11]

Quality parameters

The median time from symptom onset to tPA treatment was 155 minutes (range, 105–197 min). In one patient, the tPA infusion

was delayed until 197 minutes after symptom onset for technical reasons, although the decision to treat had been made at 170 minutes. This patient, who was the second in our series, had an NIHSS score of 16 before treatment and made a complete neurological recovery at 24 hours. There were no other protocol violations.

The median onset-to-door time was 48 minutes (range, 15–140 min), median door-to-CT time was 25 minutes (range, 7–91 min), and median door-to-needle time was 87 minutes (range, 57–145 min).

DISCUSSION

Our results indicate that a comprehensive protocol for the management of acute stroke in the ED enables identification of patients with ischaemic stroke who are eligible for thrombolysis. Rapid triage, assessment and investigation in the ED of stroke patients presenting within 3 hours of symptom onset enabled thrombolytic therapy in 95% of eligible patients; two-thirds of ischaemic stroke patients receiving thrombolysis following this protocol were functionally independent at 3 months.

In stroke centres with no experience of acute stroke thrombolysis, routine use of tPA can be implemented with the safety and efficacy demonstrated in randomised clinical trials, provided there is strict adherence to and monitoring of protocols.[10] Our 24-hour acute stroke management protocol was successful in selecting patients eligible for thrombolysis. The proportion of overall stroke patients treated with thrombolysis (14% of all stroke admissions) and the use of thrombolysis in eligible patients (95%) compare favourably with results from other multicentre[12] and single centre[13] studies. Our small sample size leads to imprecise estimates, but stroke severity at study entry and clinical improvement at 24 hours and 3 months compare favourably with the SITS registry cohort and pooled results from meta-analysis.[14] Importantly, our protocol identified patients with one or more contraindications[15] for thrombolysis (21 of 35 patients). There were no significant protocol violations, which have been associated with a higher incidence of adverse outcomes, principally ICH.[16] The absence of ICH in the treated patients is reassuring, and suggests that our protocol is safe, although a larger sample is needed to identify the true ICH rate. In the SITS registry, 1.7% of patients have symptomatic ICH.[10]

The major reason for the small proportion of stroke patients eligible for thrombolytic therapy is delayed presentation.[17] During our study period, only 40% of patients with stroke presented within 3 hours of symptom onset. For patients presenting within the 3-hour time window, the most common reasons for exclusion from thrombolytic therapy were minor or rapidly resolving symptoms, and presence of haemorrhage on initial CT.

The median time from stroke onset to treatment of 155 minutes and the median door-to-needle time of 87 minutes are similar to times reported in a large series from Canada,[16] but are longer than the "best practice guidelines" recommended by the National Institute of Neurological Disorders and Stroke (NINDS) study group.[18] Our thrombolysis working party met 3-monthly to provide ongoing staff education, assess adherence to protocols and post-thrombolysis nursing standards of care, and monitor quality parameters and discuss quality improvements. This has resulted in a downward trend for door-to-needle times, although further efficiencies are required to meet best practice guidelines.

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COMPETING INTERESTS

Bruce Brew has received reimbursement from GlaxoSmithKline, Boehringer Ingelheim, Gilead, and Biogen Idec for giving educational lectures to medical personnel. Romesh Markus has received honoraria and grants from Boehringer-Ingelheim.

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