Acute stroke thrombolysis with intravenous tissue plasminogen activator in an Australian tertiary hospital

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ABSTRACT

Objective: To report initial experience with the use of intravenous tissue plasminogen activator (tPA) to treat acute ischaemic stroke at an Australian tertiary-care hospital.

Design: Retrospective audit of computerised hospital stroke database.

Participants and setting: All patients with acute ischaemic stroke treated with intravenous tPA between April 1999 and July 2002 at the Royal Melbourne Hospital, VIC.

Main outcome measures: Times from stroke onset to arrival at the emergency department (ED) and treatment; rates of symptomatic intracerebral haemorrhage (ICH); clinical outcome at three months; and violations of treatment protocol.

Results: Of 932 patients admitted with ischaemic stroke, 30 were treated with intravenous tPA. Median time from stroke onset to tPA treatment was 2 h 48 min, and median door-to-needle time was 1 h 49 min. Door-to-needle time improved in the last 12 months of the audit, with four of 15 patients achieving the recommended 60 min. Eleven patients (37%) had excellent clinical outcomes at three-month follow-up (modified Rankin score, 0–1), and 15 (50%) were functionally independent (score, 0–2). Mortality rate was 10%, similar to that of all ischaemic stroke patients during the audit period. Two patients (7%) had symptomatic ICH. Treatment deviated from protocol in seven patients (23%), five of whom received tPA over three hours after stroke onset.

Conclusion: Rates of favourable outcomes and symptomatic ICH at our hospital were similar to those achieved in international phase III and IV trials in specialised centres.

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STROKE IS THE MOST common cause of permanent disability in the Australian community[1] and the third most common cause of death.[2] A significant therapeutic advance has been use of tissue plasminogen activator (tPA). Proof of its efficacy in ischaemic stroke came with the 1995 publication of a randomised controlled trial sponsored by the National Institute of Neurological Disorders and Stroke (NINDS).[3] This found that tPA increased the probability of excellent recovery, despite also increasing the rate of symptomatic intracerebral haemorrhage.

Intravenous tPA has been licensed for use in stroke for several years in North America and was recently approved in Europe based on pooled analysis of four trials.[3-8] This analysis supported the view that tPA should be part of the management of acute ischaemic stroke within three hours of onset in selected patients in experienced centres.

However, not all agree. The Cochrane meta-analysis of tPA recommended caution about the data supporting the three-hour "window" for treatment.[9] Furthermore, concerns remain that routine clinical use of tPA may result in higher rates of symptomatic intracerebral haemorrhage than seen in phase III and IV trials, which were conducted in expert stroke centres.[9-16] A study of tPA use in smaller community hospitals found a high rate of symptomatic intracerebral haemorrhage (15.7%), with 50% of patients treated outside the NINDS-based guidelines.[17]

Although tPA is not yet licensed for treating stroke in Australia, it was approved for use according to published guidelines at the Royal Melbourne Hospital, Victoria.[10-12] We audited our initial experience of its use at this hospital to determine whether the benefits and risks found in phase III and IV trials can be duplicated in an Australian tertiary-care hospital.

For editorial comment, see page 309; see also pages 318, 329 and 333.

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METHODS

The Stroke Care Unit at the Royal Melbourne Hospital was granted approval to use intravenous tPA in acute stroke by the hospital's Drug and Therapeutics Committee and Clinical Research and Ethics Committee. Clinical use began in carefully selected patients in April 1999.

A retrospective review of the computerised stroke database from April 1999 to July 2002 was undertaken to determine the frequency, safety and efficacy of tPA use in acute stroke at this hospital. Information for this database is collected prospectively by the Stroke Care Unit. We recorded baseline data, including patient demographic characteristics, time from symptom onset to arrival in the emergency department (ED), and time to tPA administration, pretreatment blood pressure, full blood

examination, clotting profile and serum glucose levels.

Treatment protocol

All patients presenting within three hours of symptom onset were rapidly assessed by the stroke team, comprising a stroke neurologist, "stroke" fellow, registrar and nurse. The tPA protocol was based on protocols published by the American Heart Association and the American Academy of Neurology.[10,11] Inclusion and exclusion criteria are shown in Box 1. All patients had pretreatment computed tomography (CT) scans that were read by the attending neurologist or stroke fellow, together with a radiologist. In all cases, informed consent was obtained from the patients or next-of-kin before treatment, after discussion of the potential benefits and significant risks, specifically the four-fold greater risk of symptomatic intracerebral haemorrhage.[4]

All patients were treated unblinded with intravenous tPA (0.9 mg/kg), according to the NINDS and American Heart Association protocols.[3,10] An initial bolus dose of tPA (10% of total) given over one minute was followed by a one-hour infusion. Patients were then transferred to the Stroke Care Unit for close monitoring for the next 24 hours. Antithrombotic and antiplatelet therapy was prohibited for 24 hours after tPA, as in the NINDS trial. Follow-up brain imaging was performed at the discretion of the treating neurologist, but, if significant neurological deterioration occurred during hospitalisation, an urgent CT scan was obtained to assess for intracerebral haemorrhage.

Outcome measures and analysis

Clinical outcome was assessed on the modified Rankin Scale three months after stroke onset. This scale is the validated disability measure most used in stroke studies.[19] Clinical outcome was defined as "excellent" (Rankin score, 1), "functional independence" (score, 2), "moderate disability" (score, 3), or "major disability" (score, 4–5).

Incidence of intracerebral haemorrhage was determined from follow-up CT scans, and classified as symptomatic if there was any associated neurological deterioration. In addition, all pretreatment CT scans were retrospectively reviewed by two neurologists and a neuroradiologist, who were blinded to the clinical data. Early ischaemic change was recorded as less than or greater than a third of the MCA territory by consensus opinion.[8,20] Violations of treatment protocol were also assessed.

In the last 12 months of the audit, we recorded baseline tPA eligibility and clinical outcomes for all patients presenting to the hospital within three hours of ischaemic stroke onset, together with reasons for any exclusion from tPA treatment. Outcomes were compared between patients who received tPA and those who presented within three hours but did not receive tPA.

Statistical analysis was performed using STATA software.[21]

RESULTS

Between April 1999 and July 2002, 932 patients were admitted with ischaemic stroke, and 30 (3.2%) received intrave-

1: Criteria for use of tissue plasminogen activator (tPA) in treating acute stroke at the Royal Melbourne Hospital

Clinical inclusion criteria

- Patient or family member able to give consent or approval before study procedures.
- Age ⩾ 18 years.
- Onset of symptoms of hemispheric ischaemic stroke within 0–3 hours.
- Clinical diagnosis of hemispheric ischaemic stroke causing measurable neurological deficits (defined as impairment of language, motor function, cognition, and/or gaze, vision, or neglect).
- Score for stroke severity ⩾4 on the National Institutes of Health Stroke Scale (NIHSS).[18]
- Patient able to undergo computed tomography (CT) before tPA administration.

Clinical exclusion criteria

- Severe symptoms suggesting total anterior circulation syndrome (coma or severe obtundation with fixed eye deviation and complete hemiplegia or NIHSS score >22).
- Minor stroke symptoms (NIHSS score <4) or those that are rapidly improving by the time of randomisation.
- History of stroke within previous 6 weeks.
- Any pre-existing neurological illness resulting in a modified Rankin scale score ⩾3.
- Seizure before administration of study drug.
- Previously known intracranial haemorrhage, subarachnoid haemorrhage, arteriovenous malformation, aneurysm, or previously known intracranial neoplasm that, in the opinion of the investigator, is terminal or would increase the risk of intracranial bleeding after administration of thrombolytic therapy or may confound neurological assessment.
- Clinical presentation suggestive of subarachnoid haemorrhage, even if initial CT is normal.
- Uncontrolled baseline hypertension: systolic blood pressure [BP] > 185 mmHg or diastolic BP > 110 mmHg despite acute treatment (1 cm of nitrate paste or 10–20 mg intravenous labetalol).
- Presumed septic embolus.
- Suspected recent (within 30 days) myocardial infarction.
- Recent (within 30 days) biopsy of a parenchymal organ or surgery that, in the opinion of the investigator, would increase the risk of unmanageable (eg, uncontrolled by local pressure) bleeding after administration of thrombolytic therapy.
- Recent (within 30 days) trauma, with internal injuries or ulcerative wounds.
- Any active or recent haemorrhage that, in the opinion of the investigator, would increase the risk of unmanageable (eg, uncontrolled by local pressure) bleeding after administration of thrombolytic therapy.
- Known hereditary or acquired haemorrhagic diathesis (eg, activated partial thromboplastin time [APTT] or prothrombin time [PT] greater than normal, or oral anticoagulant therapy with international normalised ratio (INR) > 1.5).
- Pregnancy, lactation, or parturition within the previous 30 days.
- Hypoglycaemia, hyperglycaemia (baseline serum glucose level <2.8 or >22.0 mmol/L), or thrombocytopenia (platelet count $< 100 \times 10^9$/L).
- Other serious, advanced or terminal illness, or any other condition the investigator feels would impose a significant hazard to the patient if intravenous tPA were initiated.
- Current participation in another research drug treatment protocol.

Computed tomography exclusion criteria

- Evidence of acute or chronic intracranial bleeding on CT.
- Likely aetiology other than acute brain ischaemia.
- Early signs indicate infarct of more than a third of the territory of the middle cerebral artery.[8]

2: Comparison of outcome between patients treated with tPA and those who presented within three hours of stroke onset but did not receive tPA

Outcome	Patients treated with tPA (n=30)	Patients not treated with tPA: Presentation within 3 h (n=59)	P*	Patients not treated with tPA: Presentation within 3 h and clinically eligible (n=17)*	P*
Excellent	11 (37%)	20 (34%)	0.18	2 (10%)	0.05
Functionally independent	15 (50%)	25 (42%)	0.14	4 (24%)	0.05
Moderate disability	3 (10%)	5 (10%)	0.29	3 (18%)	0.26
Major disability	9 (35%)	15 (25%)	0.18	6 (35%)	0.24
Death	3 (10%)	14 (24%)	0.13	4 (24%)	0.15

* Fisher's exact test (if frequency < 5) or the χ^2 test was used to compare proportions of patients achieving each outcome between the tPA group and each non-tPA group.

nous tPA (15 in the last 12 months of the audit period). These 30 patients had a median age of 73 years (range, 43–93 years); 50% were men. Median NIHSS score for stroke severity was 14 (range, 8–22).

Baseline blood pressure elevation > 185/110 mmHg was present in nine patients (30%), but was successfully treated before tPA administration. All 30 patients had a CT scan before tPA treatment, while 25 (83%) had follow-up CT or magnetic resonance imaging (MRI).

Time to presentation and treatment

Median time from stroke onset to tPA treatment was 2 hours 48 minutes (range, 1 hour 45 minutes to 3 hours 27 minutes). Twenty-five patients received tPA between two and three hours after stroke onset (15 in the last 15 minutes of the three-hour window), one in less than two hours and five in over three hours.

Eighteen patients (60%) arrived at the emergency department (ED) within 60 minutes of symptom onset. Earlier presentation to the ED after symptom onset was associated with longer delays between ED arrival and tPA treatment (Spearman's $\rho = -0.59$; $P < 0.001$).

Median time from presentation at the ED to tPA treatment ("door-to-needle time") was 1 hour 49 minutes (range, 50 minutes to 2 hours 31 minutes). In the last 12 months, a door-to-needle time within the recommended 60 minutes was achieved in four of the 15 patients who received tPA, compared with none of the 15 in the first two years (Fisher's exact test, $P = 0.05$).

Outcomes

Three patients died (10%). Median Rankin score at three-month follow-up was 2.5 (range, 0–6).

The mortality rate was comparable to that of all patients admitted to the Royal Melbourne Hospital with ischaemic stroke during the audit period (9%). Two deaths were caused by massive middle cerebral artery (MCA) infarction and cerebral oedema without intracerebral haemorrhage, confirmed on repeat CT scanning.

The third death was associated with symptomatic intracerebral haemorrhage within three days of tPA treatment, and occurred a month later. Baseline CT in this patient showed significant hypodensity in the MCA territory, but was considered by the attending neurologist and neuroradiologist to involve less than a third of this territory. Although three observers could not reach consensus on retrospective review of the scan, this case was classed as a protocol violation.

A second patient also had a symptomatic intracerebral haemorrhage within three days of tPA treatment (overall rate, 7%). This patient had major disability at three-month follow-up (Rankin score, 4). Asymptomatic intracerebral haemorrhage within three days of treatment was found in two patients on follow-up brain imaging (follow-up Rankin scores, 2 and 5, respectively). There were no cases of major systemic bleeding.

Protocol violations

Protocol violations occurred in seven of the 30 patients who received tPA (23%):

- In five patients, treatment was begun more than three hours after symptom onset — within 3 hours 10 minutes in four patients, and 3 hours 27 minutes in one.
- One patient had a prolonged APTT (47 s), but did not have an intracerebral haemorrhage.
- One patient had significant hypodensity in the MCA territory on baseline CT, as previously described; this patient had a symptomatic intracerebral haemorrhage and later died.

Patients not treated with tPA

During the last 12 months of the audit, 74 patients presented to the ED within three hours of ischaemic stroke onset (27% of all ischaemic stroke admissions), 59 of whom did not receive tPA. Forty two of these did not meet clinical eligibility criteria, as:

- Stroke was too mild (NIHSS score ⩽ 4) (23; 39%);
- Stroke was too severe (NIHSS score > 22) (17; 29%) (two of these also had major ischaemic change on baseline CT);
- Blood pressure was > 185/110 mmHg despite antihypertensive treatment (1; 2%); or
- Seizure occurred at stroke onset (1; 2%).

A further 17 patients fulfilled the clinical criteria but did not receive tPA, as:

- Treatment could not begin within three hours of symptom onset, as clinical assessment and CT extended beyond this window (15; 25%); all these patients presented 2–3 hours after stroke onset; or
- Consent was refused (2; 3%).

Baseline clinical severity tended to be milder in the 59 who did not receive tPA (median NIHSS score, 10; range, 1–22) than in the tPA group, although this difference did not achieve statistical significance (Mann–Whitney test, $P = 0.08$). Baseline severity in the 17

who did not receive tPA but were clinically eligible was similar to that in the tPA group (median NIHSS score, 13; range, 6–20).

Outcomes are compared in Box 2 between the 30 patients who received tPA and those who did not (both the group of 59 who presented within three hours and the subgroup of 17 who were clinically eligible). There were no significant differences between the groups in the proportions of patients with moderate or major disability at three-month follow-up. However, the proportions who achieved an excellent clinical outcome or functional independence were greater in the tPA group than in the group who were clinically eligible but did not receive tPA (both $P = 0.05$, Fisher's exact test).

Fourteen of the 59 who did not receive tPA died (24%), including four of the 17 who were clinically eligible (24%), compared with three of the 30 who received tPA (10%). However, these differences did not reach statistical significance. Of the 14 who died in the non-tPA group, nine were excluded from tPA therapy because stroke was severe and one because it was mild.

DISCUSSION

This audit indicates that tPA treatment of acute ischaemic stroke can achieve favourable outcomes and relatively low rates of symptomatic intracerebral haemorrhage in an Australian tertiary-care centre. Outcomes were comparable to those found in the NINDS trial[3] and major phase IV studies.[13,14,16,22]

Patients treated with tPA in our study had a median baseline NIHSS score for stroke severity of 14, identical to that of tPA-treated patients in the NINDS trial.[3] Both the benefits and risks of tPA therapy were similar in the two studies. At three-month follow-up, outcomes were excellent (Rankin score, 1) in 37% of tPA-treated patients in our study, compared with 39% in the NINDS trial.[3] Similarly, 50% of our tPA-treated patients were functionally independent at follow-up (Rankin score, 2), compared with 49% of those in the NINDS trial.

Furthermore, we found that outcomes of tPA-treated patients were equivalent, and sometimes superior, to those of patients who presented within three hours of stroke onset but were not treated with tPA. As about a third of the latter had very mild strokes (and were thus not eligible for tPA), it is not surprising that there were no differences in excellent outcomes. In contrast, the subgroup who were clinically eligible for tPA but did not receive it had less favourable outcomes than those who received tPA. However, this retrospective analysis was based on a comparison of non-randomised patients, and results should therefore be treated with caution.

Importantly, the rate of symptomatic intracerebral haemorrhage in our tPA-treated patients was 7%, very similar to that observed in the NINDS trial (6.4%)[3] and other phase IV studies,[13,14,16,22] while the mortality rate was lower than in the NINDS trial (10% v 17%). A single death in our study was related to intracerebral haemorrhage, with another two caused by extensive MCA territory infarction and associated oedema, presumably due to lack of vessel recanalisation. Overall mortality was no higher in our tPA-treated patients than in all patients with ischaemic stroke admitted to Royal Melbourne Hospital during the audit period.

One symptomatic intracerebral haemorrhage was possibly related to a protocol violation, as the patient had evidence of infarction that may have affected more than a third of the MCA territory. A link between ischaemic changes on CT and intracerebral haemorrhage is controversial; it was supported by one European study[20] but not by the NINDS data.[23]

In our study, half the patients were treated in the last 15 minutes of the three-hour therapeutic window, and five were treated beyond this window. The importance of early thrombolysis in acute stroke has been well documented; even within the three-hour window earlier treatment improves outcome.[24] As a result, current guidelines recommend a door-to-needle time of less than 60 minutes and emphasise that "*time is brain*".[10,11] Our relatively long door-to-needle time (median, 1 hour 49 minutes) suggests that considerably more effort is required to expedite emergency evaluation of these patients. This is a key issue when setting up an acute stroke thrombolysis service. On a positive note, in the last 12 months of our audit there was a significant increase in patients achieving the benchmark 60-minute door-to-needle time, which may reflect faster triage, stroke team notification and CT scanning, as well as increasing experience of the stroke team.

It is hoped that tPA will soon be licensed to treat acute ischaemic stroke in Australia, with major implications for organisation of acute stroke services. Our centre is recognised as a specialised stroke unit, with a dedicated team of stroke nurses, registrars, fellows and neurologists available 24 hours a day. Our results (and those of the major phase III trials) may not necessarily be duplicated in other settings. Use of tPA in less specialised centres could result in much greater hazards, notably an excess of early deaths caused by intracerebral haemorrhage, reducing or completely negating any potential benefits.[9,17] Development and training of an acute stroke team can have a significant impact on treatment safety and efficacy.[10,11] We argue that such infrastructure should be in place before a centre is approved to use tPA.

Additional medical and community education would also be required to deliver the message that stroke is a treatable medical emergency. In the last year of our audit, 15 patients who were clinically eligible for tPA were unable to be treated, as clinical assessment could not be completed within the three-hour window. All presented to the ED two to three hours after stroke onset. In contrast, all patients who received tPA presented within two hours of stroke onset, highlighting the importance of very early arrival at hospital.

The current challenge in our hospital is to increase the percentage of patients who can be offered tPA therapy from 3% and to consistently reduce door-to-needle times. Up to 10% of patients with stroke can be appropriately treated with tPA in well organised centres.[13,14,16,22] However, we note that most patients who presented within three hours of stroke onset were not clinically eligible for tPA. One should not undervalue the potential benefits of care by a stroke unit and aspirin therapy, which are appropriate for almost all patients.[25]

COMPETING INTERESTS

None identified.

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