Candidates for thrombolytic treatment in acute ischaemic stroke—where are our patients in Hong Kong?

Y C A Siu, T W Wong, C C Lau

Abstract

Objective—Tissue plasminogen activator (t-PA) has been approved by the Food and Drug Administration in the treatment of patients with acute ischaemic stroke presenting within three hours from onset of symptoms. This study aims to identify the potential number of stroke patients suitable for t-PA in Hong Kong.

Methods—All patients with a clinical diagnosis of acute stroke were recruited. Data collected included demographics, vital signs, medical history, contraindications to thrombolysis, severity of stroke (Canadian neurological scale), time course from onset of symptoms to computed tomography, computed tomography results, and final diagnoses by physicians.

Results—During the five month study period, 201 patients were recruited and nine were subsequently excluded from further analysis because computed tomography was not performed. Their mean age was 70.9 (range from 41–91) years. Eighty (41.7%) and 100 (52.1%) patients presented to our emergency department within two hours and three hours respectively from symptom onset. The mean severity score (Canadian neurological scale) was 7.83 (out of a maximum of 11.5). A total of 132 (68.8%) patients had acute ischaemic stroke confirmed by computed tomography. Mean delay in computed tomography was 4.91 hours. Fourteen (7.3%) and 52 (27.1%) of all patients had computed tomography of the brain done within one and two hours respectively. Only 20 patients (10.45%) could meet the three hour criteria as stated in the National Institute of Neurologic Disorders and Stroke rt-PA stroke study and seven (3.6%) of them were confirmed to have acute ischaemic stroke. Two patients were further excluded because of high systolic blood pressure and current warfarin medication.

Conclusion—At present very few patients could benefit from thrombolytic treatment. Delays in the chain of recovery in stroke management should be identified and corrected.

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Keywords: acute ischaemic stroke; delay; thrombolysis

The use of tissue plasminogen activator (t-PA) in the management of stroke has been

approved by the Food and Drug Administration since the publication of the National Institute of Neurologic Disorders and Stroke rt-PA stroke (NINDS) study.^{1,2} However, it has been shown that a better neurological outcome is restricted only to patients who can receive t-PA within three hours from onset of symptoms. According to a meta-analysis with 1297 patients, there was about 6.5% absolute reduction in poor outcome, which was defined as death or dependency in daily activities.³ The potential benefit of the drug is greatly limited by the narrow therapeutic window.

There are some studies published after the NINDS study to investigate the proportion of patients who may be eligible for thrombolytic treatment.^{4–6} Though t-PA has not been adopted in the treatment of acute ischaemic stroke in Hong Kong, we would like to investigate the potential for its use in the region. We would also like to identify the sources of delay from symptom onset to examination by computed tomography in the hospital.

Methods

STUDY SETTING

Acute stroke is the third commonest cause of death in Hong Kong.⁷ It is one of the commonest medical problems encountered in our department. In Hong Kong, most patients with acute stroke will be admitted to regional public hospitals. As in the UK patients call an ambulance by dialling “999” for the emergency services and an ambulance will arrive in less than 20 minutes in most circumstances.

Our hospital is a regional hospital serving a population of 600 000 in the eastern part of Hong Kong Island. At the time of the study, we were seeing around 450 patients a day on average. Patients are triaged by a nurse into four major categories: emergency, urgent, semiurgent, and non-urgent. Emergency cases are seen immediately and urgent ones are seen within 30 minutes. In our department, all patients with a provisional diagnosis of acute stroke will be admitted to the medical ward. There is no direct referral for computed tomography in our department. The decision for requesting computed tomography of the brain will be left to the ward physicians. The waiting time will depend on the severity of symptoms and the patient load. Stable stroke patients may need to wait up to several hours for computed tomography of the brain.

STUDY METHOD

This was a prospective study of consecutive cases. All patients admitted to our department

Accident and
Emergency
Department, Pamela
Youde Nethersole
Eastern Hospital, 3
Lok Man Road, Chai
Wan, Hong Kong SAR,
China
Y C A Siu
T W Wong
C C Lau

Correspondence to:
Dr Siu Yuet-chung Axel,
Medical and Health Officer
(e-mail: axel@hknet.com).

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Figure 1 Flow chart for the selection of patients according to the diagnosis and the time limit.

with a provisional diagnosis of acute cerebrovascular accident were recruited. Demographic data, vital signs, medical history, and risk factors for stroke of the patient were recorded. The severity of stroke was assessed by the Glasgow coma score and the Canadian neurological scale, which is expressed numerically from 0 to 11.5.⁸

A patient's eligibility for thrombolysis was assessed according to the NINDS study criteria.¹ Three hours from the onset of symptoms was the time limit. A patient was excluded if any contraindication to thrombolysis was present (fig 1).

The decision for performing computed tomography of the brain was made by the ward physicians. They read most of the films and their interpretations were used as the reference unless a formal report was made by a radiologist. Medical records were then traced after the patients were discharged and the final diagnosis made by the physicians was recorded.

The time intervals from the onset of symptoms to the time of computed tomography were documented. The time of onset of stroke was defined as the time when the symptoms were noticed by either the patient or the witness. The time of decision made to seek medical help was defined as the time when the patient or the witness decided a medical consultation was required. It depended either on their recall or according to the record from the ambulance control if the emergency ambulance service was called. If the time interval was greater than 24 hours, it would be categorised into the group of "equal or greater than 24

hours". The time of ambulance arrival to the scene was also obtained from the ambulance run sheet. The time when the patient arrived at our emergency department, the doctor contact time, and the time when the patient was transferred out were recorded in the patient's medical records. The time when brain scan was performed was retrieved from the computer record of the radiology department.

The descriptive and analytical statistics were performed with SPSS PC statistical package. Multivariate analysis with logistic regression was used to determine the possible association between the success in meeting the time criteria and the demographic data, history of stroke or transient ischaemic attack, severity of stroke, transfer method to the emergency department, and the different time intervals. They were expressed in terms of odds ratio (OR) and a *p* value of 0.05 was used as the significant level. Similar methods and variables have been used in a previous study.⁹

Results

During the five months from 25 July 1997 to 24 December 1997, there were 201 patients with a clinical diagnosis of acute stroke admitted to the accident and emergency department. Only 192 of them underwent computed tomography of the brain and the rest were considered not to have clinical stroke by the admitting physician and they were excluded from further analysis. There were 105 male and 87 female patients. Their ages ranged from 41 to 91 (mean age 70.9) years. Hypertension was found in 90 patients (46.9%) and was the commonest risk factor, followed by previous cerebrovascular accident (52/27.1%) and smoking (45/23.4%). The prevalence of atrial fibrillation was low (11/5.7%) (table 1).

Hemiplegia was the commonest presenting symptom (146/76.1%); 75 (39.1%) were left sided and 71 (37.0%) right sided. Dysphasia was found in 49 (25.5%) patients, 39 (20.3%) presented with a change in conscious level, and 29 (15.1%) suffered from dizziness or vertigo.

The majority of patients were stable and had a high score on the Canadian neurological scale (118/192 had a score ≥ 8.5) and the Glasgow coma score (163/192 had scores of at least 13). The mean score in the Canadian neurological scale was 7.83; 100 (69.8%) of the patients were assessed as urgent or above by the triage nurse.

Table 1 Medical history of the 192 patients; there were 105 males and 87 females with a mean (range) age of 70.9 (41–91) years

Patient characteristics	Present	Absent
Past medical health		
Hypertension	90	102
Diabetes mellitus	35	157
Old cerebrovascular accident	52	140
Transient ischaemic attack	7	185
Atrial fibrillation	11	181
Ischaemic heart disease	28	164
Congestive heart failure	7	185
Smoking	45	147
Major contraindication to thrombolysis		
Recent gastrointestinal bleeding	3	189
Recent major operation	1	191
Bleeding tendency	7	185

Table 2 Summary of the time courses from symptom onset to computed tomography of brain (n=192)

	Mean time (min)	Median time (min)	Interquartile range (min)
Symptom onset to decision made to seek medical help	N/A	174.50	5.00–873.75
*Decision made to arrival at emergency department (n=79)	134.54	55.0	37.0–118.00
†Decision made to ambulance arrival at scene (n=113)	12.15	10.00	7.00–13.00
†Ambulance arrival to emergency department arrival (n=113)	18.88	17.00	12.00–22.50
Contact time by medical staff	14.89	10.00	6.00–19.00
Assessment time in emergency department	35.48	26.00	17.00–42.00
Computed tomography waiting time	294.85	227.50	113.00–380.75

*For patients who did not take ambulance to emergency department.

†For patients who took ambulance to emergency department.

N/A = Not applicable.

Ischaemic stroke was the major cause of stroke among our patients (132/68.8%) whereas haemorrhagic stroke was only found in 38 (19.8%) patients. Patients or their relatives initiated the decision to seek medical help in most of the incidents (160/83.3%) and 113 (58.9%) of the patients were transferred to our department by ambulance.

Among the 132 patients with acute ischaemic stroke, only seven (3.6%) could have computed tomography done within three hours from symptom onset. The cut off point was set at three hours with reference to the NINDS study. If the limit was extended to six hours, a total of 23 patients (12.0%) could meet the criteria. However, two patients did not meet the criteria for thrombolysis. One had systolic blood pressure greater than 185 mm Hg and the other was taking warfarin for chronic rheumatic heart disease. Only five patients (2.6%) remained eligible as potential candidates for thrombolysis.

Eighty of the 192 patients arrived at our emergency department within two hours; this rose to 100 if a three hour cut off was used. The mean time interval for the ambulance to arrive at the scene was 12.15 min and the mean time interval to take the patient to the emergency department was 18.88 min. The mean waiting time for doctor assessment was

14.89 (range 0–86) min and the mean duration of stay in the emergency department after assessment was 35.48 (range 8–645) min. One patient had an extremely long stay time (645 min) because the diagnosis was initially missed by a junior doctor and subsequently identified by a senior doctor in the observation ward. Only 14 (7.3%) and 52 (27%) of the patients could have computed tomography of the brain performed within one and two hours, respectively, after admission. The mean waiting time for the scan was 4.91 hours (tables 2 and 3).

The potential factors that might affect whether patients could have computed tomography confirmation of diagnosis within three hours from symptom onset were analysed with logistic regression (table 4). A delay of less than 15 minutes from onset of symptoms to the decision to seek medical help (OR = 10.62, $p = 0.042$) and a computed tomography waiting time of less than one hour from admission (OR = 23.26, $p = 0.011$) were the only two significant factors predicting which patients could meet the time limit. Sex and age greater than 65 were not shown to be significant predictors. None of the presenting symptoms showed any value as predictors of delay. A previous cerebrovascular accident or transient ischaemic attack also did not shorten the arrival time. The severity of stroke in terms of Canadian neurological scale and Glasgow coma score were not proved to be significant predictors. A higher triage category (category 2 or above) was not found to significantly shorten the delay.

Table 3 Distribution of computed tomography waiting time

	<30 min	30–60 min	1–3 hours	3–6 hours	6–12 hours	12–24 hours	>24 hours
No (%)	7 (3.6)	7 (3.6)	65 (33.9)	61 (31.8)	43 (22.4)	8 (4.2)	1 (0.5)

Table 4 Logistic regression analysis of eligibility using three hour time limit

	OR	p Value
Patient factor		
Age >65	0.43	0.201
Sex = male	1.38	0.595
Previous history of stroke	1.00	0.997
Previous history of transient ischaemic attack	0.33	0.559
Presenting symptoms		
Hemiplegia	0.72	0.646
Dysphasia	1.46	0.472
Altered mental state	2.66	0.172
Dizziness/vertigo	3.89	0.312
Severity of stroke		
Glasgow coma score <13	1.30	0.688
Canadian neurological scale <8.5	5.30	0.128
Transfer method		
By ambulance	1.75	0.521
Triage category		
Category 1 or 2	0.59	0.616
Time intervals		
Time from onset to decision made <15 min	10.62	0.042
Time from decision made to arrival at emergency department <60 min	63.59	0.865
Medical officer contact time <15 min	0.44	0.589
Time from assessment to disposal <60 min	153.11	0.891
Computed tomography time <60 min	23.26	0.011

Discussion

In our series, only a minority of patients were eligible as potential candidates for thrombolysis. Our results were worse than most of the overseas studies of a similar nature. Zweifler *et al* found that about 36% of their patients were eligible for t-PA but only 19% of these patients received the treatment.⁶ The proportion of patients (52%, 100/192) who arrived at our emergency department within three hours from symptom onset was similar to a supplementary study to the NINDS study, which found that 39% of acute stroke patients arrived at the emergency department within 90 min and 20% at 91–180 min.⁴ Early arrival was related to the use of an ambulance, stroke at daytime, and stroke when the patient was at work. A study of 96 patients by Feldmann *et al* showed that about half of the patients presented within four hours and a sudden onset of stable deficit was the unique independent

factor associated with early presentation.¹⁰ Similar study by Azzimondi *et al* found that 59 out of 189 patients arrived within two hours and 100 patients arrived within five hours.⁵ Onset when the patient was awake, an altered mental state, and limb paralysis were the only independent predictors of early arrival. A study in Leicestershire also attempted to address the possible factors causing delay.¹¹ The delay was mainly related to admission through the bed allocation bureau, patients living alone, and stroke onset at night. In our study, making a decision to seek medical help within 15 minutes from onset was one of the significant factors to predict early presentation. We empirically chose 15 minutes, as we believed it was a reasonable time interval to let the witness or patient to call for help if they thought it was serious. All other factors relating to the mode of presentation or transfer were not found to be statistically significant. We did not look into where and when the stroke happened. A similar study in the United States, which also used logistic regression, found that the use of emergency medical services and being white increased the odds of early presentation to the emergency department.⁹

A previous study in Hong Kong showed that 63% of patients arrived at hospital within 12 hours after a stroke.¹² We have achieved a similar result with 70.6% of patients arriving at our hospital within 12 hours from onset. Their results also showed a higher tendency for patients with haemorrhagic stroke to present earlier. It may be related to the higher chance of experiencing severe symptoms, for example altered mental state in haemorrhagic stroke. However, we could not confirm the significance of this symptom in our logistic regression analysis.

IMPLICATIONS OF OUR STUDY

We showed that about 69% of our patients had strokes that were ischaemic in origin and would be potential candidates for thrombolysis; however, only a few were eligible and the major reason was delay. The delay was mainly caused by late presentation to the emergency department and delay in obtaining a computed tomography scan. In fact, delay in presentation to the emergency department was the commonest reason for ineligibility.¹³ In order to allow more patients to benefit from thrombolytic treatment, we should understand the current concept of the chain of recovery in stroke.

CHAIN OF RECOVERY IN STROKE

In the past, treatment of stroke was mainly supportive and aimed to prevent further complications. This was changed after the implementation of thrombolytic treatment and a chain of recovery for stroke was suggested similar to the chain of survival in cardiac arrest.¹⁴ The chain involves the early identification of symptoms of stroke by the patient or bystanders, dispatch of specific pre-hospital life support services, rapid access and transport by emergency medical service personnel to the receiving hospital, and the notification of a special team that can coordinate the specific

investigation and intervention for stroke patient: the stroke team.

EARLY IDENTIFICATION OF STROKE SYMPTOMS

Obviously, decreasing the delay in recognition of stroke symptoms is very important to meet the short therapeutic window. Educating the public and patients at risk of "brain attack" of the potential benefits of early presentation may be helpful. Members of the public were generally not aware of their own risk for stroke. Samsa *et al* found that only 41% of their respondents noticed their increased risk for stroke.¹⁵ Most of them recalled that they had been informed by a physician. Younger patients, depressed patients, patients with poor general health, and those with a history of transient ischaemic attacks were more likely to be aware of their stroke risk. In a study published in 1997, the authors found that only one fourth of patients could correctly interpret their symptoms as stroke.¹⁶ A majority of the late presenters thought that their symptoms were not serious. A more recent survey on public knowledge of stroke warning signs and risk factors found that 57% of the 1066 respondents from telephone interviews could identify at least one stroke warning sign and 68% could list at least one risk factor of stroke.¹⁷ Only 57% of those respondents with a history of hypertension knew that hypertension was a risk factor for stroke. Respondents with a history of smoking and diabetes mellitus were even worse as only 35% and 13% of them could identify their own risk. Public education is essential to reduce the delay. Alberts *et al* started a multifaceted programme of public and professional education that yielded a 49% increase in the number of acute ischaemic stroke patients who presented within 24 hours from symptom onset.¹⁸ Delay in making the decision to seek medical help was one of the major causes of ineligibility in our study. However, we have not explored the reasons for the late decision. Further studies are required to address this issue and to develop local strategies of public education to encourage early presentation to the emergency department.

PRE-HOSPITAL PHASE

Many studies have found ambulance transfer to facilitate early arrival.^{4,16} A local study showed that the mean time interval for the ambulance staffed by emergency medical assistants, who have intermediate level training, to arrive at the scene was 6.99 min and at the patient's side was 9.07 min.¹⁹ The mean time the ambulance crews spent at the patient's side was about 12 min and the travel time to hospital was about 11 min. Our results were comparable with the results of that study. Educating ambulance staff on the concept of "brain attack" may help to expedite the transfer process. Though patient transfer by the emergency services was shown to be associated with early presentation, we could not demonstrate its association with the success to meet the time criteria.¹⁰ Since the main delay is in patients' delay in seeking medical attention, the

impact of quicker ambulance transfer may not be that great.

An accurate pre-hospital diagnosis by paramedics is also another important element that may affect the delay. A review of 86 cases with a pre-hospital diagnosis of stroke or transient ischaemic attack showed that the emergency medical service dispatcher and the paramedics could correctly identify 52% and 72% of cases respectively.²⁰ Patients requiring advanced life support by paramedics could be seen by physicians and undergo computed tomography earlier. In another study of 81 patients, the sensitivity of paramedic diagnosis of stroke was 61% and the positive predictive value was 77%.²¹

PROMPT DIAGNOSIS IN EMERGENCY DEPARTMENT

In the emergency department phase, accuracy of nurse triage is another important issue. In our series, 58 (30.2%) of our patients were categorised as semiurgent at triage; this may result in prolonged waiting time in the emergency department. Under-triage will definitely cause a certain degree of delay. The triage guidelines may need to be revised to facilitate earlier medical attention. The other issue is the accuracy of the clinical diagnosis of stroke made by emergency physicians. Kothari *et al* found that emergency physicians made an incorrect diagnosis of stroke or transient ischaemic attack in 19 out of 365 (5%) patients.²² In our 201 patients with a clinical diagnosis of acute stroke, 22 (10.4%) patients had a final diagnosis other than acute stroke. Lack of computed tomography support in the emergency department made it more difficult for the attending doctor to reach the correct diagnosis. Various conditions could mimic acute stroke. Libman *et al* suggested that decreased conscious level would increase the odds and history of angina would decrease the odds of "stroke mimic" conditions in a multivariate analysis.²³ We do not know how many stroke cases were initially missed in the emergency department and were subsequently identified by the physicians in our study. In order to enhance the coordination and reduce the delay after arrival, some centres have established a stroke team to coordinate the investigation and subsequent thrombolysis.²⁴ However, very few hospital emergency departments had their own protocol for thrombolytic treatment in acute ischaemic stroke.²⁵ A consensus should be established among emergency physicians and neurologists on the use of t-PA in acute stroke.

EARLY COMPUTED TOMOGRAPHY AND ACCURATE INTERPRETATION

In our study it was found that performing computed tomography of the brain within an hour after admission was predictive of meeting the time limit. However, only 7.2% of our patients could meet this criteria (table 4). The median time was 227.5 min, which was much longer than the 72 min reported in a similar study in the United States.⁹ The delay in getting a scan was mainly for administrative reasons. Because of the great demand for computed tomography, the service is usually available only for critically ill patients. Stable

patients usually have to wait for several hours. The problem of delay was also observed in overseas centres. Aziz *et al* reported that there was a reduction in time interval from symptom onset to arrival at the emergency department after the approval of t-PA in the management of acute stroke. However, the door to computed tomography time did not change much and was around two hours on average.²⁶ If thrombolysis is to be implemented for treatment of acute ischaemic stroke in Hong Kong, a direct referral for computed tomography examination from the emergency department is required to shorten the delay.

According to the NINDS study, patients with intracranial haemorrhage will be excluded from thrombolysis. The doctor who interprets the computed tomogram will make the final decision and the accuracy will depend on the capability of the interpreter. A study to evaluate accuracy in interpretation found that the accuracy of emergency physicians was only 67% whereas neurologists and radiologists achieved 83%.²⁷ A radiologist should also be available to interpret the film without delay to avoid inappropriate administration of a thrombolytic agent.

CONTROVERSIES IN THROMBOLYTIC TREATMENT

t-PA—to use it or not?

Though the Food and Drug Administration has approved the clinical use of t-PA for acute ischaemic stroke, there is still debate about it. The NINDS group reported 11%–13% absolute increase in favourable outcome at three months in the group receiving t-PA.¹ The effect was not limited by age and stroke subtypes. There was a roughly 10-fold increase in symptomatic intracerebral haemorrhage (6.4% *v* 0.6%) in the treatment group, though the mortality rate was not proved to be significantly different.

Some authors believed that the benefit reported in the NINDS study was too generous and the benefit was not equally distributed among various causes of ischaemic stroke.²⁸ The only established effective use was to lyse acute thromboemboli. Furlan and Kanot also had queries about the preciseness of subgroup analysis in the original study.²⁹ On the other hand, there were other authors who insisted that thrombolytic treatment should be the first line treatment for those who could fulfil the criteria.³⁰ This controversy will continue to be hotly debated until further large scale studies can bring us the definitive answer.

Margin of benefit for mild symptoms

The role of thrombolytic treatment in patients with mild symptoms is unclear. All patients with mild symptoms were excluded from the European Cooperative Acute Stroke Study.³¹ The NINDS study recruited patients with different severity.¹ However, there was no detailed description on the extent the group with mild symptoms improved with t-PA. The risk of intracerebral haemorrhage needed to be balanced with the extent of benefit from the treatment. Our patients belonged mainly to the group with mild symptoms. More than 60% of

them had a score of at least 8.5 on the Canadian neurological scale. If the benefit is confined only to severe cases, the application of thrombolytic treatment in our locality will be limited. The extent of benefit of thrombolytic treatment in patients with mild symptoms needs to be addressed with further studies.

LIMITATIONS OF THE STUDY

The major limitation of our study is the dependence on patient or witness recall for the pre-hospital time intervals. The inaccuracy in memory may be a major contribution to the great variability of data. If thrombolysis is implemented in Hong Kong, there will be a strong need to make sure that the time of onset is accurately ascertained so as to avoid the catastrophic side effects.

Conclusions

With the current setting, the number of stroke patients eligible for thrombolysis is very small. To increase the number of potential candidates for thrombolysis, major efforts to educate the public are needed to decrease pre-hospital delay. Also, arrangement must also be made to shorten the delay in performing computed tomography and a stroke team should be established to coordinate patient care.

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