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Original Contributions

THE USE OF INTRAVENOUS RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR IN ACUTE ISCHEMIC STROKE

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□ **Abstract—We sought to determine the frequency of use of intravenous (i.v.) recombinant tissue plasminogen activator (rt-PA) in patients presenting to our institution with acute ischemic stroke (AIS). This observational study involved keeping a log of all patients presenting to our institution with symptoms consistent with AIS who were potential candidates for emergency thrombolysis over a 3-year period. The log included brain computed tomography (CT) scan results, whether or not rt-PA was administered, and contraindications to thrombolysis. It also included each patient's time flow through the system, from symptom onset to decision time regarding (and administration of) thrombolytics. Over the 36-month period of the study, there were 142 patients who presented to the Emergency Department (ED) who initially were thought to be potential candidates for thrombolysis for AIS. Ninety-five (68.5%) of these 142 patients had a confirmed diagnosis of AIS. On further clarification of symptom onset, 77 (81%) of these 95 patients with AIS actually presented within 3 h, and 17 (22%) of these 77 patients met criteria for thrombolysis and had no contraindications. All 17 (100%) patients with AIS presenting within 3 h of onset and without contraindications received i.v. rt-PA in the ED. In conclusion, i.v. rt-PA can be administered for AIS within the 3-h window if a hospital is committed to providing this treatment. Thrombolysis remains a treatment for a minority of AIS patients. © 2005 Elsevier Inc.**

□ **Keywords—stroke; acute ischemic stroke; thrombolysis; recombinant tissue plasminogen activator**

INTRODUCTION

Based on the results of The National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) Study Group, thrombolytic therapy was proven as the first effective therapy for acute ischemic stroke (AIS) (1,2). The use of intravenous (i.v.) rt-PA within 3 h of stroke onset resulted in significantly improved neurological function at 90 days without an increase in mortality due to treatment complications (1,3). The success of the NINDS trial led to widespread dissemination of the therapeutic advantages of thrombolytic treatment in AIS. Because the effectiveness of therapy is time sensitive, Emergency Departments (EDs) are at the forefront of its implementation. The successful implementation of a thrombolysis program in AIS involves a chain of events that includes: rapid awareness of stroke symptoms by the public; early recognition of stroke by emergency medical services (EMS) with advanced notification of the ED; prompt and efficient triage nursing, physician assessment, head computed tomography (CT) imaging and interpretation; rapid turnaround time for blood glucose and clotting profiles; and prompt access to neurologic consultation (4–7).

The primary objectives of this study were to determine the frequency of use of i.v. rt-PA in patients presenting to our institution with AIS who meet the estab-

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lished criteria for thrombolysis, and to identify factors that lead to thrombolytics not being administered in patients who meet eligibility criteria and who have no identified contraindications. Additionally, we examined patient time flow through the system.

MATERIALS AND METHODS

Study Design

This prospective, observational study included ED patients at our institution between March 1998 and March 2001 who presented with symptoms consistent with AIS and who were potential candidates for emergency thrombolysis.

Selection of Participants

Inclusion criteria for rt-PA administration were symptoms and signs consistent with new ischemic stroke with clearly defined onset; period from first symptoms to proposed rt-PA administration of less than 3 h; patient evaluation by in-house neurology resident or stroke fellow; National Institute of Health Stroke Scale (NIHSS) score between 7 and 21, inclusive; and rt-PA administration approval by stroke attending (based on clinical assessment and CT evaluation). Exclusion criteria for rt-PA administration were: CT evidence of intracranial hemorrhage (ICH); minor neurologic deficit (defined as NIHSS < 7); rapidly improving symptoms; ischemic stroke or head trauma within the past 3 months; any history of ICH; cocaine-induced stroke; known intracranial neoplasm; arteriovenous malformation (AVM) or aneurysm; symptoms suggestive of subarachnoid hemorrhage (SAH); seizure at stroke onset; major surgery within 2 weeks; known bleeding diathesis; internal hemorrhage (gastrointestinal or urinary tract) within 3 weeks; pretreatment systolic blood pressure (BP) > 185 mm Hg or diastolic > 110 mm Hg; blood glucose < 50 or > 400 mg/dL; platelet count less than 100,000; current use of oral anticoagulants or an international normalized ratio (INR) greater than 1.7; use of heparin in the previous 48 h and partial thromboplastin time (PTT) of 35 or greater; pregnancy; age > 80 or < 18 years; or an arterial puncture at a noncompressible site within 1 week. Patients were not excluded but caution was recommended in using rt-PA if there was an ischemic lesion on CT scan involving more than one-third of the middle cerebral artery (MCA) territory; severe neurologic deficit (NIHSS score of 22 or greater); age > 75 years; history of intravenous drug use or clinical suggestion of endocarditis; toxic screen positive for ethanol, cocaine, opiates, or amphetamines (if available); or history of hemorrhagic diabetic retinopathy. These relative contraindications were weighed into the risk benefit analysis when deciding whether or not to give rt-PA to individual patients. The following conditions were not considered absolute or relative contraindications to thrombolytic therapy: current aspirin (ASA), nonsteroidal anti-inflammatory drug (NSAID), ticlopidine, or clopidogrel use; history of peptic ulcer disease (not active); recent myocardial infarction.

Setting

This ED is part of an academic medical center, with approximately 90,000 patient visits per year. The hospital has a dedicated stroke service that is available 24 h daily, consisting of a neurology resident, stroke fellow, and stroke attending. The stroke beeper is activated whenever a patient presents who on first evaluation by EMS or the ED triage nurse or physician has features suggestive of AIS within 3 h of onset.

Data Collection

This study includes data collected on each patient for whom the stroke team was activated. Information collected included precise time of symptom onset, time of EMS activation (if activated), time of patient's arrival at the ED, time of activation of stroke beeper, time of evaluation by ED physician, time of CT scan performance, time of stroke fellow's arrival in ED, time of decision about use of rt-PA, and time of administration of rt-PA (if given). Reasons for not giving rt-PA were also recorded. The hospital discharge log was reviewed for the time period of the study and the number of patients discharged from the hospital with diagnosis of stroke was tallied.

The primary outcome variables are the number of patients who presented with all inclusion criteria and no exclusion criteria for rt-PA, and how many of these patients received rt-PA. Secondary outcome variables included the other entries on the stroke log as described above. This study was approved by the hospital's institutional review board.

RESULTS

Characteristics of Study Subjects

During the 36-month study period, the stroke beeper was activated 142 times for ED patients who initially were

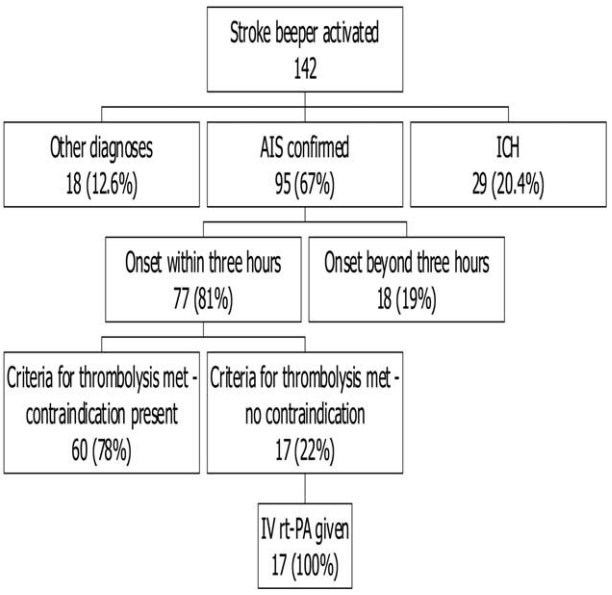

Figure 1. Flow diagram of patients evaluated by stroke service during the study period.

thought to possibly have had a stroke within 3 h of arrival. Over this same time period, review of the hospital discharge log revealed that 926 patients were discharged from the hospital with the final diagnosis of ischemic stroke. The hospital discharge log includes all patients discharged with the diagnosis of stroke, including those who presented well outside the 3-hour window for thrombolysis. A flow chart of our study population is shown in Figure 1.

Main Results

Of the 142 enrolled patients, 95 (68.5%) had a confirmed diagnosis of AIS and 29 (20.3%) had ICH. The diagnoses of the remaining 18 patients included seven with seizure disorder (4.9 %), four with hypoglycemia (3.5%), two with migraine (1.4%), and one each with valproate toxicity (0.7%), syncope (0.7%), hyperglycemia (0.7%), conversion reaction (0.7%), and no diagnosis (0.7%). Final diagnoses of patients are summarized in Table 1.

On further questioning of the family members or caregivers of the 95 patients diagnosed with AIS, 77 (81%) presented within 3 h, with the remaining 18 (19%) presenting outside the 3-h window for thrombolysis. This clarification of the time of onset of symptoms was generally due to questioning of arriving family members who were with the patient when symptoms occurred or who had last seen the patient before symptom onset. Of the 77 AIS patients who presented within 3 h, 17 (22%) met criteria for thrombolysis and had no contraindications. All 17 (100%) of these patients received i.v. rt-PA in the ED. Some of the 60 (78%) patients with contraindications had more than one contraindication (Table 2). The most common contraindications were: 31 patients with rapidly resolving symptoms or signs (48.4%), 10 with stroke symptoms or signs that were minor (15.6%), and five with strokes that were too severe (7.8%).

Patient throughput times from time of symptom onset to time of rt-PA administration are summarized in Table 3. Of note, the mean time from symptom onset to EMS activation was 90 min. System delays occurred in 12 cases, none of which delayed the decision to thrombolyse beyond the 3-h window. These included delay in obtaining a CT scan when a trauma case was being evaluated simultaneously or primary CT scanner was down (n = 6); delay in emergency physician activating stroke beeper (n = 3), delay in obtaining INR results (n = 2), and delay in stroke service arrival in ED (n = 2). One patient fit into two of these categories. Five of these 12 patients received rt-PA within the 3-h window. The other seven had other contraindications and did not receive rt-PA.

Table 1. Final Diagnoses of Patients in the Study

Final diagnosis	Frequency (percentage) n = 142
Acute ischemic stroke	95 (66.9%)
Intracranial hemorrhage	29 (20.4%)
Seizure	7 (4.9%)
Hypoglycemia	4 (2.8%)
Migraine	2 (1.4%)
Depakote toxicity	1 (0.7%)
Syncope	1 (0.7%)
Hyperglycemia	1 (0.7%)
Conversion reaction	1 (0.7%)
No diagnosis	1 (0.7%)

Table 2. Contraindications to Thrombolysis in Patients with AIS who Presented within 3 Hours of Symptom Onset*

Contraindication	Number of patients n = 63 (100%)
Rapidly resolving deficits	31 (48.4%)
Stroke too minor	10 (15.6%)
Stroke too severe	5 (7.8%)
Elevated INR or currently on warfarin	3 (4.7%)
Age > 80 years	4 (6.2%)
Glucose < 50	1 (1.6%)
Seizure at onset	1 (1.6%)
Recent stroke	1 (1.6%)
Other	7 (10.9%)

* The total is greater than 60 due to multiple contraindications in three patients.
Other = aortic dissection, recent trauma, previous ICH, hemodynamically unstable, cavernous angioma on CT (2), and recent GI bleed.

Table 3. Throughput Times from Symptom Onset to rt-PA Decision and Administration

	Time in minutes Mean (95% confidence interval)	n
Time from symptom onset to calling EMS (minutes)	89.93 (43.01–136.86)	58
Time from calling EMS to arrival in ED (minutes)	30.19 (25.49–34.88)	59
Time from symptom onset to ED arrival (minutes)	100.91 (68.09–133.72)	86
Time from ED arrival to MD at bedside (minutes)	4.17 (1.66–6.69)	70
Time from ED arrival to calling stroke service (minutes)	10.17 (4.20–16.14)	88
Time from ED arrival to stroke fellow at bedside (min.)	30.41 (23.75–37.07)	83
Time from ED arrival to obtaining CT scan (minutes)	42.23 (32.69–51.76)	80
Time from ED arrival to rt-PA decision (minutes)	59.44 (50.95–67.92)	87
Time from rt-PA decision to rt-PA administration (min.)	19.88 (6.59–33.18)	17
Time from ED arrival to rt-PA administration (minutes)	109.44 (91.35–127.52)	16*
Time from symptom onset to rt-PA administration (minutes)	153.41 (139.61–167.21)	17

* One missing data point.

Of the 17 patients who received rt-PA for AIS during the study period, five underwent hemorrhagic transformation during their subsequent hospital course. This hemorrhagic transformation was asymptomatic in three patients, and two patients had worsening of their neurological status. None of these patients died during their hospitalization.

DISCUSSION

During the period of this observational study, there were 926 patients with ischemic strokes admitted to our hospital and only 17 (1.8%) were treated with thrombolysis. This low percentage is comparable to that of the NINDS study and other published series (1,8–10). Thus, several years after FDA approval, thrombolysis remains a treatment for a minority of patients. One reason for this low treatment rate is the relatively few patients who present within 3 h from onset of symptoms—only 77 (8.3%) in our series, which is similar to findings from other studies (4,6).

The most frequent contraindication to thrombolysis (among patients presenting within 3 h) was rapidly resolving symptoms. Taken together with patients with minor deficits (NIHSS < 7), 68% of patients arriving within 3 h were not eligible for thrombolysis because their strokes were either mild or resolving. Our data are consistent with the reasons for exclusions in the NINDS trial (1). It has been suggested that thrombolysis has the greatest benefit in patients with more severe strokes (NIHSS > 20) (11). Consequently, we excluded patients with an NIHSS < 7.

Four of our patients were excluded from treatment with i.v. rt-PA due to age > 80 years. This was our original institutional policy in line with the NINDS study. Subsequently, as more data have become available from published clinical series, we have altered our policy (12). Current policy lists age > 70 years as a caution based on the higher rate of ICH in older patients, but age alone is not a contraindication.

Of the 142 times the stroke beeper was activated by the ED, the ultimate diagnosis was stroke (ischemic and hemorrhagic) 127 times, or 89% of the time. Another 11 times (8%) the diagnoses were common mimics of stroke (hypoglycemia and seizure) in which the initial impression in the field by EMS should appropriately initiate activation of the stroke beeper. We have no data on how many acute ischemic strokes may not have been recognized. However, our data suggest that the ED system in our urban-based teaching hospital diagnosed stroke with high specificity.

In retrospect, keeping a prospective log of all patients presenting with stroke, not just those presenting within the 3-h window, would have been helpful. We had to review hospital discharge records to identify the other patients presenting with stroke. From our data, we do not know if there were patients who presented to the ED with AIS within 3 h of onset in whom the diagnosis was missed.

During the period of this study, monthly meetings were held to identify system problems. Participating in these meetings were staff from Emergency Medicine, Nursing, Neurology, Radiology, and Laboratory Medicine. The NINDS has developed time targets for the evaluation and treatment of acute stroke patients with i.v. rt-PA (13,14,15). The two system features identified as critical in our center were time to CT scan and time for INR determination. By identifying the CT scanner wait time as a problem and making acute stroke patients a priority, CT scan wait time decreased from 45 to 20 min within the first year of this study. In addition, laboratory delays in processing INR were reduced.

Relevant to community hospital use of i.v. rt-PA, we believe our experience shows that thrombolysis can be successfully administered if a concerted effort is made by the hospital as a whole: ED staff can diagnose stroke with high specificity and a concerted effort by multiple departments can reduce system delays. Two issues not addressed in our report relate to the role of expertise especially in interpreting CT scans and administering the NIHSS (16). The NIHSS can be mastered by ED staff

(18). There is evidence that recognition of early ischemic edema on CT scans can be improved by attendance at a short training course (17). Another small series has found that there was no significant difference in outcomes when ED physicians or neurologists administered rt-PA, and that occurrence of protocol violations could be reduced with staff training (18).

Two of 17 patients (11.8%) who received rt-PA had symptomatic hemorrhagic transformation of their strokes. Although this rate of symptomatic hemorrhage after rt-PA administration is slightly higher than seen in other studies (Tanne et al. 6%, Grond et al. 5%), the low number of patients (17) who received rt-PA in our study make the symptomatic hemorrhage rate comparable to the experience at other hospitals (19,20).

This study has several limitations. One limitation of this study is the small number of patients who were actually eligible for thrombolysis over the 3-year period. Another limitation is the fact that there were some missing data points in the throughput times recorded. Our log was kept only for patients who were initially thought to have an acute ischemic stroke; patients who presented with stroke clearly outside of the 3-h window were not included in the acute stroke log and had to be identified through hospital discharge records. These discharge records include all patients with a discharge diagnosis of stroke, even if the patient presented hours or even days outside the 3-h window for thrombolysis. A strength of the study is that all patients presenting to the ED with suspected AIS during the 3-year time period of the study were entered into the study, reducing the chance for selection bias.

In summary, we find that system obstacles to successful administration of i.v. rt-PA to AIS patients, such as delay to CT scanning and delay to INR results, can be overcome if a hospital is committed to providing this treatment. Thrombolysis nevertheless remains a treatment for a minority of patients. Major reasons for stroke patients not getting treatment were late presentation and mild or improving symptoms. Continued efforts in community education (especially in early action) are necessary if more patients are to have access to thrombolysis.

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