

Utilization of Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke

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Background: Intravenous tissue plasminogen activator (tPA) is the only approved therapy for acute ischemic stroke, although only 2% of patients with stroke receive intravenous tPA nationally.

Objective: To determine the rate of tPA use for stroke in the Cleveland, Ohio, community and the reasons why patients were excluded from thrombolysis treatment.

Design: Retrospective cohort study.

Setting: Community.

Subjects: Patients admitted because of stroke to the 9 Cleveland Clinic Health System hospitals from June 15, 1999, to June 15, 2000.

Main Outcome Measures: Utilization of intravenous tPA and reasons for ineligibility.

Results: There were 1923 admissions for ischemic stroke in the 1-year period. Of these, 288 (15.0%) arrived within

the 3-hour time window, and approximately 6.9% were considered eligible for tPA. The most common reasons for exclusion among patients arriving within 3 hours were mild neurologic impairment and rapidly improving symptoms. The overall rate of tPA use among patients presenting within 3 hours was 19.4%, and the rate of use among eligible patients was 43.4% (n=56). The use of tPA did not differ significantly according to race or sex.

Conclusions: Only 15% of patients arrived within the 3-hour time window for intravenous tPA, making delay in presentation the most common reason patients were ineligible for IV thrombolysis. Neurologic criteria were the second most common group of exclusions. Overall tPA use was low, but it was used in nearly half of all patients with no documented contraindications. Intravenous tPA use in a community setting can compare favorably with the rate of use seen in academic medical settings.

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THROMBOLYSIS WITH INTRAVENOUS (IV) tissue plasminogen activator (tPA) for patients with acute ischemic stroke of less than 3 hours' duration was approved by the US Food and Drug Administration in 1995.¹

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System changes have occurred in many emergency departments (EDs) throughout the United States to enable the rapid evaluation of patients with stroke. Nevertheless, national estimates suggest that IV tPA is still used in only about 2% of such patients.^{2,3} Identifying barriers to thrombolysis, in addition to time, in acute stroke would help target opportunities for improvement in the delivery of IV tPA.

The purpose of this study was to determine the rate of IV tPA use and the reasons for lack of treatment among pa-

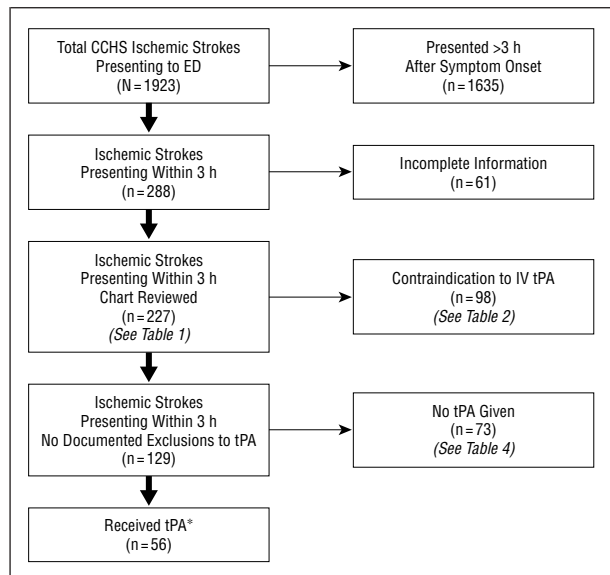
tients presenting with acute ischemic stroke within the Cleveland Clinic Health System (CCHS), Cleveland, Ohio. The CCHS consists of 1 tertiary and 8 community hospitals and comprises 43% of stroke admissions in the Cleveland area.

METHODS

This study was approved by each hospital's institutional review board. A chart review was performed of all patients admitted with a diagnosis of ischemic stroke to the 9 CCHS hospitals for the 1-year period from June 15, 1999 to June 15, 2000. Patients were initially identified by means of principal *International Classification of Diseases, Ninth Revision, Clinical Modification* discharge diagnosis codes (433.x1, 434.x1, 436.xx, and 997.02). Data abstractors at each hospital then reviewed all charts and identified patients who arrived within 3 hours of symptom onset. Finally, a neurologist reviewed the charts of all patients arriving within 3 hours by means of a standardized template.

Information abstracted included patient demographics, comorbid conditions, blood

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Stroke admissions to the Cleveland Clinic Health System (CCHS) from June 15, 1999, to June 15, 2000. ED indicates emergency department; IV, intravenous; tPA, tissue plasminogen activator; and asterisk, the 56 patients included 9 patients treated with intra-arterial tPA.

pressure, initial laboratory values, and initial computed tomographic scan results. The National Institutes of Health Stroke Scale (NIHSS) score was also collected; if not documented, the NIHSS score was estimated through the use of physician notes within the first 24 hours of admission.⁴ Documented absolute contraindications to IV tPA as defined by national guidelines were abstracted.^{1,5} We defined minor symptoms, which are a contraindication to IV tPA, as an NIHSS score less than 4 without evidence of aphasia or visual field loss. Age was not considered an absolute contraindication, as there is no specific age cutoff for thrombolysis.

Patients arriving within 3 hours and with no documented contraindications according to national guidelines were considered “potentially eligible” for thrombolysis. To ensure that we identified all patients who received IV tPA, records from patients with a primary discharge diagnosis of stroke were cross-referenced with pharmacy records and hospital billing codes for tPA.

Potentially eligible patients who received IV tPA were compared with those who did not. The χ^2 and Fisher exact tests were used to compare dichotomous variables, Wilcoxon rank sum test was used for quantitative variables with nonnormal distributions, and the unpaired, 2-tailed *t* test was used to compare continuous variables.

RESULTS

Between June 15, 1999, and June 15, 2000, 1923 patients presented to the CCHS with ischemic stroke (**Figure**). Of these, 1635 (85.0%) presented longer than 3 hours after stroke onset or with an indeterminate time of onset, and thus were ineligible to receive IV tPA. Most patients with indeterminate onset awoke with a neurologic deficit.

Medical records were available for detailed review in 227 of the 288 patients with ischemic stroke arriving within 3 hours, including all patients who received IV tPA. In the patients seen within 3 hours, the mean age was 72.9 years, 49.3% were female, and 20.3% were Af-

Table 1. Demographic Information From 227 Patients With Acute Ischemic Stroke Arriving Within 3 Hours of Symptom Onset

Characteristic	No. (%)
Age >77 y	93 (41.0)
Female sex	112 (49.3)
Race	
White	156 (68.7)
African American	46 (20.3)
Other/not documented	26 (11.4)
Medical history	
Hypertension	164 (72.2)
Coronary artery disease	88 (38.8)
Diabetes mellitus	68 (30.0)
Previous transient ischemic attack or stroke	65 (28.6)
Tobacco use	56 (24.7)
Atrial fibrillation	51 (22.5)
Hyperlipidemia	44 (19.4)
Cancer	25 (11.0)
Dementia	18 (7.9)

Table 2. Absolute Contraindications to IV tPA in Patients With Acute Ischemic Stroke Arriving Within 3 Hours of Symptom Onset

Absolute Contraindications (n = 98)*	No. (%)
Minor symptoms (NIHSS <4)	75 (77)
Rapidly resolving symptoms	43 (44)
Active gastrointestinal tract bleeding	5 (5)
Presented with seizure	4 (4)
Uncontrolled hypertension	3 (3)
Taking anticoagulant with INR \geq 1.7	2 (2)
Recent brain surgery	1 (1)

Abbreviations: INR, international normalized ratio; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

*Some patients had more than 1 exclusion.

rican American (**Table 1**). The most frequent associated medical problems were hypertension (72.2%) and coronary artery disease (38.8%).

IV tPA USE

Forty-seven patients received IV tPA, representing 2.4% (47/1923) of all patients with ischemic stroke and 16.3% (47/288) of those who arrived within 3 hours. An additional 9 patients with stroke who arrived within 3 hours received intra-arterial tPA, resulting in an overall rate of tPA use of 19.4% among patients in this subgroup.

ELIGIBILITY

Absolute contraindications to IV tPA were documented in 43.2% (98/227) of patients with ischemic stroke arriving within 3 hours (**Table 2**). The most frequent absolute contraindications were minor symptoms, defined as NIHSS score less than 4 (77%; n=75), and rapidly resolving symptoms (44%; n=43). Contraindications based on increased bleeding risk, such as recent sur-

Table 3. Percentage of Eligible Patients and IV tPA Use According to Hospital

Hospital	Patients Seen Within 3 h and Potentially Eligible for IV tPA,* No. (%)	IV tPA Use Among Potentially Eligible Patients,* No. (%)
A	19/37 (51.4)	11/19 (57.9)
B	10/16 (62.5)	3/10 (30.0)
C	20/43 (46.5)	1/20 (5.0)
D	22/44 (50.0)	4/22 (18.2)
E	7/19 (77.8)	5/7 (71.4)
F	16/31 (51.6)	14/16 (87.5)
G	3/3 (100.0)	2/3 (66.7)
H	15/21 (71.4)	8/15 (53.3)
I	17/23 (73.9)	8/17 (47.1)

Abbreviations: IV, intravenous; tPA, tissue plasminogen activator.
*Patients with no documented exclusions to IV tPA use according to national guidelines.^{1,5}

Table 4. Possible Reasons for Not Receiving IV tPA Among Patients With Ischemic Stroke With No Documented Contraindications

Reason	No.
Potentially justifiable reasons for withholding IV tPA	
Poor prognosis (dementia, 8; renal cancer, 1)	9
Elderly patients with mild deficit (NIHSS = 4) (94, 95, and 85 years old)	3
Elderly patient with severe deficit (88-year-old with NIHSS = 26)	1
Family refused	1
Not enough time to complete the workup	8
Vasculitis	1
Patient with NIHSS of 4 whose blood pressure was not controlled with nitropaste and enalapril	1
Elderly patient with NIHSS of 6 who fell during stroke (83-year-old)	1
Some improvement in symptoms	3
Subtotal	28
Other possible reasons	
Diagnosis missed by emergency department physician	8
Workup slow	1
Physician noted different exclusions than in general guidelines	9
Subtotal	18
No indication in chart	27
Total	73

Abbreviations: IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

gery, were uncommon. Of the 129 patients with ischemic stroke presenting within 3 hours of symptom onset and without any documented contraindications, 56 (43.4%) received IV or intra-arterial tPA. The rate of tPA use in these potentially eligible patients varied widely among the hospitals, ranging from 5.0% to 87.5% (**Table 3**).

Records from the 73 potentially eligible patients (56.6%) who did not receive tPA were scrutinized for possible explanations as to why they were not treated (**Table 4**). In 28 cases, apparent reasons for withholding tPA were discerned from the medical record. The most common apparent reasons for withholding IV tPA were poor baseline functional status (n=9), insufficient time

Table 5. Use of tPA According to Patient Characteristics Among Potentially Eligible Patients*

Patient Subgroup	tPA Use, No. (%)	P Value
Race†		
African American	15/28 (54)	.17
White	35/90 (39)	
Sex		
F	27/64 (42)	.72
M	29/64 (45)	
Age >77 y		
Yes	23/59 (39)	.31
No	33/69 (48)	

Abbreviation: tPA, tissue plasminogen activator.
*Potentially eligible patients had no documented contraindications to intravenous tPA according to national guidelines.
†Race information missing in 10 patients.

to complete the initial workup (n=8), and relatively mild deficits in patients of advanced age (n=3).

In 9 (12.3%) of the 73 potentially eligible patients who did not receive tPA, the reason documented in the medical record differed from generally accepted guidelines. Anemia, positive result of a guaiac test, an incidental pneumothorax, and an embolic mechanism for the stroke were each claimed once as a contraindication. Old computed tomographic findings were thought to be contraindications in an additional patient. Three patients were taking anticoagulants but with an international normalized ratio less than 1.7. A 67-year-old patient with an NIHSS score of 5 was considered to have too minor a stroke for IV tPA. In 27 patients there was no documented or apparent explanation why IV tPA was not given.

FACTORS ASSOCIATED WITH IV tPA USE AMONG POTENTIALLY ELIGIBLE PATIENTS

There was no difference in the rate of IV tPA use according to race or sex among the patients arriving within 3 hours with no documented contraindication to IV tPA (**Table 5**). The percentage of patients older than 77 years, which is listed as a "caution" in the package labeling, did not differ significantly between treated and untreated patients. However, potentially eligible patients who received IV tPA were younger overall than those who did not (71.4 vs 76.0 years; $P = .048$). Patients receiving IV tPA had higher median NIHSS scores than potentially eligible patients who did not (10.5 vs 6; $P = .001$).

COMMENT

Delay to ED presentation was the primary reason that patients with acute stroke did not receive IV tPA in our 9-hospital system in northeastern Ohio; only 15% of patients with stroke arrived within 3 hours of symptom onset. The percentage of patients with stroke arriving at the ED within 3 hours varies widely in published studies, ranging from 18% in a series of academic centers⁶ to 46% in a community system.⁷ However, even the highest rates are suboptimal, and shortening ED arrival times will have the single greatest impact on increasing IV tPA use in the United States.

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Approximately half of patients arriving within 3 hours were ineligible for IV tPA according to national guidelines. The most frequent contraindications were neurologic, usually minor or rapidly resolving symptoms. This finding has been seen in clinical trials and other studies.^{7,8}

Patients who presented within 3 hours and had no documented contraindications were considered potentially eligible to receive IV tPA. We found that only about half of the potentially eligible patients received treatment. Surprisingly, this compares favorably with other published studies of IV tPA use. In a report of 42 academic medical centers, only 26% of patients meeting the strict criteria as stated in the national guidelines received IV tPA.⁶ There was a 32% rate of IV tPA use among eligible patients in a Canadian academic medical center.⁸

Our study found no significant difference between treated and untreated eligible patients with respect to sex or race. This differs from the recent report by Johnston and colleagues,⁶ in which there was a significantly lower rate of IV tPA use among eligible African American patients with stroke than among eligible white patients in 42 academic medical centers.

Attempting to assess the appropriateness or inappropriateness of interventions from retrospective review of medical records is difficult.⁹ We first identified patients with absolute contraindications according to the national guidelines. Since guidelines do not define appropriate care for the individual patient and do not take into account all possible management scenarios, we identified several additional reasons why community physicians withheld IV tPA. One reason often cited for failure to administer IV tPA, lack of neurologic expertise, was not encountered in our system. If all absolute and apparent contraindications are taken into account, only 46% of patients arriving within 3 hours were potentially eligible to receive IV tPA. This represents 6.9% of all patients with ischemic stroke in our system, a discouragingly low figure.

In several cases, physicians appeared to have notions different from national guidelines as to what constituted contraindications to IV tPA use. These instances may have been a result of either unfamiliarity or disagreement with the thrombolysis guidelines. Disagreement and unfamiliarity are common barriers to guideline adherence¹⁰ and may be issues in the use of IV tPA for stroke.¹¹

This study demonstrates a clear need for improvement in medical record documentation of ineligibility for IV tPA. Inadequate documentation is also an issue in

thrombolysis for myocardial infarction.⁹ Documentation is an important aspect of minimizing medicolegal risk.¹²

There was wide variability in the percentage of potentially eligible patients across hospitals, which may reflect differences in referral patterns or medical record documentation practices. There was also a wide variation across hospitals in the rate of IV tPA use among potentially eligible patients, which may be due to different levels of enthusiasm toward IV thrombolysis for acute stroke.

There are several limitations to this study. First, data abstractors at each hospital may have missed patients arriving within 3 hours. Second, our evaluation was limited to the information available in the medical record. Poor medical record documentation in patients with acute stroke may have restricted our ability to draw conclusions, but in itself was a significant finding. In addition, the inability to obtain complete information for detailed review in 61 patients arriving within 3 hours may have introduced a selection bias. Finally, the study involved 9 hospitals belonging to 1 hospital system and may not be representative of other hospitals in the United States. However, the hospitals were spread throughout the greater Cleveland area and consisted of patients from widely different socioeconomic and cultural backgrounds.

Despite these limitations, this study provides new insights into how IV tPA for acute stroke is used in a community setting. The most common community reasons for exclusion from IV tPA use are late ED arrival and minor neurologic deficits. Many community physicians seem to apply a variety of relative contraindications, including prestroke functional status and age. In a sizable number of potentially eligible patients, the reason for lack of treatment was not apparent from the medical records. Attention to these and other treatment barriers should increase IV tPA use among patients with acute stroke.

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mer, Abou-Chebl, and Nadzam and Mr Hixson); study supervision (Drs Furlan and Nadzam).

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Correction

Errors in Figure Legends. In the Observation titled "Anterior Spinal Artery Syndrome Complicated by the Ondine Curse," published in the December issue of the ARCHIVES (2003;60:1787-1790), the legends to Figures 1, 2, and 3 were incorrect. The legends are reprinted correctly as follows. **Figure 1.** Axial T2-weighted magnetic resonance image shows linear hyperintensity in the anterior spinal cord, extending from C2 to C6, suggesting infarction in the territory of the anterior spinal artery. Note that the cervicobulbar junction is normal. **Figure 2.** Continuous central apneas in stage 2 of non-rapid eye movement sleep during spontaneous respiration. During the apneas, no thoracic or abdominal movements or intercostal muscle activity were observed. Abdom Resp indicates abdominal respirations; ECG, electrocardiogram; EMG, electromyogram; EOG, electro-oculogram; Interc, intercostal; Mylo, myloioideus muscle; Oral Nasal Resp, oral nasal respirations; and Thor Resp, thoracic respirations. **Figure 3.** Normal sleep architecture with slow-wave sleep and rapid eye movement sleep during mechanical ventilation. ECG indicates electrocardiogram; EMG, electromyogram; EOG, electro-oculogram; Interc, intercostal; Oral Nasal Resp, oral nasal respirations; REM, rapid eye movement; NREM, non-rapid eye movement; Thor Resp, thoracic respirations.