Thrombolysis for Acute Stroke in Routine Clinical Practice

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Background: Studies have demonstrated that thrombolytic therapy for acute stroke can be given safely and effectively in study settings with experienced clinicians, but the patient outcomes associated with thrombolytic therapy in routine clinical practice require investigation.

Objectives: To compare outcomes among patients given intravenous thrombolysis in routine clinical practice with the results of the National Institute of Neurological Disorders and Stroke rt-PA Study (NINDS cohort) and to examine whether protocol deviations are associated with adverse events.

Methods: Retrospective cohort of community-based patients given thrombolysis for acute stroke from May 1, 1996, through December 31, 1998, in 16 Connecticut hospitals (Connecticut cohort).

Results: Forty-two (67%) of 63 patients in the Connecticut cohort had at least 1 major protocol deviation, and 61 (97%) had major or minor protocol deviations. Overall, the in-hospital mortality was higher in the Connecticut cohort (16/63 [25%]) compared with the NINDS cohort (40/312 [13%]; $P=.01$). The serious extracranial hemorrhage rate was also higher for the Connecticut cohort (8/63 [13%] vs 5/312 [2%]; $P=.001$). Patients in the Connecticut cohort without major protocol deviations had outcomes similar to those in the NINDS cohort; however, patients in the Connecticut cohort with major protocol deviations had higher rates of in-hospital mortality (13/42 [31%] vs 40/312 [13%]; $P=.002$) and serious extracranial hemorrhage (7/42 [17%] vs 5/312 [2%]; $P=.001$).

Conclusions: Protocol deviations occur commonly when thrombolytic therapy is given to stroke patients in routine clinical practice. Patients who receive thrombolysis with major protocol deviations have higher rates of in-hospital mortality and serious extracranial hemorrhage than patients in the NINDS cohort.

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ACUTE ISCHEMIC STROKE is a major medical problem in the United States, where approximately 600 000 new events occur each year. Although few specific treatment options exist, thrombolytic therapy with tissue plasminogen activator (tPA) improved neurological outcomes in a randomized controlled trial.[1,2] The beneficial effects of tPA therapy appear to be long lasting[2] and cost-effective,[3] and thrombolytic therapy is now part of nearly every treatment guideline and consensus statement for acute ischemic stroke.[4] Despite these recommendations regarding the use of thrombolytic therapy, only a minority of eligible patients are treated with tPA,[5,6] and national efforts are under way to increase the use of tPA.

Although enthusiasm for tPA therapy in acute ischemic stroke is strong, little information exists about whether the results of the clinical trials can be replicated in clinical practice. Of the available studies, most have reported favorable clinical outcomes and low rates of intracranial hemorrhage, but these have been based on voluntary reporting[7-9] or administrative data,[10] have originated from centers that participated in clinical trials of thrombolysis,[8,11] or have come from centers that had experience with protocols for acute stroke care.[5,7,12,13]

Other data have suggested cause for concern. Results of a statewide, mailed survey of neurologists and emergency medicine physicians documented that, even among those who had prescribed tPA, knowledge of its contraindications was poor.[14,15] Overall, less than 20% of the respondents were able to identify cases with definite exclusion criteria. A study of Indianapolis, Ind, hospitals suggested a rate of symptomatic intracranial hemorrhage twice as high (12%) as that reported in the National Institute of Neurological Disorders and Stroke rt-PA Study (NINDS) (6%).[16] A report from hospitals in the Cleveland, Ohio, area found a rate of symptomatic intracranial hemorrhage (16%) nearly 3 times higher

than that of the NINDS trial.[17] The same report found deviations from national treatment guidelines in half of the treated patients.

The Cleveland report suggested that the community experience with tPA for acute ischemic stroke may differ from that of the clinical trials, but this study was limited to a single metropolitan area, nearly all cases had the direct involvement of a neurologist, and the study did not include a comprehensive review of medical records. Consequently, only a few potential protocol deviations were assessed, and extracranial bleeding complications, commonly seen in thrombolytic therapy for myocardial infarction, were not considered.

Therefore, to our knowledge, no study has comprehensively evaluated whether tPA protocols are being adhered to in routine clinical practice, although the importance of adhering to stroke tPA protocols has been established by clinical trials.[1,18] It is therefore essential to determine whether thrombolytic therapy is, or can be, used safely in the community.

The objectives of the current study were to compare the outcomes of patients given tPA in routine clinical practice with the results of the NINDS trial, and to determine whether protocol deviations are associated with higher rates of adverse events. We herein report the tPA experience in Connecticut across a broad range of practice settings, using a detailed medical record review that included a comprehensive assessment of possible protocol deviations and clinical outcomes.

PATIENTS AND METHODS

DESIGN AND SETTING

We performed a comprehensive medical record review of patients given tPA for a diagnosis of acute ischemic stroke at 16 acute care hospitals in Connecticut from May 1, 1996, to December 31, 1998. Institutional review board approval was obtained at all participating hospitals.

The goal of the sample selection was to include all patients in the state of Connecticut who had received tPA for a diagnosis of stroke during our study period. Therefore, we included all hospitals where the investigators had personal knowledge that tPA had been given for stroke. For other acute care hospitals in the state, we inquired of the chairpersons of the departments of neurology and/or emergency medicine if they knew of any occasions when tPA had been prescribed for stroke during the study period and included the hospitals where the chairperson thought that tPA had been prescribed. Some acute care hospitals in Connecticut had policies in place that stated that they did not give tPA for stroke; we did not include these hospitals in our study.

PATIENT IDENTIFICATION

We used several strategies to identify patients who received tPA for acute stroke. The primary identification method consisted of using hospital administrative data and looked at both an *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis code for stroke or transient ischemic attack (430.0-438.9) and a procedure code for intravenous thrombolysis or anticoagulation. We used additional (secondary) approaches to avoid missing patients owing to variations in coding practices: we searched hospital pharmacy databases, examined hospital stroke team records, and surveyed emergency department physicians and chairpersons of the neurology departments. Finally, to confirm these procedures, we examined 50% of the medical records of all patients discharged with a diagnosis of stroke for 1 year at one of the participating hospitals. These 4 confirmatory methods did not identify any additional patients receiving tPA beyond those identified with the primary ascertainment scheme.

MEDICAL RECORD REVIEW

Two of us (D.M.B. and N.K.) abstracted the medical record data using standard definitions and an extraction form developed for this study. These authors were not involved in the clinical care of any of the patients included in this study. Any coding uncertainties were documented, resolved by consensus by 3 of us (D.M.B., N.K., and L.M.B.), and recorded in a coding dictionary. Two of us (D.M.B. and N.K.) reviewed 10% of the medical records to assess interrater reliability. A comparison of these charts demonstrated complete coding agreement for all abstracted variables, confirmed that both authors used the same methods for recording questions about the medical record data, and established that both authors had documented the same information when there was conflicting or uncertain data recorded in the medical record.

STROKE SEVERITY

The stroke severity for the patients in the NINDS trial was evaluated using the National Institutes of Health Stroke Scale (NIHSS). To compare the stroke severity of patients in the Connecticut cohort with that of the NINDS cohort, we converted descriptions of admission stroke symptoms into an NIHSS score using previously described techniques.[19,20] We used 3 severity categories (0-10, 11-20, and >20) based on analyses from the NINDS trial.[21]

OUTCOME MEASURES

Patient Outcomes

We examined in-hospital mortality, intracranial hemorrhage (symptomatic and asymptomatic), and extracranial hemorrhage (serious and minor). In-hospital mortality was defined as death owing to any cause at any time during the admission. Intracranial hemorrhages were defined as hemorrhages that were reported on any brain imaging study performed after admission. Symptomatic intracranial hemorrhage was defined as an intracranial hemorrhage with the new onset of an appropriate syndrome (eg, headache, change in mental status, or decreased motor function). Serious extracranial hemorrhages were defined as symptomatic extracranial bleeding, including lower extremity, genitourinary, gastrointestinal, orbital, retroperitoneal, pulmonary, or intra-articular hemorrhage. Minor extracranial hemorrhages were defined as asymptomatic bleeding, including mucosal bleeding, purpura, petechiae, bruising, epistaxis, asymptomatic heme-positive stool, asymptomatic vaginal bleeding, microscopic hematuria, central access site bleeding, or asymptomatic intraparenchymal pulmonary hemorrhage (hemoptysis). We also recorded the administration of blood transfusions and other therapies for extracranial bleeding.

Protocol Deviations

A protocol deviation was defined as any deviation from the American Heart Association (AHA) Guidelines for Thrombolytic Therapy for Acute Stroke.[4] Major protocol deviations were defined as the presence of any item classified as a contraindication on the tPA package insert, all of which were included in the AHA guidelines. Minor protocol deviations were defined as any item listed

Table 1. Baseline Characteristics of Patients Receiving tPA in the Connecticut and NINDS Cohorts*

Characteristic	Connecticut Cohort (n = 63)	NINDS Cohort (n = 312)	*P* Value†
Age, y			
Range	39-92	NA	. . .
Median	73	NA	. . .
Mean ± SD	71 ± 12	68 ± 16	.16
White, No. (%)	52 (83)	205 (66)	.01
Female, No. (%)	34 (54)	133 (43)	.10
Weight, kg			
Range	40-114	NA	. . .
Median	73	NA	. . .
Mean ± SD	73 ± 17	76 ± 22	.31
Medical history, No. (%)			
Previous stroke	3 (5)	44 (14)	.04
Previous TIA	13 (21)	54 (17)	.53
Aspirin	17 (27)	126 (40)	.05
Diabetes	13 (21)	69 (22)	.80
Hypertension	46 (73)	208 (67)	.33
Myocardial infarction	10 (16)	73 (23)	.19
Atrial fibrillation	14 (22)	60 (19)	.59
Congestive heart failure	8 (13)	66 (21)	.12
Valvular disease	4 (6)	26 (8)	.60
Admission NIHSS score			
Range	3-37	1-37	. . .
Mean ± SD	15 ± 6.7	14	. . .
Scores, No. (%)			
0-10	16 (25)	110 (35)	.13
11-20	37 (59)	139 (45)	.04
>20	10 (16)	63 (20)	.43
Median ± interquartile range	15 ± 9.0	14	. . .
Blood pressure, mean ± SD, mm Hg			
Systolic	151 ± 23	154 ± 31	.47
Diastolic	77 ± 18	85 ± 18	.001
Glucose level, mean ± SD, mg/dL‡	131 ± 54	149 ± 101	.17
CT findings of edema or mass effect, No. (%)	6 (10)	23 (7)	.56

*The Connecticut cohort is described in the "Patients and Methods" section of the text; the NINDS cohort, in the NINDS cohort description by the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group.[1] NA indicates not available; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; tPA, tissue plasminogen activator; and ellipses, not applicable.

†Obtained using the *t* test for dimensional variables and the Fisher exact test or χ^2 test for binary variables. A *t* test could not be performed to compare the NIHSS scores between the Connecticut and NINDS cohorts because no SDs are available for the NINDS cohort.

‡To convert to millimoles per liter, multiply by 0.0555.

in the AHA guidelines that was not classified as a major protocol deviation (eg, admission blood glucose level of <50 mg/dL [<2.8 mmol/L] or >400 mg/dL [>22.2 mmol/L]). Other related factors were also assessed, including process variables (eg, recording a patient's weight) and contraindications to the use of thrombolytic therapy for myocardial infarction (eg, motor vehicle collision within the previous 6 months). We also examined the medical record for documentation of whether the clinicians were aware of the presence of protocol deviations.

STATISTICAL ANALYSIS

The baseline characteristics and outcomes of the Connecticut and NINDS cohorts were compared using *t* tests for dimensional variables and Fisher exact and χ^2 tests for binary variables. The Bonferroni method was used to adjust for multiple comparisons (for the 3 patient outcome measures); the null hypothesis for these comparisons was rejected when the 2-sided *P* values were less than .016.

Table 2. Total Adverse Events for Patients Receiving tPA in Connecticut vs NINDS Cohorts*

Outcomes	Cohort, No. (%)		*P* Value
	Connecticut (n = 63)	NINDS (n = 312)	
Mortality†	16 (25)	40 (13)	.01
Serious hemorrhage‡	12 (19)	19 (6) ≤*x*≤25 (8)	.001 ≥*x*≥.007
Total extracranial hemorrhage‡	23 (37)	72 (23) ≤*x*≤77 (25)	.03 ≥*x*≥.06
Serious	8 (13)	5 (2)	.001
Minor	17 (27)	72 (23)	.51
Total intracranial hemorrhage§	11 (17)	34 (11)	.14
Asymptomatic	7 (11)	14 (4)	.04
Symptomatic	4 (6)	20 (6)	.99

*Cohorts and abbreviations are explained in the first footnote to Table 1.

†The NINDS data represent 30-day mortality; the Connecticut data, in-hospital mortality.

‡Because the published NINDS data regarding extracranial hemorrhage are in summary form, one cannot determine how many patients had minor and serious extracranial hemorrhages. Accordingly, the NINDS rates for serious hemorrhage and extracranial hemorrhage are reported in the form of a range of possible values.

§The NINDS data are for intracranial hemorrhage within 36 hours of treatment, whereas the Connecticut data refer to intracranial hemorrhage during the hospital stay.

RESULTS

Sixty-three patients were given tPA in 10 of the 16 hospitals surveyed. These 10 hospitals were diverse in terms of size, location, academic affiliation, and stroke services. Only 1 of the 10 hospitals had neurology and radiology in-hospital services available 24 h/d. Nine hospitals had internal medicine or family practice house staff, including 3 with neurology house staff. The baseline characteristics of the patients in the Connecticut (n=63) and the NINDS (n=312) cohorts who received tPA differed with respect to race, history of prior stroke, and diastolic blood pressure, but we found no difference in stroke severity as measured by the NIHSS except for the moderate severity category (NIHSS, 11-20) (**Table 1**). All 63 patients in the Connecticut cohort underwent non–contrast-enhanced computed tomographic (CT) scanning of the head at admission, with results as follows: normal in 12 (19%); old infarct in 18 (29%); acute infarct in 13 (21%); mass effect, edema, or sulcal effacement in 6 (10%); and new blood in 1 (2%); hydrocephalus in 1 (2%); atrophy in 31 (49%); calcification in 6 (10%); white matter disease in 8 (13%); and plaque or atherosclerosis in 1 (2%).

ADVERSE EVENTS

In-hospital mortality was substantially higher in the Connecticut cohort (16/63 [25%]) compared with the NINDS cohort (40/312 [13%]; *P*=.01) (**Table 2**). The NINDS reported data for 30-day mortality, whereas the Con-

Table 3. Major Protocol Deviation Frequency and Adverse Event Rates in the Connecticut Cohort*

Deviations	Frequency	In-Hospital Mortality	Serious Extracranial Hemorrhage	Intracranial Hemorrhage
Incorrect dose	22 (35)	6/22 (27)	4/22 (18)	4/22 (18)
tPA given beyond 3 h of symptom onset	14 (22)	4/14 (29)	2/14 (14)	2/14 (14)
Bleeding diathesis	6 (10)	2/6 (33)	0	0
Active internal bleeding	5 (8)	2/5 (40)	1/5 (20)	1/5 (20)
SBP >185 mm Hg or DBP >110 mm Hg before tPA	3 (5)	2/3 (67)	1/3 (33)	0
Head injury within past 3 mo	2 (3)	1/2 (50)	0	0
New bleeding on admission brain CT image	1 (2)	0	0	0
Stroke within past 3 mo	1 (2)	0	0	1/1 (100)
History of intracranial hemorrhage	1 (2)	1/1 (100)	0	0
Intracranial surgery within past 3 mo	0	. . .	. . .	. . .
Seizure at stroke onset	0	. . .	. . .	. . .
Intracranial neoplasm, aneurysm, or AVM	0	. . .	. . .	. . .

*Data are given as number (percentage) of events. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and AVM, arteriovenous malformations. Other abbreviations and the cohort are explained in the first footnote to Table 1.

Table 4. Minor Protocol Deviation Frequency and Adverse Event Rates in the Connecticut Cohort*

Deviations	Frequency	In-Hospital Mortality	Serious Extracranial Hemorrhage	Intracranial Hemorrhage
Blood pressure not monitored per recommendations	50 (79)	14/50 (28)	6/50 (12)	8/50 (16)
Stroke diagnosis not made by stroke expert	13 (21)	5/13 (38)	2/13 (15)	2/13 (15)
Edema, shift, or herniation on admission brain CT image	6 (10)	1/6 (17)	0	2/6 (33)
Antithrombotic, anticoagulant, or antiplatelet aggregating medication within 24 h of tPA dose	6 (10)	2/6 (33)	1/6 (17)	0
Head CT image not read by radiologist or neurologist	5 (8)	0	0	0
Improving symptom course	3 (5)	1/3 (33)	1/3 (33)	0
Major surgery within preceding 14 d	1 (2)	1/1 (100)	0	0
Streptokinase as thrombolytic agent	0	. . .	. . .	. . .
Minor neurological deficit	0	. . .	. . .	. . .
Blood glucose level, <50 mg/dL or >400 mg/dL†	0	. . .	. . .	. . .
Gastrointestinal or urinary tract bleeding within preceding 21 d	0	. . .	. . .	. . .
Recent myocardial infarction	0	. . .	. . .	. . .
Facility not capable of treating bleeding complications and blood pressure management	0	. . .	. . .	. . .

*Data are given as number (percentage) of events. Cohort and abbreviations are explained in the first footnote to Table 1.
†To convert to millimoles per liter, multiply by 0.0555.

necticut data refer to in-hospital mortality (3 of the 16 deaths occurred within the first 24 hours after the administration of the tPA; 9, between the second and seventh day; 3, during the second week; and the final death, on hospital day 36).

The rate of any intracranial hemorrhage in the Connecticut cohort was 11 (17%) of 63 compared with 34 (11%) of 312 in the NINDS cohort ($P=.14$) (Table 2). The rates of symptomatic intracranial hemorrhages were similar in the Connecticut (4/63 [6%]) and NINDS (20/312 [6%]) cohorts ($P=.99$). The asymptomatic intracranial hemorrhage rates were higher in the Connecticut (7/63 [11%]) than in the NINDS (14/312 [4%]) cohorts, but this difference did not reach statistical significance ($P=.04$). Given that the NINDS trial identified intracranial hemorrhages on the basis of a CT scan at 24 hours, we examined the time from symptom onset to CT scan in our cohort. Sixty-two of 63 patients received at least a second CT during their admission (in addition to the admission CT scan on the day of symptom onset), 57 within 24 hours of admission, and 5 within 48 hours of admission. Of the 11 patients with any new intracranial hemorrhage, 10 had a second CT scan within 24 hours. One patient had a second CT scan within 48 hours of symptom onset, and his intracranial hemorrhage was asymptomatic.

The rate of serious extracranial hemorrhages was much higher in the Connecticut cohort (8/63 [13%] vs 5/312 [2%]; $P=.001$). Rates of minor extracranial hemorrhages were similar (Connecticut cohort, 17/63 [27%]; NINDS cohort, 72/312 [23%]; $P=.51$). In the Connecticut cohort, 6 patients (10%) were given blood transfusions, 3 (5%) were given phytonadione (vitamin K), 3 (5%) were given fresh frozen plasma, 2 (3%) were given cryoprecipitate, and 1 (2%) underwent surgery specifically for extracranial bleeding.

PROTOCOL DEVIATIONS

Forty-two (67%) of the 63 patients treated with tPA in Connecticut had at least 1 major protocol deviation, and 57 (90%) had at least 1 minor protocol deviation. Over-

Table 5. Comparison of Adverse Outcomes Between the NINDS and Connecticut Cohorts With or Without Major Protocol Deviations*

Adverse Outcome	Cohort, No. (%)		
		Connecticut, Major Protocol Deviation Status	
	NINDS (n = 312)	Without (n = 21)	With (n = 42)
Mortality	40 (13)	3 (14)	13 (31)†
Serious extracranial hemorrhage	5 (2)	1 (5)	7 (17)†
Intracranial hemorrhage	34 (11)	4 (19)	7 (17)

*Cohorts and abbreviations are explained in the first footnote to Table 1.
†$P \leq .002$ value for the comparison between NINDS and Connecticut cohorts with major protocol deviations.

Table 6. Patient Characteristics of the Connecticut Cohort by Major Protocol Deviation Status*

Characteristic	Major Protocol Deviation Status		
	Without (n = 21)	With (n = 42)	*P* Value†
Age, y			
Median	68	76	. . .
Mean ± SD	66.8 ± 13.7	72.5 ± 11.4	.09
Female, No. (%)	12 (57)	22 (52)	.72
Race, No. (%)			
White	16 (76)	36 (86)	.35
African American	3 (14)	1 (2)	.50
Hispanic	0	2 (5)	.10
Other	2 (10)	3 (7)	>.99
NIHSS score			
Median	14	15	. . .
Mean ± SD	14.2 ± 7.4	15.6 ± 6.3	.44
Score, No. (%)			
0-10	8 (38)	8 (19)	.10
11-20	11 (52)	26 (62)	.47
>20	2 (10)	8 (19)	.33

*Cohort and abbreviations are explained in the first footnote to Table 1.
†Obtained from results of the Fisher exact test or the χ^2 test for binary variables and from the *t* test for dimensional variables.

all, 61 (97%) had at least 1 protocol deviation (major or minor).

The 4 most common major protocol deviations were tPA dosing errors (ie, dose >0.9 mg/kg; total dose >90 mg; or bolus >10% of total dose) in 22 (35%); initiation of therapy more than 3 hours after symptom onset (including patients with unknown symptom onset or awakening with symptoms) in 14 (22%); known bleeding diathesis (ie, prothrombin time of >15 seconds, elevated activated partial thromboplastin time, or platelet count of $<100 \times 10^3/\mu L$) in 6 (10%); and evidence of active internal bleeding in 5 (8%) (**Table 3**). These 4 protocol deviations accounted for 47 (85%) of all 55 major deviations. The most common minor protocol deviations included lack of blood pressure monitoring per AHA recommendations (50/63 [79%]); lack of a stroke diagnosis made by a neurologist or clinician using an NIHSS (13/63 [21%]); the presence of edema, shift, or herniation on the admission CT image (6/63 [10%]); and the use of an antithrombotic, anticoagulant, or antiplatelet medication within 24 hours after tPA therapy (6/63 [10%]) (**Table 4**). Together, these 4 protocol deviations accounted for 75 (89%) of all 84 minor protocol deviations.

Table 7. In-Hospital Mortality by Major Protocol Deviations and Stroke Severity in the Connecticut Cohort*

NIHSS Score	Total No. (%) of Patients (n = 63)	In-Hospital Mortality, Major Protocol Deviation Status, No. (%)	
		Without	With
0-10	10 (16)	1/5 (20)	1/5 (20)
11-20	43 (68)	2/14 (14)	9/29 (31)
>20	10 (16)	0/2	3/8 (38)

*Cohort and abbreviations are explained in the first footnote to Table 1.

In-hospital mortality increased as the number of major protocol deviations increased. The in-hospital mortality rate was 3 (14%) of the 21 patients with no major protocol deviations, 9 (29%) of the 31 patients with 1 major protocol deviation, and 4 (36%) of the 11 with 2 or more major protocol deviations. A similar relationship was found for the number of minor protocol deviations and in-hospital mortality (no deviations, 1/6 [17%]; 1, 8/35 [23%]; ≥2, 7/22 [32%]).

When we compared the results of the Connecticut and NINDS cohorts, we found that the mortality rates were similar for the patients in the Connecticut cohort without major protocol deviations and the NINDS cohort (Connecticut, 3/21 [14%]; NINDS, 40/312 [13%]; $P = .85$), and rates of serious extracranial hemorrhage were also similar (Connecticut, 1/21 [5%]; NINDS, 5/312 [2%]; $P = .29$). The mortality for patients in the Connecticut cohort with at least 1 major protocol deviation was much higher than the mortality of the NINDS patients (Connecticut, 13/42 [31%]; NINDS, 40/312 [13%]; $P = .002$) (**Table 5**). Similarly, serious extracranial hemorrhage was more common among patients in the Connecticut cohort with at least 1 major protocol deviation (Connecticut, 7/42 [17%]; NINDS, 5/312 [2%]; $P = .001$).

When comparing patients treated despite major protocol deviations with the patients without major protocol deviations, no statistical differences were found with respect to age, sex, ethnicity, and stroke severity (**Table 6**). However, the mean age for patients with protocol deviations was higher, and a greater proportion of patients with protocol deviations were in the most severe stroke category. To determine whether the excess mortality seen in patients with major protocol deviations was due to differences in stroke severity, we examined the in-hospital mortality within stroke severity stratum. The in-hospital mortality was the same or worse among patients with major protocol deviations compared with those without major protocol deviations in each of the stroke severity categories (**Table 7**).

Several processes of care were not categorized as protocol deviations because they are not included in the AHA guidelines; however, they are clinically relevant. For example, although tPA dosing is weight based, in 22 (35%) of the 63 patients in the Connecticut cohort, no actual or estimated weight was recorded before the tPA was administered. Furthermore, results of a rectal examination were not documented in 18 (29%) of 63 patients. Three patients had a history of recent trauma or motor vehicle collision, and all of these patients had an adverse event. For 2 patients the trauma or motor vehicle collision occurred on the day of stroke symptom onset (one patient died; the other had an intracranial hemorrhage and was transferred to a facility with neurosurgical expertise); for 1 patient the trauma or collision occurred 2 months before the stroke onset (this patient had a major extracranial hemorrhage).

We also evaluated the relationship between a particular hospital's experience (ie, the total number of patients receiving tPA for stroke during the study period) and the number of major or minor protocol deviations. The number of patients treated at any single hospital ranged from 1 to 16; patient volume was not related to the type or size of the hospital. In addition, no relationship appeared to exist between patient volume and the number of major or minor protocol deviations (data not shown).

We examined the relationship between patient outcomes and the clinicians' knowledge about the existence of protocol deviations before ordering the tPA. For 19 (30%) of the 63 patients, the clinicians documented that they were aware of the protocol deviation. The in-hospital mortality, however, was not related to whether the clinicians had documented that they were aware of the protocol deviation (aware, 6/19 [32%]; unaware, 10/44 [23%]; $P = .46$).

Patients without major protocol deviations had better discharge dispositions, including mortality, than patients with major protocol deviations. For example, 1 (2%) of the 42 patients with a major protocol deviation was discharged home independently (ie, without visiting nurse assistance), compared with 5 (24%) of the 21 patients without a major protocol deviation. Viewed from another perspective, among the 6 patients who were discharged to home without visiting nurse assistance, 5 (83%) had been treated without major protocol deviations, whereas 1 (17%) had been treated with a major protocol deviation ($P = .025$).

COMMENT

We found higher overall rates of hemorrhage (serious intracranial and extracranial bleeding, 19%; total extracranial bleeding, 37%; and total intracranial bleeding, 17%) and mortality (25%) associated with tPA use than previously reported in the published literature. These findings suggest that the clinical application of thrombolytic therapy has not replicated the results of the clinical trials. Serious protocol deviations occur in two thirds of all cases, and hemorrhagic complications and mortality rates are significantly higher than those seen in clinical trials. These adverse outcomes occur more frequently in patients who were treated despite deviations from treatment guidelines.

Two findings lend strength to the conclusion that major protocol deviations were associated with adverse outcomes within the Connecticut cohort and were not due to differences in baseline characteristics between the patients in the Connecticut and NINDS cohorts. First, stroke severity and early changes detected on CT images were the only factors associated with the occurrence of intracranial hemorrhage in the NINDS trial,[1,22] and we found no significant differences in the results of admission CT scans (eg, edema, sulcal effacement, or shift) or in the proportion of patients with the most severe strokes (NIHSS, >20) between the 2 cohorts. In addition, older age was not a predictor in the NINDS trial, but was a predictor of intracranial hemorrhage in a post hoc analysis in the European Cooperative Acute Stroke Study.[23,24] Overall, our cohort was similar in age to patients included in the NINDS trial.

Second, if stroke severity, but not protocol violations, were associated with adverse events, then examination of outcomes within stroke severity strata should demonstrate no difference between patients with and those without protocol deviations. Despite our finding that more of the patients with major protocol violations were in the category of highest stroke severity, we also found that within every stroke severity stratum, the in-hospital mortality rate was the same or greater for patients with major protocol deviations compared with patients without major protocol deviations.

MEDICIAL ERRORS

We found that the medical errors leading to protocol deviations occurred throughout the patient care path, including initial screening questions and laboratory testing (eg, treatment of patients with active bleeding or bleeding diathesis), diagnostic imaging (eg, misinterpretation of CT findings), administration of medication (eg, overdosing), and posttreatment care (eg, mismanagement of blood pressure).

Some physicians gave tPA outside of the recommended guidelines. In 17 cases, the treating clinician documented that tPA was being given outside of recommended guidelines. In other cases, physicians might have been aware that guidelines were not being followed, but did not document this awareness. In most cases, however, it appeared that the deviations in care represented errors in the application of tPA therapy. This finding is consistent with reports documenting a lack of experience and knowledge about thrombolytic therapy among physicians.[14,15]

Clinical guidelines and treatment recommendations may not be followed for a variety of reasons.[25] This problem is not unique to stroke, and lessons can be learned from other vascular, neurological, and acute diseases. Because a small number of trials have been documented, and because the recommendations are based on a pair of nearly identical trials, a high degree of uniformity exists in the guidelines for thrombolytic therapy for stroke. Despite this, most patients were treated outside of the guideline recommendations.

IMPLICATIONS FOR THE USE OF THROMBOLYTIC THERAPY

The absolute increases in favorable outcomes in the NINDS trial of 11% and 13%[1] must be weighed against the higher adverse events rates seen in clinical practice when patients are treated with protocol deviations. The increased mortality rate found in routine practice (12% absolute increase in mortality, from 13% to 25% overall; or 18% absolute increase in mortality, from 13% to 31%, for patients with major protocol deviations), even without consideration of the excess hemorrhages, likely negates the overall benefit of tPA therapy. However, since we found no increase in mortality for patients treated without major protocol violations, patients treated according to guidelines should receive benefit from thrombolysis.

Our report also suggests that the frequency of the use of thrombolytic therapy for stroke is low. In a state where approximately 6500 hospital admissions for stroke or transient ischemic attacks occur each year, we found 63 cases during the 18-month study period. Therefore, the thrombolytic therapy was used in approximately 0.6% of all stroke admissions in the state. Although we could not determine the number of ideal candidates for thrombolysis or what proportion of ideal patients were treated, the rate of patients treated in participating hospitals or across the state as a whole appears to be less than that in reports from other communities. In cities and regions that have adopted aggressive community and hospital efforts, the rates of use are higher by an order of magnitude.[5]

LIMITATIONS

The retrospective nature of this study permitted us to evaluate clinical practices without altering physicians' behavior. Our retrospective study design has limitations, and we faced important challenges to ensure that these data accurately described the care provided to patients in routine clinical practice. For example, we needed to identify potentially eligible cases. Concern has been raised about the use of codes for ischemic stroke from the *International Classification of Diseases, Ninth Revision, Clinical Modification,*[26] but patients receiving thrombolytic therapy for acute stroke seem likely to be recognized and to receive a code with a stroke diagnosis. Because tPA is given to a small percentage of stroke patients, and because administrative coding practices vary, we used multiple case-finding methods that took advantage of local expertise when possible. We also needed to demonstrate that our abstraction process was accurate and reliable. Therefore, this study was based on a comprehensive medical record review in which 2 authors abstracted the data. Since these authors were aware of the research objectives, they used standardized definitions and procedures to ensure accurate data abstraction. Double-entry techniques were used to improve the reliability of data processing. Previous medical record reviews have been shown to be effective for quality enhancement projects.[27]

CONCLUSIONS

Our report is a comprehensive evaluation of thrombolytic therapy for acute ischemic stroke in routine clinical practice, and we found that the overall rates of hemorrhage and mortality were higher than expected, given the published randomized control trial results. An aggressive approach to acute stroke therapy can be justified,[28] and our results demonstrate the importance of adhering to treatment guidelines, since patients who were treated without major protocol deviations had rates of adverse events similar to the accepted standard (the NINDS trial). Systems should be put in place that ensure the identification of all eligible patients and the appropriate treatment of patients in a timely manner, including measures that guarantee that physicians have the necessary information to promote the optimal care of patients with acute stroke. It took more than a decade for organized systems of care to be instituted for myocardial infarction and trauma due to motor vehicle crashes, and subsequently for patient outcomes to improve.[29] The results of our study offer a point of departure for strengthening this process for stroke care.

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