

Mortality of stroke patients treated with thrombolysis: Analysis of nationwide inpatient sample

Abstract—The authors performed a retrospective cohort comparison using the Nationwide Inpatient Sample for 1999 through 2002 of acute ischemic stroke admissions. Mortality was compared based on the use of thrombolysis. Hospital mortality was significantly greater for the thrombolysis cohort (10.1% vs 5.8%) as was the rate of secondary intracranial hemorrhage (4.2% vs 0.4%). US community experience in the use of thrombolysis has higher rates of complications and mortality than in controlled clinical trials.

NEUROLOGY 2006;66:1742–1744

Richard Dubinsky, MD, MPH; and Sue-Min Lai, PhD

Since the 1996 Food and Drug Administration approval of tissue-type plasminogen activator (tPA), treatment that can potentially reverse the symptoms of acute ischemic stroke is available. Community experience has shown conflicting rates of death and intracranial hemorrhages when compared with the National Institute of Neurologic Disorders and Stroke study. To determine the rates of in-hospital mortality and secondary intracranial hemorrhage associated with a national sample of the use of thrombolysis, we analyzed the Nationwide Inpatient Sample (NIS).

The Healthcare Cost and Utilization Project (HCUP, Agency for Healthcare Research and Quality) collects and disseminates administrative data on hospital admissions. The NIS provides yearly data of hospital admission and discharge information from almost 1,000 hospitals, stratified by region, hospital size and ownership, and urban, rural, and teaching status to represent a 20% sample of all hospital admissions nationwide. Each entry represents a single hospitalization. Information on diagnoses and procedures are identified using *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM) codes for diagnoses and procedures and the Clinical Classification Software (CCS, HCUP, <http://www.ahrq.gov/data/hcup/ccsfact.htm>). This large, stratified sample of US hospitalizations is a unique source to analyze nationwide mortality and morbidity associated with thrombolytic treatment of acute ischemic stroke.

Methods. We identified admissions for ischemic stroke in the NIS data sets for 1999 through 2002 by searching for the diagnostic CCS code 109 (acute cerebrovascular accident) and 110 (precerebral artery occlusion, with or without infarction) as the

primary diagnosis. All nonischemic strokes in this CCS classification were identified using ICD-9 codes and excluded from the data analysis. Using only the primary diagnosis has a sensitivity of 84%, with a high specificity in identifying hospitalizations for acute stroke.¹ The following criteria were used to further identify acute ischemic strokes: adult older than 21 years and younger than 85 years (to match the published studies of thrombolysis for stroke),² with an emergent or urgent admission from an emergency department, and disposition data available. Patients were excluded if they underwent neurosurgical procedures or had a secondary diagnosis of sickle cell disease, CNS infections, gynecologic diagnosis associated with contraception or birth, congenital CNS abnormalities, trauma, or poisoning due to medications or external substances. If the patient was transferred to another hospital by day 2, the record was excluded, because the same patient may be represented twice in the data set. We identified those that received thrombolytic therapy by searching for the procedure code for infusion of thrombolytic agent (ICD-9-CM 991.0, introduced October 1998) performed on the day before, the day of, or the day after admission. Those with thrombolysis after day 1 were excluded from the data set. Complications were identified by searching for intracerebral hemorrhage (ICD-9-CM 431 or 432.9), and gastrointestinal hemorrhage (CCS 153) among the secondary diagnoses. Comorbidities were identified using CCS and ICD-9-CM codes.

Statistical analysis. SAS version 8.2 was used for statistical analyses. Secondary analyses were planned to control for comorbidities, using the Charlson comorbidity index, a weighted composite score of 19 different chronic conditions, with scores ranging from 0 (indicating no comorbidities) to a maximum of 37 (having all 19 chronic conditions).³ To avoid the effects due to multicollinearity between the Charlson comorbidity index and a series of individual risk factors simultaneously included in the model, separate logistic regression models were analyzed to explore the interaction of comorbidities and thrombolysis on in-hospital mortality. The significance level was set a priori at $p < 0.001$.

Results. Of the original cohort, 99,400 admissions were available for analysis after cases were excluded (table 1). The difference in primary insurance coverage between the two groups was not significant when we controlled for age. Over the 4 years, there was a trend in decreasing mortality in the thrombolysis cohort from 12.5% in 1999 to 8.7% in 2002 ($p = 0.2$), whereas the mortality of the control group remained constant.

The significant difference in mortality between the thrombolysis and comparison cohorts persisted when we controlled for comorbidities using the Charlson index, but only for Charlson indices of 1, 2, and 3 compared with an index of 0, not for 4 or greater (data not shown).

The adjusted odds ratios for thrombolysis, age, female sex, and Charlson index were greater than 1, indicating these factors were associated with higher in-hospital mortality (table 2). This logistic regression model confirmed

From the University of Kansas Medical Center, Departments of Neurology (R.D.) and Preventive Medicine and Public Health (S.-M.L.), Kansas City, KS.

Disclosure: The authors report no conflicts of interest.

Presented in part at the annual meeting of the American Academy of Neurology, April 2005.

Received November 11, 2005. Accepted in final form February 22, 2006.

Address correspondence and reprint requests to Dr. Richard Dubinsky, Department of Neurology, University of Kansas Medical Center, 3599 Rainbow Blvd., Mail Stop 2012, Kansas City, KS 66160; e-mail: rdubinsky@safetyresearch.com or rdubinsk@kumc.edu

Table 1 Demographics of stroke patients by cohorts

	Thrombolysis, n = 1,239	Comparison, n = 98,161	<i>p</i>
Female	565 (45.6%)	52,217 (53.2%)	<0.0001*
Mean age, y	66.7 ± 12.4	69.9 ± 11.7	<0.0001†
Race/ethnic group*			NS‡
White	806 (83.0%)	53,929 (74.6%)	
Black	94 (9.7%)	12,270 (16.9%)	
Hispanic	33 (3.4%)	3,623 (5.0%)	
Other	38 (3.9%)	2,507 (3.5%)	
Payer, primary			<0.0057*
Medicare	722 (58.3%)	66,646 (67.9%)	
Medicaid	50 (4.0%)	5,321 (5.42%)	
Private and HMO	390 (31.48%)	20,817 (21.2%)	
Self pay, no charge and other	77 (6.2%)	5,377 (5.5%)	
Mean duration of stay, d	6.9 ± 4.9	5.7 ± 4.2	<0.0001†
Intracranial hemorrhage	52 (4.2%)	425 (0.4%)	<0.0001†
GI hemorrhage	16 (1.3%)	1,354 (1.4)	0.7918*
CVA risk factors			
Hypertension	772 (62.3%)	67,390 (68.7%)	<0.0001*
Coronary artery disease	636 (51.3%)	46,314 (47.2%)	0.0036*
Diabetes mellitus	234 (18.9%)	31,808 (32.4%)	<0.0001*
Previous CVA	32 (2.6%)	5,788 (5.9%)	<0.0001*
Disposition			
Routine/home	414 (33.5%)	39,771 (40.6%)	<0.0001*
Home health care	79 (6.4%)	9,685 (9.9%)	
Skilled nursing facility and rehabilitation	576 (46.6%)	40,204 (41.0%)	
Transfer to another hospital	43 (3.5%)	2,626 (2.7%)	
Died	125 (10.1%)	5,649 (5.8%)	

* Chi-square.

† Two-sided *t* test.

‡ Does not include the 23.4% of the total sample where data was missing or suppressed.

NS = not significant; HMO = health maintenance organization; CVA = cerebrovascular accident; GI = gastrointestinal.

that tPA associated with higher in-hospital mortality persisted even after controlling for all risk factors. The observed higher in-hospital mortality in the tPA study group remained unchanged when individual comorbidities (rather than the Comorbidity index) were analyzed (results not shown).

Discussion. In this nationwide cohort from 1999 through 2002, we have found that the mortality rate for stroke treated with thrombolysis is more than reported in meta-analysis clinical trials of tPA² and some reports of retrospective cohorts from community hospital^{4,5} but less than in other

Table 2 Logistic regression model for in-hospital mortality

Effect	Comparison	Odds ratio	95% CI	<i>p</i>
Thrombolysis	Yes vs no	1.9	1.6–2.4	<0.0001
Age	> Median age vs. < median age	1.9	1.7–2.0	<0.0001
Female	Vs male	1.1	1.04–1.15	0.0011
Charlson Index	For each 1-point increase	1.174	1.157–1.191	<0.0001

reports.^{6–9} Use of thrombolysis is low in the United States. Only 1.25% of stroke patients in the data set received thrombolysis, presumably with tPA, compared with 1.8% reported in Cleveland in 1997 and 1998,⁶ 3% in the report of the German Stroke Registers Study Group,⁸ and 9.4% of all stroke patients in a single Berlin hospital.⁴ How many patients may have been eligible for tPA based on time from symptoms onset and how many may have been excluded because of contraindications (e.g., previous hemorrhagic stroke, recent stroke or surgery, seizure at onset of stroke) cannot be determined from this administrative data set. The number of stroke patients in our retrospective analysis of an administrative data set is larger than other community cohort reports and provides a realistic picture of the community use and mortality of thrombolysis for acute stroke in the United States.

The limitations of the use of administrative data sets are case ascertainment, diagnostic accuracy, and the lack of measurements of disease severity. In a recent comparison of ICD-9 primary diagnosis codes for stroke to abstraction and recoding by a trained examiner, the true-positive rate was 83% and case ascertainment was 84%.¹ Our case yield may be higher because the data cleansing that we used excluded 20.5% of cases with a primary diagnosis of ischemic stroke that seemed to be miscoded. Another limitation of our cohort assembly is that procedure code (991.0) does not distinguish between IV and intra-arterial thrombolysis and does not specify the agent. Last, although comorbidities are available, there are no direct measures of disease severity or the level of function. The shorter duration of stay and the greater proportion of the comparison cohort who were discharged to home may be due to a lower initial severity of deficits from the ischemic stroke.

The promise of benefit from clinical trials is not always seen in the use of new techniques and therapeutics in community hospitals. Thrombolysis with tPA is proven to be beneficial in terms of reduction in stroke severity and improved survival. Although the mortality rate in clinical trials of tPA has declined over time, it remains high in community hospitals. Only the healthiest of the sick are recruited into clinical trials, which have rigid protocols for treatment administration. The level of benefit from a clinical trial cannot always be generalized to the community, where the patients have other comorbidities and rigid treatment protocols are not always followed.

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The American Academy of Neurology is offering workshops for Treatment of Dystonia and Spasticity, demonstrating the use of botulinum toxin. They will be held in Philadelphia, Los Angeles, Chicago, and Washington, DC, beginning in late summer. Class size is limited to provide more personal instruction and live, small-group demonstration sessions. Attendees can obtain 7.0 hours of AMA PRA Category 1 credits. Visit www.aan.com/dsworkshop for more information.