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Tissue Plasminogen Activator for Acute Ischemic Stroke in Clinical Practice

A Meta-Analysis of Safety Data

Glenn D. Graham, MD, PhD

Background and Purpose—Concerns persist regarding the safety of tissue plasminogen activator (tPA) therapy for acute ischemic stroke. Numerous case series of clinical experience with tPA have been published that provide additional data on the safety of thrombolytic therapy.

Methods—This is a meta-analysis of 15 published, open-label studies that broadly followed approved indications and guidelines for tPA use in nonselective patient populations.

Results—In 2639 treated patients, the symptomatic intracerebral hemorrhage rate was 5.2% (95% confidence interval, 4.3 to 6.0), slightly lower than the 6.4% rate in the treated group of the randomized, placebo-controlled National Institute of Neurological Disorders and Stroke (NINDS) trial. The mean total death rate (13.4%) and proportion of subjects achieving a very favorable outcome (37.1%) were comparable to the NINDS trial results. Protocol deviations were reported in 19.8%. Comparing across studies showed that the mortality rate was correlated with the percentage of protocol violations ($r=0.67$, $P=0.018$).

Conclusions—Postapproval data support the safety of intravenous thrombolytic therapy with tPA for acute ischemic stroke, especially when established treatment guidelines are followed. (*Stroke*. 2003;34:2847-2850.)

Key Words: cerebral hemorrhage ■ cerebral infarction ■ cerebrovascular accident
■ meta-analysis ■ tissue plasminogen activator

Although tissue plasminogen activator (tPA) has been approved in the United States for treatment of acute ischemic stroke since mid-1996, concerns regarding its safety remain. Although most neurologists support the use of tPA according to recognized guidelines, the emergency medicine community has yet to endorse tPA for acute ischemic stroke. Possible imbalances between the treatment and control groups in the National Institute of Neurological Disorders and Stroke (NINDS)-sponsored study¹ and allegations of conflicts of interest² have added to the lingering controversy surrounding tPA.

The NINDS-sponsored trial³ of tPA in acute stroke was conducted at a relatively small number of experienced stroke centers. One commonly expressed concern is that similar results might not be obtained when tPA is used in a variety of clinical settings. The high symptomatic intracerebral hemorrhage (ICH) rate reported in a series of 70 patients treated at hospitals in the Cleveland area⁴ is frequently cited as evidence that the risks of tPA may be greater in clinical practice than in a clinical trial setting. Since publication of the NINDS trial results, more than a dozen reports of experience with tPA in open-label, routine clinical use have been published.⁴⁻¹⁸

The goal of this project was to examine the overall safety data from this large, collective experience with tPA.

Methods

A meta-analysis was performed of all identified open-label reports of tPA use for acute ischemic stroke published through April 2003 that purported to follow approved indications and guidelines¹⁹⁻²¹ in a nonselective patient population. Potential studies for inclusion in the meta-analysis were identified through Medline searches, bibliographies of review articles,^{22,23} and presentations at international symposia. Data from the large Canadian Activase for Stroke Effectiveness Study (CASES),⁵ currently available only in abstract form, were also included. Reports limited to special populations (ie, the elderly), those using target time windows for treatment other than 3 hours, and series of <15 patients were excluded, as were studies that did not state symptomatic ICH rates. When cases from single-center reports were also compiled in larger, multicenter series, data from the single-site articles were not included unless unique patients could be clearly identified. The number of patients, symptomatic ICH rate, and, when reported, baseline National Institutes of Health Stroke Scale (NIHSS) score, percentage of protocol violations, total ICH rate, deaths, and very favorable outcomes (defined as a modified Rankin Scale score of 0 or 1) were tabulated. Combined statistics, weighted by study size, were calculated for comparison to the treated group of the NINDS tPA study. When possible, only the symptom-

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Source Data

Trial	Type	Patients, n	Median Baseline NIHSS	Symptomatic ICH, %	Deaths, %	Very Favorable Outcomes, %	Protocol Violations, %	Reference
CASES	P	1099	15	4.6			15.0	5
STARS	P	389	13	3.3	13.4	34.6	32.6	6
Houston	P	269	14	4.5	15.0		13.0	7
Cologne	P	150	11	4.0	10.7	41.0	1.3	8
Berlin	P	75	13	2.7	15.0	40.0	20.0	9
Cleveland	P	70	12	15.7	15.7		50.0	4
Calgary	P	68	15	8.8	16.2		16.2	10
OSF Stroke Network	P	57	15	5.3	8.8	47.0	8.8	11
Mercy/Sacramento	P	43	14	7.0	16.3	42.0	18.6	12
Oregon	P	33	17	9.1	18.2	36.4		13
tPA Stroke Survey	R	189	11–15	5.8	9.5	34.0	29.6	14
Connecticut	R	63	15	6.3	25.4		66.7	15
Indianapolis	R	50	11	8.0	10.0		16.0	16
Cleveland Clinic HS	R	47		6.4			19.1	17
Michigan	R	37	6–10	10.8	5.4		18.9	18
All studies		2639	14	5.2	13.0	37.1	19.8	
All prospective studies		2253	14	4.9	13.8	37.9	18.1	
NINDS (treated)		312	14	6.4	12.8	39.0		3

P indicates prospective study; R, retrospective study; STARS, Standard Treatment With Alteplase to Reverse Stroke; and HS, Health System. Summary statistics are an average of individual study values weighted by the number of patients in each study. To facilitate comparison to the NINDS trial results, symptomatic ICH percentages are for bleeding within the first 36 hours or the closest reported time point. Deaths and other outcome measures are at 90 days or the closest time point. NINDS trial data are from parts 1 and 2 combined, except for the percentage of very favorable outcomes, which is from part 2 only.

atic ICHs that occurred during the first 36 hours after treatment were included to parallel the reporting of symptomatic ICH rate in the NINDS trial. Usually, however, only the overall in-hospital symptomatic ICH rate was reported in the individual case series. Similarly, although the NINDS trial reported 90-day outcomes, most of the reports included in this meta-analysis provided outcome data at an earlier time point such as hospital discharge.

Results

Data were abstracted from 15 studies (10 prospective, 5 retrospective or mixed) incorporating 2639 total patients (the Table). The median baseline NIHSS score was 14. The overall symptomatic ICH rate was 5.2% (95% confidence interval [CI], 4.3 to 6.0, binomial statistics) and was 4.9% (95% CI, 4.0 to 5.8) in the 2253 patients studied prospectively. Both of these values are slightly lower than the 6.4% rate in the treated group of the NINDS trial,³ as illustrated in Figure 1. Combining data from the 6 studies that reported the total (symptomatic plus asymptomatic) ICH rate gave an overall frequency of 11.5%, which was close to the NINDS trial value of 10.9%. When reported, the mean total death rate (13.4%) and the proportion of subjects achieving a very favorable outcome (37.1%) were also comparable to the NINDS trial results.

Protocol deviations were reported in 19.8% of the cases overall. Comparison across studies without adjustment for the number of cases showed that mortality rate was correlated with the percentage of protocol violations ($r=0.67$,

$P=0.018$), as shown in Figure 2. However, the highest mortality rate occurred in the series with the highest percentage of protocol violations,¹⁵ and if this data point is excluded, the correlation loses statistical significance. The greatest symptomatic ICH rate was found in the study with the second highest proportion of protocol deviations,⁴ although the symptomatic ICH rate was not significantly correlated with the frequency of protocol violations overall ($P=0.19$).

Discussion

Postapproval data from >2500 treated patients support the safety of tPA therapy for acute ischemic stroke. The incidence of early symptomatic ICH, perhaps the most feared complication of tPA use in stroke patients,²⁴ was slightly but statistically significantly less than in the placebo-controlled NINDS study. Although more difficult to evaluate from unblinded series, the efficacy of tPA in this meta-analysis is similar to that found in the NINDS trial. The average stroke severity in these case series as assessed by the pretreatment median NIHSS score was 14, the same as in the NINDS study, suggesting that the complications and outcomes should be comparable. The tendency for series with more protocol violations to be associated with higher death rates emphasizes the importance of adherence to established treatment guidelines.

There are several important limitations to these results. As is typical of meta-analyses, data are combined from individ-

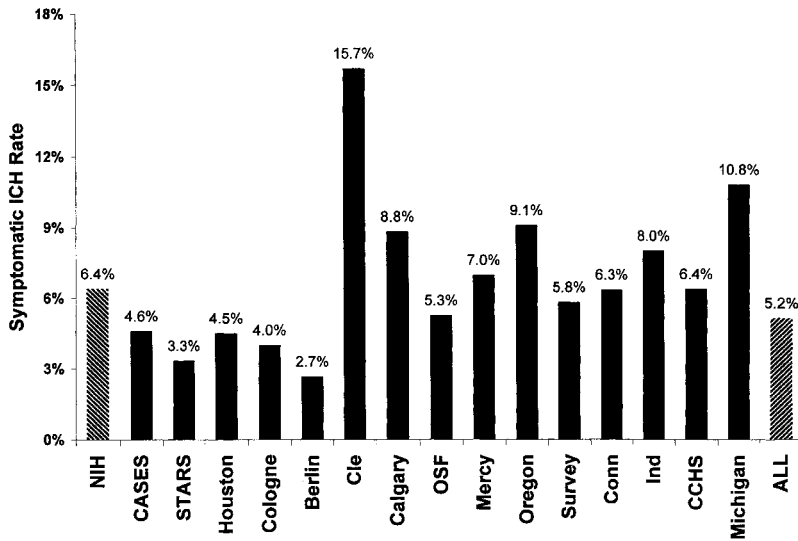


Figure 1. Symptomatic ICH rates ordered by decreasing sample size. Retrospective studies are shown last. Studies are ordered as in the Table.

ual series that used slightly different treatment inclusion and exclusion criteria, although all followed the broad outlines of the NINDS protocol. Five of the case series were collected retrospectively, which may be less accurate than prospective data acquisition. Retrospective surveys may introduce investigator bias in the extraction of data from the medical record and are more likely to rely on estimation of items such as the NIHSS score rather than actual measurement. The threshold and criteria used to determine whether an ICH is symptomatic may vary between individual series, whereas total ICH rates may be unavailable or inaccurate when derived from studies in which not all patients underwent routine follow-up imaging.

Reporting of outcomes was not standardized. Individual studies used modified Rankin scores of 0 to 1 or 0 to 2, NIHSS scores of 0 to 1, or Barthel Index scores of 95 to 100 to define the very favorable outcome group, whereas some provided no outcome data. Failure to report outcomes at a consistent time point (such as 30 or 90 days after stroke) or to use consistent criteria limits any comparative assessment of treatment efficacy. Such comparisons would be problematic even in the best circumstances because of the lack of a control group. It is hoped that future case series of thrombolytic

therapies will provide more consistent and detailed data on patient outcomes.

Many of the individual series included here are single-center series rather than multicenter compilations and may be susceptible to publication bias in which only especially favorable, or unfavorable, results are reported. Also, centers treating a high volume of stroke patients, which are more likely to report results, may have better outcomes than lower-volume institutions. A recent pooled analysis of registries incorporating data from 104 German hospitals found a significantly increased risk of in-hospital mortality for stroke patients treated with tPA in institutions using thrombolytic therapy for stroke ≤ 5 times per year but no increase for hospitals treating larger numbers.²⁵ These factors may limit the applicability of these results to institutions with small numbers of acute stroke presentations. Even with these limitations, this compilation provides the largest patient experience to date documenting the safety of intravenous thrombolytic therapy for acute stroke outside a clinical trial setting.

The high incidence of protocol violations and the suggestion of a correlation between protocol deviation frequency and adverse outcomes are troublesome. Some patients were treated years after the publication of the NINDS study and approval of tPA in the United States, affording providers sufficient time to become familiar with details of the appropriate use of the drug. Some publications included in this meta-analysis did not have a prespecified goal of accurately detecting the frequency of protocol deviations and may underestimate the true incidence of variance from tPA treatment guidelines. These data support the necessity of adequate provider education and adherence to approved indications in institutions treating acute stroke patients with tPA. For example, in Cleveland, where a 50% protocol deviation rate was initially reported,⁴ implementation of additional training and quality improvement measures decreased the frequency of protocol violations and reduced the symptomatic ICH rates to levels close to the NINDS results.¹⁷ Many physicians, especially nonneurologists, remain hesitant to use tPA in

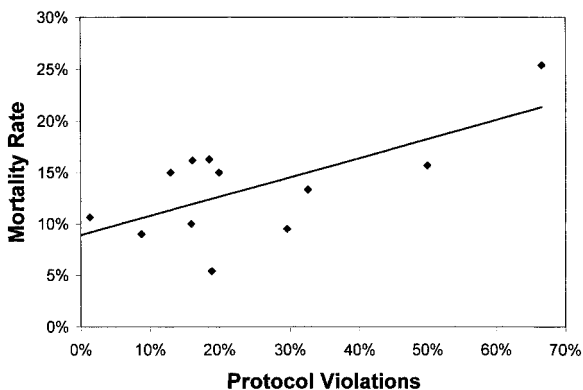


Figure 2. Mortality rate vs percentage of protocol deviations in each of the 12 studies reporting death rates.

acute stroke patients, suggesting that additional education and training may still be needed in many communities.

Overall, however, the data from open-label tPA use present a compelling argument that thrombolytic therapy for stroke can be used safely across a wide variety of practice settings. Safety results from community hospitals were comparable to those of large, tertiary medical centers.¹¹ Although efficacy claims still must rely on data from randomized trials, the published postapproval experience with tPA in clinical practice compiled here should be considered in assessments of the safety of thrombolytic therapy for ischemic stroke by advocates and skeptics alike.

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