Brief Communications

Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: A multicenter survey

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Article Abstract

We assessed initial clinical experience with IV tissue plasminogen activator (t-PA) treatment of acute ischemic stroke in a standardized retrospective survey of hospitals with experienced acute stroke treatment systems. The incidence of symptomatic intracerebral hemorrhage (ICH) was 6% (11 of 189 patients; 95% CI 3 to 11%), similar to that in the National Institute of Neurological Disorders and Stroke (NINDS) t-PA Stroke Study. Deviations from the NINDS protocol guidelines were identified in 30% of
patients (56 of 189). The incidence of symptomatic ICH was 11% among patients with protocol deviations as compared with 4% in patients who were treated according to the NINDS protocol guidelines, suggesting that strict adherence to protocol guidelines is prudent.

## Introduction

IV tissue plasminogen activator (t-PA) is the first available effective therapy for acute ischemic stroke (AIS).\(^1\)\(^-\)\(^6\) Symptomatic intracerebral hemorrhage (ICH), the most ominous complication associated with this therapy, occurred in 6.4% of patients in the t-PA arm of the National Institute of Neurological Disorders and Stroke (NINDS) t-PA Stroke Study.\(^3\)\(^-\)\(^4\) Despite proven efficacy in a clinical trial setting, limited data are available on the risks associated with this therapy in routine clinical practice.\(^7\)\(^-\)\(^8\) The present study details a multicenter assessment of the initial clinical experience with IV t-PA for AIS, evaluating, in particular, hemorrhagic risks and the effect of deviations from NINDS protocol guidelines.

## Methods.

We retrospectively surveyed hospitals within several selected cities in the United States that have an organized stroke triage system and experience with the use of IV t-PA for AIS (at least four patients treated per hospital) per published protocols.\(^1\)\(^-\)\(^3\) A standardized form was used to collect data systematically. Investigators at each hospital reviewed records of all consecutive patients treated with t-PA after publication of the NINDS t-PA trial results.

Data were obtained from 13 of 16 identified hospitals meeting our selection criteria. Patient demographics and medical histories were abstracted from medical records. The National Institutes of Health Stroke Scale (NIHSS) scores, measuring neurologic impairment, were reported categorically in 5-point intervals (\(\leq 5\), 6 to 10, 11 to 15, 16 to 20, or >20). The modified Rankin scale (mRS) was used to assess disability at discharge categorized as none, mild-moderate, or severe (0–1, 2–3, 4–5, respectively). Both NIHSS and the mRS categories were estimated by the local investigators from the medical records, unless available as part of the routine treatment protocol. Each local investigator retrospectively determined deviations from NINDS protocol guidelines. Severe strokes and early CT changes, not contraindications in the NINDS trial, were not considered protocol deviations in the current analysis.

Follow-up brain CTs considered to have any ICH by an investigator were centrally reviewed by the study neuroradiologist (S.C.P.) following criteria used in the NINDS trial.\(^4\) Differentiation among asymptomatic, symptomatic, and fatal ICH was determined by the judgment of the treating physicians or site investigators. Symptomatic ICH was defined as a CT-documented hemorrhage that was judged to be temporally related to
deterioration in the patient’s clinical condition; fatal ICH was defined as a hemorrhage associated with a potentially related in-hospital death; and asymptomatic ICH was defined as a CT-documented hemorrhage identified on a routine follow-up and judged not to be associated with clinical deterioration. Patients having in-hospital follow-up scans (CT or MRI) showing no evidence of hemorrhage were considered as not having an ICH. Any systemic hemorrhage considered life threatening by the treating physician that resulted in a decrease in the hemoglobin of ≥5 g/dL or that required more than two units of blood cell transfusion was considered a major systemic hemorrhage. ICH within 36 hours from onset of t-PA infusion was considered as likely related to t-PA.

Univariate comparisons were conducted with Fisher exact test for dichotomous variables, Wilcoxon rank sum test for ordered categorical variables, and Student’s t-test for normally distributed variables. For multivariate modeling, the variables significant at the 0.20 critical level in the univariate analyses were included in the stepwise logistic regression models.

Results.

The overall treatment period was between January 1996 and December 1997. The study sample included 189 patients with AIS treated with IV t-PA at 13 hospitals. All hospitals included in the study were urban, including 5 university hospitals and 8 community hospitals with academic affiliations. All hospitals had experience with therapeutic trials for AIS. Two of the 13 hospitals used a baseline CT exclusion criterion of ischemic changes exceeding a third of the middle cerebral artery territory. Six hospitals had treated fewer than 10 patients with t-PA, 3 had treated 10 to 19 patients, and 4 had treated 20 patients or more. Patients were often treated by more than one member of a stroke team. A stroke specialist was primarily responsible for treatment in nearly two thirds of cases. The remaining physicians primarily responsible for treatment were general neurologists (20%), emergency physicians (15%), or other physicians (1%).

Baseline characteristics of patients are presented in table 1. Infusion of t-PA was started in 2% of patients during the first hour from onset of stroke symptoms, in 18% during the second hour, and in 72% in the third hour. Therapy was initiated beyond the 3-hour window in 8% of patients, most within 30 minutes of the 3-hour window. Median length of hospital stay was 7 days (range 1 to 84), and in-hospital mortality was 10%. Baseline stroke severity and disability categories on discharge are presented in table 2.

View this table:  Table 1. Baseline characteristics of patients with acute ischemic stroke treated with tissue plasminogen activator (t-PA)
The incidence and characteristics of ICH as well as other complications likely related to t-PA are summarized in table 3. The incidence of symptomatic ICH was 6%. Deviations from NINDS protocol guidelines were identified in 30% of patients (56 of 189 patients). Common deviations included use of heparin within the first 24 hours (15%), initiation of t-PA infusion beyond 3 hours (8%), excessively elevated blood pressure (3%), and abnormal baseline coagulation (4%). Although the presence of protocol deviations had little effect on the overall risk of any ICH, the relative risk of symptomatic ICH was nearly three times greater among protocol deviations (11% versus 4%, \( p = 0.09 \)). The specific deviations noted among patients with symptomatic ICH were IV heparin use (2 patients), treatment beyond 3 hours (2 patients), abnormal baseline coagulation studies (1 patient), and excessively elevated blood pressure (1 patient).

Neither specialty of the treating physician (stroke specialist, general neurologist, or emergency physician) nor magnitude of experience with IV t-PA within each hospital predicted symptomatic ICH. Increasing age \( (p = 0.13) \), baseline NIHSS score \( (p = 0.07) \), male gender \( (p = 0.05) \), diabetes mellitus \( (p = 0.14) \), and deviations from protocol guidelines \( (p = 0.09) \) tended to be associated with symptomatic ICH in univariate analysis (screening criteria of \( p < 0.20 \)), but none reached conventional statistical significance \( (p < 0.05) \) in a logistic regression model.

In-hospital mortality was 4.5-fold greater among patients with symptomatic ICH (36%) compared with patients without symptomatic ICH (8%). The proportion of patients with severe disability at discharge (mRS 4 to 5) was almost threefold greater (86% versus 31%), as was NIHSS score \( \geq 11 \) (57% versus 21%). Disposition to a nursing home was over fourfold greater (29% versus 6%) among patients with symptomatic ICH.

**Discussion.**

There are notable similarities and some differences between patients selected in the...
current study and those in the NINDS trial. Demographics and baseline characteristics of patients were comparable. The proportion of patients with very severe strokes was somewhat lower in our study than in the NINDS trial. Two hospitals used CT exclusion criteria other than hemorrhage that were not used in the NINDS trial. In the NINDS trial, patients were stratified into 0 to 90 versus 91 to 180 minutes, whereas in the current study the majority of patients were treated between 120 and 180 minutes. In-hospital outcome and rates of disability on discharge and of disposition to a nursing home in the current study were comparable to the NINDS trial.

Incidence of symptomatic ICH was similar to that seen in the NINDS trial. Most symptomatic hemorrhages were intracerebral hematomas, often with some intraventricular extension, and were rarely multifocal or outside the area of the infarction. Deviations from protocol guidelines were identified in nearly one third of our patients. The incidence of symptomatic ICH was 4% if protocol guidelines were strictly followed, well within a favorable risk-benefit profile as demonstrated in the NINDS trial. However, the incidence was 11% when deviating from protocol guidelines and should prompt caution against deviating from recommended guidelines when selecting and treating AIS patients with t-PA. Further analysis to identify factors associated with symptomatic ICH including the individual effects of specific protocol deviations requires a substantially larger sample size than available for the current analysis.

Experienced stroke centers are included in our survey, and therefore our findings cannot be generalized to different clinical settings such as community hospitals. This study is limited by its retrospective design, and prospective studies are necessary to critically assess the effectiveness of this novel therapy in different patient populations and clinical settings and to assess the effects of training and experience on complication rates and outcome.

Appendix

The t-PA Stroke Survey Group included the following participants and institutions: Dent Neurological Institute (Drs. Bates and Vereczkey-Porter), Buffalo, NY; Henry Ford Hospital (Drs. Tanne and Mansbach, and S. Daley), Detroit, MI; Medical College of Wisconsin (Drs. Binder and Book), Milwaukee, WI; Seton-Hall University (Dr. Verro), E. Orange, NJ; University of Pennsylvania Medical Center (Drs. Kasner and Raps), Philadelphia, PA; Marshfield Clinic (Dr. Karanjia), Marshfield, WI; St. John Hospital (Dr. Giancarlo and A. Schuster), Detroit, MI; University of Michigan Medical Center (Dr. Scott), Ann Arbor, MI; Thomas Jefferson University Hospital (Drs. Dayno, Bell, and Brock, and K. Hartnett and J. Strause), Philadelphia, PA; Sparrow Hospital (S. Wehner), Lansing, MI; University of Rochester (Dr. Benesch), Rochester, NY; Wayne State University (Dr. Coplin and Chaturvedi), Detroit, MI; University of Wisconsin (Dr. Dulli), Madison, WI.
Footnotes

*See Appendix on page 426 for a list of participants in the t-PA Stroke Survey Group.

Coordinated at Henry Ford Hospital and Health Science Center (Drs. Tanne, Mansbach, Schultz, Patel, and D’Olhaberriague; S. Daley and L. Salowich-Palm; and Dr. Levine, Detroit, MI).

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