SELECTED ARTICLES

Intravenous tPA for acute stroke: Any and all hospitals? Any and all docs?

Clinical question

Can community hospitals administer tissue plasminogen activator (tPA) for acute stroke and achieve outcomes comparable to those reported by the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS trial)?

Article chosen

Katzan I, Furlan A, Lloyd L, Frank J, Harper D, Hinchey J, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. JAMA 2000;283:1151–8.

The search

PubMed and MEDLINE

MeSH headings: intravenous AND tissue plasminogen activator factor AND acute stroke.

Yield: 55 citations. This was reduced to 21 by limiting to: English, human, only IV therapy, and 1995 to present. The final yield was 3 articles.[2,3] References 2 and 3 were excluded from consideration because they did not represent community or general hospital experience. The majority of physicians in reference 2 had used tPA in other acute stroke trials, and the study protocol in reference 3 required immediate referral of all enrolled patients to a university stroke centre.

Clinical bottom line

Numerous trials have studied thrombolysis for acute stroke, but only the NINDS study[1] showed clear benefit. In doing so, it changed the standard of care and launched a new industry. However, because the benefit seen in NINDS was modest and confined to a small proportion of stroke patients carefully selected for an efficacy trial, it is important to know whether similar outcomes are achievable if thrombolytic therapy is extended into community settings.

In this study, Cleveland area investigators reported their experience with intravenous (IV) tPA stroke thrombolysis. They documented an alarming rate of intracranial hemorrhage (ICH) and five-fold higher early mortality than reported in the NINDS trial. The large number of protocol violations and adverse outcomes seen in this study cast doubt on the safety of community hospital stroke thrombolysis and suggest that simpler and more effective protocols are necessary.

Reviewer: David J. Rhine, MD
Chairman, Department of Emergency Medicine, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

Date appraised: April 2000
Received: Apr. 25, 2000; final submission received: May 5, 2000; accepted: May 10, 2000

The evidence

Design: A historical prospective cohort study.

Objectives: To study the rate of IV tPA use, to assess inpatient outcomes, to determine the incidence of ICH, and to evaluate compliance with guidelines for stroke thrombolysis.

Centres: Patients admitted to one of 29 teaching and nonteaching facilities in the Cleveland area with a diagnosis of ischemic stroke were studied. Hospitals were representative of mid- to large-sized US city hospitals (mean = 324 beds). tPA eligibility criteria were like those in the NINDS study, and included absence of hemorrhage on CT and time-to-treatment <3 hours after symptom onset.

Intervention: Treatment was based on the NINDS[1] and American Heart Association protocols.[4] Intravenous tPA was given in a dose of 0.9 mg/kg to a maximum of 90 mg. Ten percent of this dose was given in bolus form and the rest infused over 60 minutes.

Outcomes: Three subgroups were compared: patients who received tPA, matched patients who presented within 3 hours but did not receive tPA, and all ischemic stroke patients. Primary outcomes included ICH rate, in-hospital mortality, and protocol violations. A predictive model was prepared using Cleveland area stroke data from 1991–99, so that observed mortality could be compared to expected mortality.

Study population: During the study period, 3948 patients presented with acute stroke, and 672 (17%) presented within 3 hours of symptom onset. Of these, 70 (10.4%) received tPA, representing a 1.8% treatment rate. Forty-eight percent of patients who arrived within 2 hours of symptoms received tPA, compared to 4% of those who arrived between 2 and 3 hours.

Protocol deviations: Therapy deviated from published guidelines[4] in 35 of 70 tPA recipients. Nine received tPA more than 3 hours after symptom onset (range, 191–373 minutes) and 26 received anticoagulants or ASA within 24

hours of tPA dosing. Blood pressure monitoring appeared to be inadequate in 86% of variant cases.

Results: ICH occurred in 16 of 70 tPA patients (22%). Eleven of these (15.7%; 95% CI, 8.1%–26.4%) were symptomatic ICH (SICH) and 6 caused death. TPA recipients suffered higher early mortality than untreated patients (15.7% vs. 5.1%, $p < 0.01$) and higher mortality than predicted (15.7% vs. 7.9%, $p < 0.006$). Conversely, mortality rates for non-treated patients were similar to predicted values (Table 1).

Comments

The NINDS study, published in the December 1995 issue of the *New England Journal of Medicine*, reported that tPA treatment within 3 hours of stroke onset increased the proportion of favourable neurological outcomes by 12%. Shortly thereafter, *Time* magazine promoted the notion that "clot-buster therapy" was a safe, effective and widely available miracle therapy for stroke. While most would agree that miracle therapies should be rapidly incorporated into clinical practice, many physicians saw tPA as something less than this and viewed the NINDS data with skepticism. Before embracing thrombolysis for stroke, emergency physicians (who man the front-lines of acute stroke care) must be convinced that it offers their patients more benefit than risk and that this benefit is possible in non-research settings.[5–7]

The Cleveland study is the first to assess tPA stroke thrombolysis in community hospitals, where physicians lack thrombolytic trial experience. The high rate of protocol violations, ICH and death seen in this study raise doubts about the safety of IV thrombolysis in non-research settings, and suggest that "real world" outcomes may differ from those published by the NINDS investigators.

However, while the Cleveland outcomes are alarming, several methodologic problems limit the conclusions we can draw. First, because there was no control group, the study does not prove that tPA increased mortality — only that mortality was higher than "expected," based on historical data. Second, although age, comorbidity, blood pressure and NIH stroke scores were similar in the two studies (Table 2), stroke severity data was only available for 40% of the Cleveland patients; therefore it is possible that higher risk patients were enrolled. Finally, the Cleveland authors did not report whether adverse outcomes originated from specific physicians or hospitals.

In previous studies, protocol violations have been identified as determinants of symptomatic ICH.[4,8–10] For example, Tanne and colleagues[8] reported a 30% incidence of protocol violations in 189 patients treated with tPA and showed that patients with protocol violations suffered a three-fold higher rate of symptomatic ICH (10.7% vs. 3.8%). Interestingly, there was no statistical association between protocol violations and ICH in the Cleveland study.

Conflicting data exists. In the same issue of *JAMA*, the STARS group[2] published experience from 57 centres that treated 389 patients over a 22-month period. Despite a 33% rate of protocol violations, these investigators reported 13% 30-day mortality and an 11.5% rate of ICH (only 3.3% symptomatic). There is no obvious explanation for the dramatically different study outcomes. Perhaps the STARS investigators, who had more experience in thrombolytic stroke trials, were somehow able to select patients more likely to benefit from the intervention.

Table 1. In-hospital mortality

Treatment group	Mortality, *n* (%)
All study patients not treated with tPA (*n* = 3,878)	198 (5.1)
Patients admitted within 3 h of onset (*n* = 739)	
Not treated with tPA (*n* = 669)	48 (7.2)
Treated with tPA (*n* = 70)	11 (15.7)

Table 2. Events in patients receiving tPA

Event	Cleveland study (*n* = 70)	NINDS study (*n* = 312)
NIH stroke score, median	14	12
Early mortality, *n* (%)	11 (15.7)	9 (2.9)
Symptomatic intracranial hemorrhage (SICH), *n* (%)	11 (15.7)	20 (6.4)
SICH mortality, *n* (%)	6/11 (55)	9/20 (45)

Conclusion

Stroke thrombolysis in community hospitals may be hazardous rather than beneficial. Hospitals wishing to administer thrombolytics for stroke must provide immediate access to CT imaging and to stroke specialists and should admit patients to ICU or stroke unit equivalents for post-lysis care. Most importantly, they must select patients carefully, adhere to strict drug administration protocols and introduce pathways to reduce "door-to-needle" time.[8,11–13] Even with these factors in place, the likelihood of benefit remains uncertain. Competing therapies such as antiplatelet agents and subcutaneous heparin are easier to apply, can be offered to many more patients, and offer similar benefits with less risk and at lower cost.

References

1. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333:1581-7.
2. Albers G, Bates V, Clark W, Bell R, Verro P, Hamilton S.

Intravenous tissue-type plasminogen activator for treatment of acute stroke: the standard treatment with alteplase to Reverse Stroke (STARS) Study. JAMA 2000;283:1145-50.
3. Grond M, Stenzel C, Schmulling S, Rudolf J, Neveling M, Lechleuthner A, et al. Early intravenous thrombolysis for acute ischemic stroke in a community-based approach. Stroke 1998; 29:1544-99.
4. Adams HR Jr, Brott TG, Furlan AJ, Gomez CR, Grotta J, Helgason CM, et al. Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic stroke. Circulation 1996;94:1167-74.
5. Grotta J. Should thrombolytic therapy be the first-line treatment for acute ischemic stroke? TPA: the best current option for most patients. N Engl J Med 1997;337:1309-10.
6. Caplan LR, Mohr JP, Kistler JR, Koroshetz W. Thrombolysis: not a panacea for ischemic stroke. N Engl J Med 1997;337:1309-10.
7. Scott PA, Smith RW, Grant RJ, Chudnofsky CR, Fredriksen SM. Emergency physician administration of rtPA therapy in acute stroke: analysis of treatment and outcome [abstract]. Stroke 1999;30:244.
8. Tanne D, Bates VE, Verro P, Kasner SE, Binder JR, Patel SC, et al. Initial clinical experience with IV tPA for acute ischemic stroke: a multicenter study. Neurology 1999;53:424-7.
9. NINDS tPA Study Group. ICH after IV tPA for ischemic stroke. Stroke 1997;28:2109-18.
10. Lopez-Yunez AM, Bruno A, Zurru C. Protocol variations in community-based rtPA use are associated with symptomatic intracerebral hemorrhage [abstract]. Stroke 1999;30:264.
11. del Zoppo GJ. Thrombolytic therapy in the treatment of stroke [discussion]. Drugs 1997;54 Suppl 3:90-8.
12. Tong DC, Yenari MA, Albers GW. Intravenous thrombolytic therapy in acute stroke. Vasc Med 1997;2:51-60.
13. Mohr JP. Thrombolytic therapy for ischemic stroke [editorial]. JAMA 2000;283:1189-91.

Correspondence to: Dr. David Rhine, PO Box 3354, MBC 84, Riyadh 11211, Saudi Arabia; drhine@hotmail.com

Amiodarone for out-of-hospital cardiac arrest

Clinical question

Does intravenous amiodarone improve outcomes in patients with out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation (VF) or tachycardia (VT)?

Reviewers: Michael J Bullard, MD; Joseph Vipond, MD
University of Alberta, Edmonton, Alta.
Date appraised: April 2000
Received: May 5, 2000; accepted: May 10, 2000.

Article chosen

Kudenchuk PJ, Cobb LA, Copass MK, Cummins RO, Doherty AM, Fahrenbruch CE, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation or tachycardia. N Engl J Med 1999;341:871-8.

Objective

To determine, in out-of-hospital cardiac arrest patients with refractory VF or VT, whether intravenous amiodarone, given within a standard ACLS (advanced cardiac life support) protocol following a minimum of 3 shocks, increases survival to hospital with a perfusing rhythm.

Background

There are more than 250,000 cardiac deaths annually in the US, many due to ventricular fibrillation. ACLS guidelines state that antiarrhythmic medications are "acceptable and probably helpful" for patients with VF or pulseless VT persisting after 3 or more shocks.[1] However, to date, there is little supporting evidence for this statement.

Population studied

Victims of non-traumatic, out-of-hospital cardiac arrest in a city served by well trained emergency medical services (EMS) providers, including emergency medical technician (EMT)-defibrillation first responders and paramedics dispatched simultaneously for life-threatening calls.

Study design

This was a double-blind randomized clinical trial of single-dose intravenous amiodarone (300 mg) versus its diluent, polysorbate 80, as placebo. Eligible patients were those with persistent VF or pulseless VT following 3 or more precordial shocks, intubation and intravenous epinephrine (1 mg). All other resuscitative efforts were based on existing standard protocols. Data were collected from dispatch records, EMS records, ECG and defibrillator recorders, hospital records, and survivors or their family members.

Outcomes measured

The primary end point was admission to hospital with a spontaneously perfusing rhythm. Secondary end points were adverse effects, number of precordial shocks required after study drug administration, duration of resuscitative efforts, and the need for additional antiarrhythmics. Survival to discharge and functional neurological status at