



Clinical Use of tPA in Acute Ischemic Stroke

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A 62-year-old female acutely developed aphasia and right-sided weakness while in the grocery store. The store clerk immediately called 911, with the arrival of CFD paramedics within 9 minutes, at 6:43 PM. She arrived at the ED at 7:05 PM, completed her head CT at 7:25 PM, and obtained a neuro consult at 7:35 PM, approximately one hour after the onset of her symptoms. On exam, BP 116/63, P 90, RR 16, T 98, and pulse oximetry showed 99% saturation. The patient appeared alert, and was able to slowly respond to simple commands. The patient had a patent airway, no carotid bruits, clear lungs, and a regular cardiac rate and rhythm. The pupils were pinpoint, and there was neglect of the R visual field. There was facial weakness of the R mouth, and R upper and lower extremity motor paralysis. DTRs were 2/2 on the left and 0/2 on the right. Planter reflex was upgoing on the right and downgoing on the left. The patient's estimated weight was 50 kg. What are the next Rx steps?

Key Clinical Questions

What did the NINDS clinical trials demonstrate regarding the use of tPA in stroke patients?

What are the characteristics of tPA use in clinical practice? What do the phase IV clinical trials suggest about the use of tPA in clinical practice as compared to in the NINDS clinical trials?

What protocol violations most often will cause the complication of intracranial hemorrhage in stroke patients treated with tPA?

What does the time data from the phase IV clinical trials suggest regarding the need for systems for acute stroke care?

What must be documented in the medical record when treating a patient with tPA for ischemic stroke?

Key Learning Points

1. The NINDS clinical trials demonstrated the efficacy of tPA in the treatment of acute ischemic stroke in the Emergency Department. Patients treated with tPA were more likely than standard therapy patients to have a favorable neurological outcome at 90 days.
2. Although there is a narrow therapeutic window for the use of tPA in stroke, phase IV studies have demonstrated that it can be utilized effectively in the Emergency Department. Outcomes similar to those seen in the NINDS clinical trials can be duplicated in clinical practice if a protocol for tPA use similar to that used in the NINDS trials is successfully implemented.
3. Complications such as intracranial hemorrhage can occur with tPA use, especially when the protocol utilized in the NINDS clinical trials is not adhered to in clinical practice. Protocol violations such as the use of anti-coagulants after tPA administration must therefore be avoided in order to maximize patient outcome.
4. In clinical practice, many patients receive tPA toward the end of the 180 minute window for its use. As such, patients need to be educated about presenting to the Emergency Department soon after stroke symptoms occur, and Emergency Physicians must have systems in place for the rapid diagnosis and use of tPA in ischemic stroke patients.
5. When treating a stroke patient with tPA, it is necessary to document the following:
 - * With tPA use, there is a 30% greater chance of a good neurologic outcome at three months.
 - * With tPA use, there is a 10x greater symptomatic hemorrhage risk within 36 hours.
 - * That there is a comparable three-month mortality rate, even if there are more hemorrhages in the tPA group (confirming the high mortality of acute ischemic stroke, itself).
 - * The rationale for the use of tPA, given the significant morbidity and mortality risk of both the use of tPA and of the underlying disease state, in acute ischemic stroke.

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Introduction

It has been over 5 years since the NINDS clinical trials showed the efficacy of tPA in the treatment of patients with acute ischemic stroke.¹ Since that time, the opportunity to use this treatment modality in the clinical setting has resulted in thirteen studies of its clinical use.²⁻¹⁴ This discussion addresses the important clinical issues that must be considered by the Emergency Medicine physician when considering the use of tPA in patients with acute ischemic stroke, based on both the results of the NINDS clinical trials and these subsequent nine clinical reports. This discussion will focus on the most important issues regarding tPA use, especially what these published studies tell us about how it should be used, with what expected outcomes, as well as how decisions regarding its use must be documented in the medical record.

The NINDS Efficacy Trials of tPA in Stroke:

The NINDS study was the landmark clinical trials that examined the efficacy of tPA in acute ischemic stroke.¹ Patients who received tPA within 180 minutes of symptom onset had a 30% greater chance of a good three month neurologic outcome than did those treated with standard therapy. These data support the use of tPA in the emergency management of patients with an acute ischemic stroke. This thrombolytic therapy is the only specific therapy that has shown to be effective in improving the outcome of patients with ischemic stroke.

The overall rate of intra-cranial hemorrhage (ICH) at 36 hours was 3x greater (10.9 vs. 3.5%, $p<.001$), and symptomatic ICH rates were 10x greater in patients treated with tPA (6.4 vs. 0.6%, $p<.001$). Although the risk of ICH was greater in tPA-treated patients, mortality in the treatment group was similar at three months to those treated with our standard therapy (17 vs. 21%, $p=.30$). This comparable mortality rate in tPA treated patients, despite a higher symptomatic hemorrhagic rate, underscores the significant mortality risk of ischemic stroke patients who are treated with our best standard emergent therapy.

Several important design issues in this NINDS tPA stroke trials should be considered when analyzing outcome, symptomatic ICH and mortality rates, and the apparent “treatment errors” from the nine subsequent clinical use reports. These study design issues include:

1. All patients with a blood pressure above 185/110 mm Hg were excluded.
2. All patients requiring “aggressive treatment” to reduce BP were excluded.
3. All patients anti-coagulated within the prior 48 hours were excluded.
4. No anticoagulants or antiplatelet drugs were to be given for 24 hours after infusion.
5. Blood pressure was to be maintained “within pre-specified values” after infusion.

Documentation of the Use of tPA in the Acute Setting

Given the complexity of the data from the NINDS study and the significant risk of ICH associated with the use of tPA, the Emergency Physician must be careful when considering the use of this therapy. For each ischemic stroke patient, it must be documented that tPA therapy was considered, and why it was or was not used. Whether or not tPA is ultimately used, it must be documented that the inclusion and exclusion criteria were considered, as was the overall risk/benefit profile of its use for the individual patient for whom it is being considered. In addition, the Emergency Physician must also document that the facts about tPA use were explained to the patient and/or family members. These facts include:

1. With tPA use, there is a 30% greater chance of a good neurologic outcome at three months.
2. With tPA use, there is a 10x greater symptomatic hemorrhage risk within 36 hours.
3. That there is a comparable three-month mortality rate, even if there are more hemorrhages in the tPA group (confirming the high mortality of acute ischemic stroke, itself).
4. The rationale for the use of tPA, given the significant morbidity and mortality risk of both the use of tPA and of the underlying disease state, in acute ischemic stroke.

Whether or not a consent document must be completed by the Emergency Physician prior to tPA use is dependent on the policies and practices of each institution. Suffice it to say that the thought process behind its use and the discussion regarding its risk/benefit profile must be documented for each patient who presents to the Emergency Department with an acute ischemic stroke.

Clinical Efficacy and the Effective Use of tPA in Acute Ischemic Stroke Patients

When the FDA approved the use of tPA for acute ischemic stroke, it was based on the efficacy demonstrated in the NINDS phase III clinical trials. Efficacy is defined as “the power or capacity to produce a desired effect”. Once a therapy has been approved based on demonstrated efficacy, the next question is whether or not the drug can be used effectively in clinical practice. When asking if a drug can be effectively used, the issues regarding the use of a drug outside of the rigid controls of a phase III clinical trial are taken into account. In other words, is it reasonable to expect that the front line Emergency Physician can use tPA safely and effectively, given the need to appropriately identify patients who are eligible for its use, and manage these patients in a way that is consistent with the efficacy trials, in the hopes of safely achieving a similar improvement in outcome?

Even if a drug efficacy is shown in a randomized, placebo-controlled clinical trial that includes specific management guidelines, it may or may not be effectively used in broad clinical practice by the many different clinicians who practice outside of the constraints imposed by a clinical trial. If differences in outcome and safety are observed, they may occur because of differences in the following:

1. Patient selection: the patients identified and enrolled in the clinical trial can't be consistently identified in clinical practice.
2. Intervention administration: the drug cannot be administered as it was in the clinical trials.
3. Concomitant therapy administration: the use of other therapies cannot be adequately standardized in order to achieve a consistently good outcome.
4. Outcome measurement: problems in outcome assessment lead to different results of the intervention in clinical practice as compared to the clinical trials.

An additional consideration for the use of a therapy in clinical practice is the frequency with which patients who can receive the therapy occur in clinical practice. If the frequency with which these patients are identified is significantly low, then the individual practitioner may not be adequately skilled to administer the therapy in an effective way. This must be considered when examining the results of the nine trials that have described the clinical use of tPA in ischemic stroke.

If reports subsequent to an initial clinical efficacy trial suggest that similar outcomes cannot be achieved in clinical practice, it suggests that there are clinically important factors that are influencing outcome, such as difficulties in identifying suitable patients or in managing the patients who receive the therapy. If these clinical factors adversely influence the safety or efficacy results that were seen in the initial efficacy trials, a narrow therapeutic window for the therapy is suggested. That is to say, if the therapy cannot be used in clinical practice as successfully as it was in a clinical trial, then the strength of the therapy's effect is relatively weak, or narrow, as compared to the other clinical factors that influence patient selection, management and outcome. This concept will be discussed in more detail when considering the clinical reports of the use of tPA in acute ischemic stroke.

The NINDS Efficacy Trials: Issues Relevant to the Phase IV Clinical Reports of tPA Use

In order to best understand the significance of the clinical reports of tPA use, it is important to further examine the results reported in the NINDS phase III efficacy trials. The first issue to consider is stroke severity in the patients treated in these clinical trials. To put this in perspective, the authors state in the methods, under outcome measures, "the NIHSS, a serial measure of neurologic deficit, is a 42-point scale that quantifies neurologic deficits in 11 categories. For example, a mild facial paralysis is given a score of 1, and a complete right hemiplegia with aphasia, gaze deviation, visual field deficit, dysarthria, and sensory loss is given a score of 25." The median NIH stroke scale (NIHSS) score was 14, somewhere in between these two stroke severity levels. This is but one issue to consider when examining the patients who ultimately are chosen for infusion with tPA for stroke; others which will be looked at in the phase IV studies are age and the presence of stroke with greater than one third involvement of the cerebral cortex supplied by the middle cerebral artery as determined by brain computed tomography.

The next issue to consider is how many patients had to be screened in order to find enough patients who were eligible for tPA stroke therapy. This information is important in that it suggests how often this therapy can be utilized, which in turn suggests a favorable risk/benefit profile and the potential for broad application in clinical practice. The NINDS study does not specifically state what number of patients was screened in order to successfully randomize those patients who were treated and included in the analysis. The results do state that between 90 and 95% of patients were successfully infused in each group, but this information does not tell the reader what percentage of stroke patients could be reasonably expected to receive tPA in clinical practice given the experience in these phase III efficacy trials.

Another relevant issue as we consider the clinical use of tPA is when the tPA was administered in the efficacy trials. The NINDS clinical trials' discussion highlights the fact that 48% of patients were successfully treated within 90 minutes. Does this mean that in order to achieve similar efficacy and safety results in clinical practice, that at least half should be treated within 90 minutes? The data reported in these efficacy trials do not suggest improved outcome with therapy within 90 minutes (as compared to 90-180 minutes), even though the pathophysiology of acute cerebral vessel occlusion would suggest that patients treated early after a stroke would have a better outcome than those treated in a more delayed manner. More importantly, given data that suggests that tPA therapy three to five hours after symptom onset is associated with a higher complication rate¹⁵, is it necessary to treat at least half of all stroke patients within 90 minutes in order not to have a higher symptomatic ICH rate than that seen in the NINDS clinical trials?

Lastly, how were the patients managed in the clinical trials? Most importantly, how was blood pressure managed, and to what effect? Given that patients who required blood pressure management did less well than those without the need for blood pressure management¹⁶, how is the practitioner in clinical practice able to judge the need for blood pressure management in patients who are eligible for tPA therapy? These are some of the important factors for consideration as we look at the subsequently published un-controlled reports of tPA use in ischemic stroke.

The Phase IV Reports of tPA Use in Acute Ischemic Stroke: An Overview

Since the publication of the NINDS efficacy trials, there have been thirteen publications in seven different journals regarding the clinical use of tPA, between January 1998 and September 2002.²⁻¹⁴ Nine are based on the US experience, two are from Canada, and three from Germany. (Table 1) The studies vary from the report of one hospital to that of 57 hospitals, including a mix of community and academic hospitals. The number of patients treated with tPA ranges from 30 to 389 in these case series (similar to the 312 patients treated in the efficacy trials), and the treatment of between 1.8 and 47% of eligible patients. As was seen in the NINDS efficacy trials, which included patients with a mean age of 68 years, the mean age of patients treated in these clinical reports was between 63 and 71 years old. (Table 2) The median NIHSS scores seen in these phase IV studies ranged from 10-15, which is similar to the median NIHSS scores in the NINDS efficacy trials, which was 14. Although the median time to therapy was not stated in the NINDS efficacy trials, the median time to treatment in the seven reports that reported this statistic ranged from two hours and six minutes to two hours and forty-five

minutes. These data suggest that in the subsequent reports, although the mean age and stroke severity was comparable to that in the NINDS efficacy trials, the median time to tPA therapy was greater in clinical use than in the well controlled efficacy trials.

The NINDS clinical trials reported a favorable clinical outcome in 31-54% of patients. (Table 3) Although it is difficult in the subsequent reports to determine parity in the determination of this outcome measure, the reports suggest a favorable outcome in 30 to 95% of patients. The overall mortality rate observed at three months in the NINDS clinical trials was 17%. In the subsequent reports, mortality, measured at a time period ranging from hospital discharge to five months, was 5.3 to 25%. The overall ICH rate was 10.9% in the NINDS efficacy trials, and ranged from 8 to 31% in the later published clinical reports. The symptomatic ICH rate was 6.4% in the NINDS trials, and 2.7 to 15.7% in the subsequent reports. This outcome data suggests that both the safety and efficacy of tPA in clinical use is similar to that seen in the efficacy trials. The most important observation from the clinical use trials is the occurrence of symptomatic ICH in 10.8 and 15.7% of patients in two of the subsequent reports.^{6,8} These studies did not, however, report significantly higher mortality rates than were seen in the other phase IV studies, suggesting, as did the NINDS studies, that ischemic stroke itself carries with it a significant risk of death.

Eight of the thirteen clinical reports also reported the overall frequency with which protocol deviations occurred, ranging from 1.3 to 67% of patients treated with tPA. Between 0 and 18.9% of patients were treated outside of the three hour window in ten of the reports, and anticoagulant use was reported in 2.2 to 37% of patients in five of the clinical tPA use reports. Other protocol deviations included inadequate blood pressure control in 3 to 79% of cases (four studies) and two studies reported that 1.5 and 4% of patients had a baseline coagulopathy prior to infusion. CT findings suggestive of a stroke larger than one third of the distribution of the middle cerebral artery distribution (precluding tPA infusion) was seen in 2 to 15% of patients (four studies), and two studies reported cerebral edema in 2 to 10% of patients (comparable to the 3-5% rate seen in the NINDS efficacy trials). These data suggest that there are clear areas for improvement in the adherence to the strict tPA protocol, which generated efficacy in the NINDS clinical trials.

Clinical Considerations: The Clinical Use of tPA in Acute Ischemic Stroke

The NINDS efficacy trials showed that tPA can be used to improve outcome in acute ischemic stroke patients if a rigid treatment protocol is followed. The subsequently published reports of a series of patients treated with tPA suggest that, despite its narrow therapeutic window, patients can be managed effectively with this therapy outside of the rigid guidelines that controlled its use in the NINDS efficacy trials. The recently published article by Lewandowski and Barsan stresses the need to closely adhere to the NINDS studies inclusion and exclusion criteria when giving tPA, a recommendation that highlights the relatively narrow therapeutic window of tPA use in acute ischemic stroke.¹⁷ This review article states that the most difficult aspect of tPA use is the ability to determine that symptom onset occurred less than three hours prior to the time of tPA infusion onset. This article also states that the clinical experience with tPA is favorable when considering all of the published phase IV studies, and reiterates the need to not deviate from established guidelines and to not treat patients with CT findings suggestive

of an acute CVA. Although this article states that only eight patients need to be treated in order to return one patient to full function, the clinical experience with tPA as seen in the subsequently published cases series suggests that significant complications can occur, often as a result of protocol violations that occur in general clinical use. As such, the number of patients needed to treat in order to achieve full recovery in one patient may actually be higher in clinical practice than is suggested by the NINDS data itself.

Conclusions

1. Although tPA is effective in improving long-term outcome in ischemic stroke, the complications associated with its use, especially symptomatic ICH, are significant.
2. There is a relatively narrow therapeutic window, such that informed consent should be considered prior to the use of tPA in ischemic stroke.
3. A limited number of stroke patients are treated with tPA in clinical practice.
4. Outcomes similar to those seen in the NINDS clinical trials can be duplicated in practice.
5. A checklist of exclusion criteria should be used prior to tPA use in ischemic stroke.
6. Blood pressure should be maintained below 185/110 mm Hg.
7. Protocol violations occur frequently in clinical practice, often leading to higher ICH rates.
8. Most patients are treated late in the three-hour window, and many are treated outside of this critical time frame in error. Patients should be encouraged to present themselves to the Emergency Department soon after the onset of stroke symptoms.
9. CT abnormalities that suggest a large infarct or cerebral edema should increase the likelihood that tPA use be deferred because of a higher risk of hemorrhagic complications.
10. Measures should be instituted to prevent anticoagulant use during the 24 hours after tPA use.
11. Education that standardizes the clinical use of tPA across institutions should be provided.
12. Documentation should explicitly address the relevant issues in the use of tPA in stroke, including what information is provided to the patient or family members prior to obtaining informed consent and/or the administration of the drug.
13. Further research should verify that the guidelines established by the NINDS efficacy trials are, indeed, being followed in the clinical setting of acute ischemic stroke.

Table 1. Institutional and Patient Data from the Case Series of tPA in Ischemic Stroke.

Author	Journal	Date	Location	# Hospitals	# Eligible Patients	# Patients Receiving tPA, (%)	Hospital Type
NINDS	NEJM	12/95	US	8		312	8 Academic
Chiu	Stroke	1/98	US	3	1035	30 (2.9%)	1 Academic 2 Community
Grond	Stroke	8/98	Germany	1	453	100 (22%)	1 Academic
Smith	AEM	6/99	US	4		37	1 Academic 3 Community
Tanne	Neurology	7/99	US	13		189	5 Academic 8 Community
Wang	Stroke	1/00	US	20	900	57 (6.3%)	
Buchan	Neurology	2/00	Canada	1	1540	68 (4.4%)	1 Academic
Albers	JAMA	3/00	US	57		389	24 Academic 33 Community
Katzan	JAMA	3/00	US	29	3948	70 (1.8%)	
Koennecke	Stroke	5/00	Germany	1	161	75 (47%)	1 Academic
Chapman	Stroke	12/00	Canada	1	2556	46 (1.8%)	1 Academic
Grotta	Arch Neurology	12/01	US	4	1689	269 (16%)	1 Academic 3 Community
Schmulling	Stroke	4/00	Germany	1		150	1 Academic
Bravata	Arch Intern Med	9/02	US	16		63	16 Community
Totals	7	5	3	151	12,282	928 (5.8%)	37 Academic 65 Community

Table 2. Patient Profile and Outcome Data from the Case Series of tPA in Ischemic Stroke.

Author	Mean Age	Median Time to Rx	Median NIHSS Score	Favorable Outcome	% ICH	% Symptomatic ICH	% Mortality
NINDS	68 y		14	31-54%	10.9%	6.4%	17% (3 month)
Chiu		2' 37"	14	63%	10%	6.6%	23% (5 month)
Grond	67 y	2' 6"	12	53%	11%	5%	12%
Smith	63 y	2' 44"	> 10	58.1%		10.8%	5.4%
Tanne	65 y	> 2'	11-15		9%	5.8%	10% (in hospital)
Wang	71 y	2' 28"	15	44-54%	9%	5%	9%
Buchan	68 y		15	95%	31%	9%	16.1% (3 month)
Albers	69 y	2' 44"	13	35-43%	11.5%	3.3%	13% (30 day)
Katzan	69 y		12		22%	15.7%	15.7% (in hospital)
Koennecke	68 y	2' 24" (mean)	13	70%	8%	2.7%	15% (in hospital)
Chapman	67 y	2' 45"	14	30-48%	9%	2.2%	22% (in hospital)
Grotta	68 y	2' 17"	14	33%		4.5%	15% (in hospital)
Schmulling	63 y	3'?	11	41%	?	?	4% (3 month)
Bravata	71 y		15		17%	6%	25% (in hospital)
Totals	63 – 71 y	2' 6" – 2' 45"	10 – 15	33 – 95%	9.6%	5.2%	13.5%

Table 3. Protocol Deviation Data from the Case Series of tPA Use in Ischemic Stroke.

Author	Favorable Outcome	% Protocol Deviation	Time >3Hrs	Anticoags Given	BP Not Controlled	Baseline Coagulopathy	CT Pos/ Large Stroke	Edema / Mass Effect
NINDS	31-54%		0%					3-5%
Chiu	63%							
Grond	53%		2%					
Smith	58.1%		18.9%					
Tanne		30%	8%	15%	3%	4%		
Wang	44-54%		9%					
Buchan	95%	16%	1.5%			1.5%	6%	
Albers	35-43%	32.6%	13.4%	9.3%	6.7%		2%	2-6%
Katzan		50%	13%	37%	7%			
Koennecke	70%		17.3%				15%	
Chapman	30-48%	17.4%	10.9%	2.2%			6.5%	
Grotta	33%	13%	0%					
Schmulling	41%	1.33%	1.33%					
Bravata		67%		10%	79%			10%
Totals		13 – 67%	0 – 18.9%					

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;333:1581-1587.
2. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA: Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA* 2000.*Mar.1.;283.(9.):1145.-50.* 283:1145-1150.
3. Buchan AM, Barber PA, Newcommon N, et al: Effectiveness of t-PA in acute ischemic stroke: outcome relates to appropriateness. *Neurology* 2000.*Feb.8.;54.(3.):679.-84.* 54:679-684.
4. Chapman KM, Woolfenden AR, Graeb D, et al: Intravenous tissue plasminogen activator for acute ischemic stroke: A Canadian hospital's experience. *Stroke* 2000.*Dec.;31.(12.):2920.-4.* 31:2920-2924.
5. Chiu D, Krieger D, Villar-Cordova C, et al: Intravenous tissue plasminogen activator for acute ischemic stroke: feasibility, safety, and efficacy in the first year of clinical practice. *Stroke* 1998;29:18-22.
6. Grond M, Stenzel C, Schmulling S, et al: Early intravenous thrombolysis for acute ischemic stroke in a community-based approach. *Stroke* 1998;29:1544-1549.
7. Grotta JC, Burgin WS, El-Mitwalli A, et al: Intravenous tissue-type plasminogen activator therapy for ischemic stroke: Houston experience 1996 to 2000. *Arch Neurol* 2001.*Dec.;58.(12.):2009.-13.* 58:2009-2013.
8. Katzan IL, Furlan AJ, Lloyd LE, et al: Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA* 2000.*Mar.1.;283.(9.):1151.-8.* 283:1151-1158.
9. Koennecke HC, Nohr R, Leistner S, Marx P: Intravenous tPA for ischemic stroke team performance over time, safety, and efficacy in a single-center, 2-year experience. *Stroke* 2001.*May.;32.(5.):1074.-8.* 32:1074-1078.
10. Smith RW, Scott PA, Grant RJ, Chudnofsky CR, Frederiksen SM: Emergency physician treatment of acute stroke with recombinant tissue plasminogen activator: a retrospective analysis. *Acad Emerg Med JID - 9418450* 1999;6:618-625.
11. Tanne D, Bates VE, Verro P, et al: Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: a multicenter survey. The t-PA Stroke Survey Group. *Neurology* 1999;53:424-427.
12. Wang DZ, Rose JA, Honings DS, Garwacki DJ, Milbrandt JC: Treating acute stroke patients with intravenous tPA. The OSF stroke network experience. *Stroke* 2000.*Jan.;31.(1.):77.-81.* 31:77-81.

13. Schmulling S, Grond M, Rudolf J, Heiss WD. One-year follow-Up in acute stroke patients treated with rtPA in clinical routine. *Stroke*. 2000 Jul;31(7):1552-4.
14. Bravata DM, Kim N, Concato J, Krumholz HM, Brass LM. Thrombolysis for acute stroke in routine clinical practice. *Arch Intern Med*. 2002 Sep 23;162(17):1994-2001.
15. Clark WM, Albers GW, Madden KP, Hamilton S: The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g) : results of a double-blind, placebo-controlled, multicenter study. Thrombolytic therapy in acute ischemic stroke study investigators. *Stroke* 2000.Apr.;31.(4.):811.-6. 31:811-816.
16. Brott T, Lu M, Kothari R, et al: Hypertension and its treatment in the NINDS rt-PA Stroke Trial. *Stroke JID - 0235266* 1998;29:1504-1509.
17. Lewandowski C, Barsan W: Treatment of acute ischemic stroke. *Ann Emerg Med JID - 8002646* 2001;37:202-216.

Patient Outcome

The patient's CT scan of the head showed no low-density areas or ICH. There were no clear contraindications for the use of tPA. The NIHSS score was approximately 20. Consultation with a neurologist cleared the use of tPA. No family was present to defer the use of tPA and tPA was administered without complication. The administration of tPA occurred at approximately 8:20 PM, about 1 hour and 45 minutes after the onset of the stroke symptoms. An initial bolus of 5 mg was given slow IV push over two minutes, followed by an infusion of 40 mg over 1 hour.

Upon re-exam at 90 minutes, the patient had some increased speech and the use of her right arm, and the amount of mouth droop and visual neglect was decreased. The repeat NIHSS score at that time was approximately 14-16. In the hospital, the patient had no ICH and had improved neurologic function. At disposition from the hospital, the patient went to a rehabilitation hospital. At the time of hospital discharge, the patient had near complete use of her right upper extremities, speech and vision were improved and there was some residual gait difficulties based on right lower extremity weakness.

Annotated Bibliography

1. NINDS Study. *N Engl J Med* 1995; 333:1581-1587

This is the landmark studies that examined the effectiveness of tPA in acute ischemic stroke. Patients who received tPA within 180 minutes of symptom onset had a better three month outcome than did those treated with standard therapy. Symptomatic ICH at 36 hours was 10x greater in patients treated with tPA (6.4 vs. 0.6%). Mortality was similar at three months. This article is a must read for all EM physicians.

2. ECASS Study. *JAMA* 1995; 274:1017-1025

This is the landmark European study that also examined the effectiveness of tPA in acute ischemic stroke. As with the NINDS studies, there was improved 90 day outcome in patients treated with tPA. Although the mortality and cerebral hemorrhage rates were similar in the two groups, there was a larger number of large parenchymal bleeds in the tPA group. The authors state that there is significant difficulty in selecting patients who are eligible for this therapy, despite its apparent effectiveness.

3. Haley. *Ann Emerg Med* 1997; 30:675-682

This is another evidence-based medicine article that addresses 10 important questions from the NINDS studies. The article does a good job of answering the most important questions from the study, and is a must if doing a journal club on tPA and ischemic stroke.

4. Wyer. *Ann Emerg Med* 1997; 30:629-638

This article methodically reviews the ECASS and NINDS and critically addresses how the data impacts our clinical decision-making regarding the use of tPA in ischemic stroke. This article addresses some of the difficult questions about CT interpretation and how the presence of an “early infarct” signs impacts our decision to use tPA.

5. Brott. *Stroke* 1998; 29:1504-1509

This is a post-hoc analysis of the NINDS studies, looking at the use of anti-hypertensive therapy and outcome when tPA is given. The study showed that patients who received tPA and then required anti-hypertensive therapy did worse than those who received tPA and did not require any anti-hypertensive therapy. This finding was not seen in the placebo group, leading to the conclusion that combined anti-hypertensive therapy and tPA therapy is perhaps sub-optimal. It was noted, however, that the use of anti-hypertensive therapy was not randomized, and that selection bias could have caused this result.

6. Osborn. *Ann Emerg Med* 1999; 34: 244-255

This review article looks at all of the thrombolytic therapy studies for stroke. It confirms that streptokinase is not useful because of increased mortality in treated patients. It also again reiterates the need for strict adherence to the NINDS protocol, since any deviation could lead to a shift in the risk/benefit profile in favor of standard therapy without tPA.

7. ATLANTIS Study. *JAMA* 1999; 282: 2019-2026

This study attempted to increase the therapeutic window time from 3 to 5 hours. The results suggest that when given during this longer window, 90 day efficacy was not improved with tPA use. Also, the intra-cerebral hemorrhage and mortality rates were higher when tPA was given outside of the 3 hour window. The results again confirm the need to strictly adhere to the NINDS protocol in order to maximize benefit and minimize risk

8. Katzan. *JAMA* 2000; 283:1151-1158

This is a one year study of tPA use in acute ischemic stroke in Cleveland, OH. It provides a good look at tPA use. Only 1.8% of eligible patients received tPA. 50% of the treated patients involved some type of national treatment guideline deviation. Of all treated patients, 16% had a symptomatic hemorrhage, and the in-hospital mortality was 3x higher with tPA use (16 vs. 5%). The authors conclude that the Cleveland experience is different than that reported in the clinical trials.

9. STARS Study. *JAMA* 2000; 283: 1145-1150

This study was a prospective, multi-centered study of tPA use in acute ischemic stroke from 57 hospitals over almost two years. The study showed a favorable 30-day mortality rate (13%), and 35% of patients had a good neurologic outcome. The article suggests that specific patients might do better with tPA use, including patients with less severe neurologic findings, the absence of CT findings, age < 85 years, and a lower mean arterial pressure at the time of treatment.

10. Lewandowski. *Ann Emerg Med* 2001; 37:202-216

This article presents a state-of-the-art review of stroke care in the Emergency Department. It addresses the pathophysiology of stroke, reviews the clinical trials to date, and provides the principles of emergency management. This is an excellent review article which supplements the data provided in this discussion of the clinical use of tPA in ischemic stroke.

Questions

- 1. All are true statements about the findings of the NINDS trial except:**
 - a. tPA therapy was provided within 3 hours of symptom onset
 - b. At 24 hours, there was no neurologic benefit to the use of tPA (vs. placebo).
 - c. At 90 days, tPA-treated patients were 30% more likely to have a good neurologic outcome.
 - d. Symptomatic intracerebral hemorrhage at 36 hours was 10x higher in tPA-treated patients..
 - e. At 90 days, mortality in tPA-treated patients was 2x higher.

- 2. In the NINDS trial all of the following patients were eligible for tPA therapy except:**
 - a. CT scan negative for intracerebral hemorrhage
 - b. Patients with a rapidly improving deficit or minor symptoms.
 - c. A measurable deficit using the NIH stroke scale.
 - d. No history of stroke or traumatic brain injury within three months..
 - e. SBP lower than 185 mm Hg and DBP lower than 110 mm Hg.

- 3. All of the following are true of the eleven published case series of tPA in ischemic stroke except:**
 - a. Stroke severity, as measured by the NIHSS, was comparable to the NINDS trial.
 - b. In most of the case series, only a small percentage of stroke patients were treated with tPA.
 - c. In most of the case series, the majority of patients were treated at least two hours after symptom onset.
 - d. The neurologic outcomes observed in these case series varied greatly from the NINDS trial.
 - e. The mortality results in these case series did not differ significantly from the NINDS trial.

- 4. The most common protocol deviations from the NINDS clinical trial seen in the eleven published case series included all of the following except:**
 - a. Treatment outside of the three-hour window (from symptom onset).
 - b. Anticoagulant use within 24 hours of infusion.
 - c. Inadequate blood pressure control.
 - d. The presence of CT findings that would preclude tPA infusion.
 - e. Infusion of patients too old to receive tPA.

- 5. Even though tPA has been shown to be effective in the NINDS clinical trial, some case series have shown different safety and outcome results. This can occur for all of the following reasons except:**
 - a. Patient selection may differ in clinical practice.
 - b. The administration of the drug may differ in clinical practice.
 - c. The drug works differently in clinical practice.
 - d. The provision of the other therapies may differ in clinical practice.
 - e. The measurement of the outcomes may differ in clinical practice.

Answers

1. Answer e.

Despite a higher rate of intra-cerebral hemorrhage, tPA therapy was not associated with a higher mortality rate.

2. Answer b.

Patients with rapidly improving symptoms or minor initial symptoms were not included in this trial, and should not be considered for thrombolytic therapy.

3. Answer d.

The neurologic outcomes in the published case series did not differ significantly from the results of the NINDS trial.

4. Answer e.

There was no age cutoff in the NINDS efficacy trial. Therefore, this is not a protocol deviation in clinical practice.

5. Answer c.

Therapies such as tPA should not work differently in clinical practice than in an efficacy trial.