

Review of Tissue Plasminogen Activator, Ischemic Stroke, and Potential Legal Issues

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The use of tissue plasminogen activator in ischemic stroke is controversial. Many practicing physicians believe that its usefulness is established, while others, including professional specialty societies, are less sanguine. A review of the literature appears to show that the use of tissue plasminogen activator is efficacious and can result in highly improved outcomes for a majority of eligible patients. These findings may implicate important potential legal issues. Informed consent concerns and, potentially, medical malpractice claims may result, particularly in the context of evidence-based practice, pay for performance, and the currently limited use of tissue plasminogen activator for eligible patients.

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The use of tissue plasminogen activator (tPA) in ischemic stroke is considered controversial. From one perspective, although widely considered a proven and effective therapy by neurologists and other physicians,¹ only a small percentage of eligible patients receive the drug.^{2,3} From another, in a recent survey of emergency department physicians, tPA use for patients with ischemic stroke was resisted and not believed to be appropriate because of the risk of adverse events associated with its use and lack of sufficient efficacy.⁴ Furthermore, educational practice guidelines from the American Academy of Emergency Medicine⁵ appear to misinterpret the effectiveness and potential for symptomatic intracerebral hemorrhage with tPA use in stroke.⁶

The challenges of appropriate treatment of stroke with tPA have tremendous clinical implications. With the graying population, appropriate treatment is essential to ensure that current and fu-

ture patients have the greatest chance of quality of life and reduced mortality.

Appropriate tPA use also has important legal implications. With increased numbers of patients presenting with stroke, there is a concomitant need for physicians to understand their obligations to provide accurate information on tPA's risks and benefits as an informed consent matter. Furthermore, tPA use raises malpractice concerns if not provided in the appropriate circumstances, a particularly important consideration because of the current limited use of tPA for eligible patients.

There is much physician interest in the medicolegal aspects of stroke and tPA use in the practice literature.⁷⁻¹⁰ Scott, in a preliminary analysis of data relating to barriers associated with tPA use, found that, in all 12 randomly selected study hospitals, medicolegal issues were reported as a barrier (Phillip Scott, MD, e-mail, November 8, 2007). In addition, a recent empirical study of trial court cases involving tPA and ischemic stroke found that the typical case involved emergency physicians, with roughly 20% of these cases also involving neurologists as defendants, and that the primary claim relevant to tPA use was the failure to provide tPA, rather than adverse events associated with its use.^{11,12}

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	Modified Rankin Scale Score			
	0 and 1	2 and 3	4 and 5	6
Placebo	26	25	27	21
tPA	39	21	23	17
	% of Patients			

Figure 1. Results of the National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator (rt-PA) Acute Stroke Trial. For the modified Rankin Scale, a score of 0 indicates entirely normal and a score of 6 indicates death. Because of rounding, percentages may not total 100. Reproduced from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group¹³ with permission from the Massachusetts Medical Society.

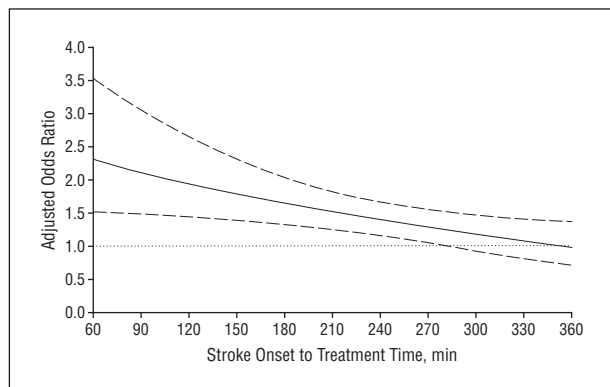


Figure 2. Pooled data analysis of all placebo-controlled trials. Solid line represents odds ratio (OR) estimated by model; dashed lines, 95% confidence interval for estimated OR; dotted horizontal line, OR of 1 (no difference between treatment and control). Reproduced from Hacke et al¹⁵ with permission from Elsevier.

Therefore, understanding the appropriate use of tPA in ischemic stroke is critical as a clinical matter that also implicates legal issues. In this report, we review the literature on tPA use in ischemic stroke as well as consider possible legal issues associated with tPA in stroke treatment.

tPA AND STROKE: EVIDENCE OF EFFECTIVENESS

Previous Assessments

The use of tPA in stroke has been widely assessed. **Figure 1** shows an essential portion of the results of the pivotal National Institute of Neurological Disorders and Stroke (NINDS) recombinant tPA (rt-PA) Acute Stroke Trial.¹³ In this figure, the modified Rankin Scale (mRS) score is shown. Three other clinical rating scales were also used and showed approximately the same results, so only the mRS findings are presented. The mRS is a simple scale in which patients are assigned 1 of 7 possible ordinal ratings. They range from entirely normal (0), through varying degrees of abnormality to death (6). The graph shows that 26% of placebo-treated patients attained a 0 or 1 rating (normal or minor neurologic abnormalities not apparent to patients) 3 months after stroke onset. That number of excellent outcomes was increased to 39% with tPA treatment, representing an ab-

solute improvement of 13 percentage points and a relative improvement of 50%.

In 2004, Saver¹⁴ published an independent analysis of the original data from the NINDS rt-PA Trial. He found that “the average estimated [number of patients needed to be treated] for 1 additional patient to have a better outcome by 1 or more grades on the mRS as a result of treatment was 3.1.”^{14(p1066)} In other words, in approximately 32% (absolute) of the patients who were treated with tPA, ratings on the mRS improved by at least 1 point (ie, a change readily detectable by a patient).

Adding these numbers together, the data show that the conditions of 26% of patients return to normal spontaneously while the conditions of an additional 13% return essentially to normal if treated with tPA (see Figure 1). Furthermore, another nearly 19% derive some lesser but clinically meaningful benefit from the tPA treatment. This is seen by noting that 61% of the patients do not completely recover (mRS score >1; Figure 1), so 61% of the 32% (absolute) of patients recover by at least 1 point on the mRS, but not to a score of 1 or less. Hence, the conditions of a total of about 58% of the patients are either normal or improved with tPA. Thus, the conditions of more than 50% of patients who experience an acute stroke and fit the Food and Drug Administration–approved criteria for tPA treatment (the criteria taken directly from the NINDS rt-PA trial) either are normal or are improved 3 months after stroke onset.

With the use of a more rigorous standard of complete or near-total recovery, the potential benefit of tPA is shown in pooled data analysis of all placebo-controlled trials.¹⁵

Figure 2 shows the results of the 5 trials analyzed in aggregate. The adjusted odds ratio indicates the chances that a group of patients will return to normal condition or have minor deficits (mRS score of 0 or 1). The results are somewhat different from those of the NINDS tPA trial because the pooled analysis includes all 2776 patients who were randomized in all the trials. A sizable number were treated within 3 hours after stroke onset in the non-NINDS trials, but most were treated after that time.

About 30% of patients treated with placebo completely recovered (90-day mRS score, 0 or 1) and about 40% treated with placebo had almost completely recovered (90-day mRS score, 0-2). When they were treated with tPA at or before 1.5 hours, the odds ratio was 2.33 or more, indicating that more than half completely recovered (90-day mRS score, 0 or 1). When they were treated at or before 3 hours, the odds ratio was 1.7 or more, indicating that almost two-thirds had almost completely recovered (90-day mRS score, 0-2). It is well established, in the preclinical literature and in other organs, that the sooner an occluded vessel is reopened, the less likely that infarction will occur. Figure 2 shows that this also applies to human stroke victims. Treatment with tPA rapidly after ischemic stroke onset can produce complete recovery more often than not.

In addition, the original data from the NINDS tPA Trial can be used to calculate the fraction of patients helped. The calculation was done in 2 ways. First, the patients were categorized by their National Institutes of Health Stroke Scale (NIHSS) scores. The NIHSS is a simplified neurologic examination scored by adding together re-

sults from 14 aspects of the neurologic findings. On the NIHSS, a score of 0 is normal and 42 is the maximum possible deficit short of death. Because of concern over some protocol-related aspects of the NINDS trial, a neutral entirely independent expert panel was assembled to review the NINDS tPA Trial. Ingall et al¹⁶ reanalyzed the results of the trial and found essentially no differences in conclusions compared with the primary report from the trial.¹³ In conducting that review, they noted the variations in grouping and chose to stratify the patients into subgroups of 5 to 10 points (ie, 0-4, 5-9, 10-14) at the time when they were randomized to receive tPA or placebo.

NINDS Reanalysis

We also reanalyzed the data. Because there were no obvious subject pairs, we formed all possible pairs of subjects with 1 treated subject and 1 placebo subject, decided within each pair whether treatment results were superior to placebo, and report herein the proportion of such pairs for which treatment was superior.

Specifically, we estimated the proportion of patients who improved more with tPA than with placebo. Given that the treatment group had 271 subjects and the placebo group had 256 subjects, we formed all possible pairs from the 2 groups, the first member of the pair from the treatment group and the second member from the placebo group, resulting in $271 \times 256 = 69\,376$ pairs. We then counted the pairs where the treatment had a better result than placebo and divided by 69 376, yielding the proportion of pairs where tPA was superior. This comparison is the explicit logical basis of the Wilcoxon test, and the proportions can be directly calculated from the sums of ranks scores for the Wilcoxon test.

To decide within a pair whether tPA treatment was better or worse than placebo, we first compared the 90-day mRS result for the tPA-treated patient with the 90-day mRS result for the placebo-treated patient. Treatment was better than placebo if the 90-day treatment mRS score was lower than the 90-day placebo score. There were many ties. To break these ties in 90-day mRS scores, we then compared the decrease from baseline to 90 days in the NIHSS score for the tPA-treated patient with the decrease from baseline to 90 days in the NIHSS score for the placebo-treated patient. The larger decrease is the superior result.

We made one further refinement. We first stratified the data according to the objectively chosen strata given by Ingall et al.¹⁶ This controlled for variations in baseline severity of disease in terms of the NIHSS category. We then carried the foregoing procedure separately within each stratum and aggregated the results to obtain the proportion of pairs in which tPA was superior to placebo.

We used the same tPA cohorts shown in the **Table**. It shows the proportions of pairs in which treatment was superior to placebo and the proportion of pairs in which the treatment was inferior to placebo. Following the method of Ingall et al¹⁶ to stratify the data, we carried out the Wilcoxon test procedure to obtain a *P* value.

Overall, the probability that tPA treatment was superior was 57.3%. This percentage significantly exceeds 50% (*P* = .002).

Table. Probabilities That tPA Is Superior and Inferior to Placebo Based on 90-Day Results for the mRS and NIHSS Scales by Baseline Category of NIHSS Score

Baseline NIHSS Category	Range of Baseline Scores	Probability		No. of Subjects in Category
		tPA Superior to Placebo	tPA Inferior to Placebo	
0	0-5	0.53	0.47	58
1	6-10	0.62	0.38	151
2	11-15	0.59	0.41	132
3	16-20	0.54	0.46	146
4	21-25	0.52	0.48	88
5	26-30	0.43	0.57	44
6	31-42	0.53	0.47	8

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

Clinical Perspective

A more clinically meaningful way to look at the data restricts the analysis to patients with a baseline NIHSS score in the range of 5 to 24. This grouping follows the pattern used by the expert review panel of Ingall et al.¹⁶ These patients had high levels of neurologic damage at stroke onset but were not so badly injured that they were essentially moribund. This middle group of patients is the most likely to have a chance to benefit or be injured by therapy. Using the same calculation as for the whole group, we found that 58.6% of the patients who were treated were better than those who were given placebo. This percentage significantly exceeds 50% by the Wilcoxon test (*P* < .001).

Hence, from several ways of examining the data, the majority of patients with acute stroke treated with intravenous tPA will either completely recover or be improved by tPA treatment.

CONCERNS OF HARM WITH tPA

There has been considerable concern that tPA can harm patients. It is true that the percentage of patients who developed symptomatic intracerebral hemorrhages was increased by tPA therapy from 0.6% in placebo-treated patients to 6.4% in tPA-treated patients.¹³ However, these numbers are not nearly as hazardous as they initially may appear.

Saver⁶ analyzed the original data from the NINDS rt-PA Trial independently and states that the trialists

[U]sed an extremely conservative protocol definition of clinical worsening, any deterioration in the patient's neurologic condition, now generally recognized as inaccurate. Under this definition, minor fluctuations in the patient's course . . . were counted as symptomatic. . . . Only increase in examination score by a substantial degree can be taken as evidence of symptomatic decline.^{6(p2281)}

He concludes that the number of treated patients needed to cause 1 bad outcome attributable to tPA therapy is approximately 100, ie, tPA treatment will cause meaningful clinical deterioration in only about 1% of patients. Furthermore, as seen in Figure 1, 21% of the placebo-treated patients died, whereas 17% of the tPA-

treated patients died within 3 months after randomization. This is not a significant difference; hence, no change in the number of deaths is attributable to tPA therapy. There was also no increase in the net number of bad outcomes (mRS score ≥ 3 , including death [score of 6]) in the subjects of all other placebo-controlled tPA trials, with treatment windows of as much as 6 hours.¹⁷⁻¹⁹

Finally, Demaerschalk¹ used data analyzed by Saver to calculate the “likelihood of being helped vs harmed” ratio. He showed that patients were at least 10 times more likely to be helped than harmed with tPA for acute stroke therapy.

POTENTIAL LEGAL ISSUES

In ischemic stroke, the evidence that tPA use under appropriate circumstances is the standard, effective treatment is consistent with other findings.¹ In light of recent work that identifies that litigation involving tPA and ischemic stroke revolves around failure to treat with tPA,¹¹ physicians must understand the relevant risks and benefits of tPA, as well as the standard of care. These issues are generally governed by individual state tort laws; however, most are thematically consistent across jurisdictions under the rule of negligence.

The Rule of Negligence

Informed consent and medical malpractice are judged under the tort rule of negligence. The rule requires that a plaintiff show a duty owed to the plaintiff and a breach of that duty that legally causes some injury or harm to the plaintiff.²⁰ In medical care, the plaintiff, usually a patient, must show a duty on the part of the physician and a breach of that duty that legally caused (ie, caused in fact in a foreseeable manner) the patient damage or harm. All factors in this action must be shown by the preponderance of the evidence standard, ie, it is more likely than not.²¹

Informed Consent

Informed consent is the process by which a physician communicates and discusses material risks and benefits associated with proposed diagnostic and treatment alternatives, including doing nothing, in a manner the patient can understand.²¹ Physicians have a duty to provide relevant, material information to allow the patient to provide informed consent for a particular treatment. If the physician does not provide this information, he or she has breached the duty. If that breach legally causes the patient injury or harm, the physician may be liable for tort damages.^{21,22}

In the case of tPA treatment for ischemic stroke, informed consent is of critical concern. Patients presenting to the emergency department with stroke must be provided with accurate and appropriate information regarding the risks and benefits of tPA use so that they may make an informed decision regarding treatment alternatives. However, a physician relying only on American Academy of Emergency Medicine educational guidelines⁵ would arguably not be providing the correct tPA risk vs benefit information. By using these materials, rather than

Saver's work,⁶ pooled data, and/or other information, physicians who counsel patients may be communicating incorrect, elevated purported risks and discounted benefits associated with tPA use. Hence, they have not provided the relevant, material information for the patient to make an informed decision. If this eventuality occurs and causes the patient injury—a likely circumstance because the patient will not obtain the benefits of the drug otherwise—physicians may be subject to damages associated with a lack of informed consent.

Damages could be high. Assuming the patient refused or was not given the opportunity to be treated with tPA because of incomplete and/or inaccurate information provided by the treating physician, damages would be measured by assessing the loss from the level of function the patient would have had if tPA had been given compared with that which the patient experienced in the absence of it. In this case, it would mean that the damages for the eligible patient not given tPA would be the status he or she would have obtained with it—potentially being virtually normal or substantially improved as reviewed in the previous section—compared with his or her functional and health status without the drug. This difference could be extremely large given the documented benefits of tPA.

Hence, it is critical that up-to-date, accurate information be provided to allow “patients, family members, [and] physicians . . . to more sensibly compare the benefits and harm conferred by [tPA] therapy.”^{9(p 2216)} Informed consent discussions should encompass accurate information on tPA and its relative benefits and risks.

Medical Malpractice

Physicians are required to provide that level of care and skill that a member of the profession in good standing would provide under similar clinical circumstances.²⁰ Under the negligence rule, physicians have a duty to provide nonnegligent care, ie, care provided by a physician in good standing, also known as the *standard of care*. If the physician does not provide that level of care, and this event legally causes the patient injury or damages, the physician is liable for damages incurred by the patient.²⁰ As with informed consent, all factors must also be shown by a preponderance of the evidence generally with expert testimony by those who have established knowledge of the standard of care.^{23,24}

Many eligible patients currently do not receive tPA.^{2,3} Under the legal standard, it is possible that, despite clinical evidence showing tPA benefits, physician liability may be avoided simply because most in the profession do not give the drug.

However, this result may not continue in the future. First, data showing the clinical benefits associated with tPA use in ischemic stroke continue to increase. In this context, courts may hold that what at one time might have been “experimental” and high risk can become accepted, then standard, and then the criterion standard of care, assuming efficacy and tolerable side effects/risks of injury and resulting morbidity or mortality. For example, in this context, the Washington State Supreme Court held that compliance with a professional standard for ophthalmology would not insulate a physician from liability when a simple, routine test would

have spared a patient harm from glaucoma that went undetected and untreated.²⁵ Similarly, a California appellate court remarked that a medical custom may be negligent.²⁶

In addition, financial forces may create pressure to engage this technology. For example, the push toward evidence-based medicine and public and private insurer pay-for-performance, particularly using reimbursement mechanisms, may create expectations that will drive medical practice and the standard of care to assess all available information on tPA and create mandates for its use that avoid preventable harm.^{27,28}

If any of these eventualities occur, providers should expect an increased amount of malpractice litigation. It has been estimated that only 3% to 8.5% of potentially eligible patients receive tPA,² and less than 2% of community hospitals use it.³ Hence, there is significant room for malpractice claims and, similar to informed consent, damages may be high because of the measure of neurologic function with tPA compared with that without it.

In addition, further derivative actions from negligence causes of action may result, including patient and family loss of consortium, loss of society, and other causes of action based on the injury claimed in the malpractice action.²⁹ Furthermore, negligence actions can drive other novel liability claims, including negligent infliction of emotional distress, fear of future injury,²⁹ and other claims such as failure to refer.²⁰ As the number of claims for failure to provide tPA increases,¹¹ these additional injury claims may become more common.

In conclusion, the use of tPA for ischemic stroke is an effective treatment that has been widely accepted. Yet, with the limited number of eligible patients receiving the drug, many patients are not obtaining its clinical benefits. These results implicate potential legal liability issues for treating physicians. Informed consent and medical malpractice actions under the negligence rule are of concern. These clinical and legal issues are likely to increase as the population continues to age and the presentation of stroke becomes more common.

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