Tissue plasminogen activator and patients with acute ischemic stroke: The litigation landscape

Latha Ganti MD, MBA1,2,5 | Bryan Kwon3 | Andrew George3
Thor Stead ScB4 | Cherian Plamoottil DO1,2 | Paul Banerjee DO1,2,5

1 Department of Clinical Sciences, University of Central Florida College of Medicine, Orlando, Florida, USA
2 Department of Emergency Medicine, Emvision Physician Services, Plantation, Florida, USA
3 Division of Biology and Medicine, Brown University, Providence, Rhode Island, USA
4 Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA
5 Polk County Fire Rescue, Bartow, Florida, USA

Correspondence
Latha Ganti, MD, MBA, Department of Clinical Sciences, University of Central Florida College of Medicine, 6850 Lake Nona Blvd, Orlando, FL 32827, USA.
Email: latha.ganti@ucf.edu

Prior presentation: American College of Emergency Physicians Research Forum, October 2021, Boston, MA.

Funding and support: By JACEP Open policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Abstract
Objective: Tissue plasminogen activator (tPA) is considered standard of care for acute ischemic stroke treatment, but some physicians withhold or delay this highly time-dependent therapy from stroke patients because they do not think it works well or they are worried about the adverse effects or fear medicolegal consequences. The authors sought to investigate whether litigation arises from physicians treating versus not treating acute ischemic stroke patients with tPA.

Methods: The authors examined closed cases from 1996 to 2020 in an online legal database, Westlaw, regarding alleged complaints for whether or not thrombolytic treatment was given for acute stroke.

Results: Sixty-six relevant cases were identified. In all 66 cases, the plaintiffs sued for issues stemming from either failure to give tPA or a delay in giving tPA. In 77% of cases the verdict was in favor of the defendant. Only 1 lawsuit included intracerebral hemorrhage after tPA, but it was brought forth owing to delay in giving tPA; the verdict was in favor of the defendant.

Conclusion: It is more common for patients to sue physicians for not administering tPA in a timely fashion or at any point. Medicolegal risks of withholding or delaying tPA are clear, whereas we found no clear medicolegal risk to providing tPA when indicated.

KEYWORDS
acute ischemic stroke, emergency medicine, litigation, tissue plasminogen activator

INTRODUCTION

1.1 Background and importance

Tissue plasminogen activator, also known as tPA, was approved to be used for acute ischemic stroke in the United States in 1996, and it was revered as a revolutionary advancement for treatment of ischemic stroke.1 However, even 25 years later, this drug is the focus of a controversial debate between advocates who urge for liberal and widespread tPA use and emergency physicians who must decide whether the risks of giving this drug justify offering the treatment at all.2–4 This reluctance exists despite American Stroke Association (ASA) guidelines that consider tPA within 4.5 hours of symptom onset for eligible patients to be standard of care.5 The most feared
complication of tPA is the risk of intracerebral hemorrhage. Most cases that involve tPA and acute stroke encompass emergency physicians. Emergency physicians fear causing harm to patients, and fear litigation.6

1.2 | Objective

We sought to determine whether stroke and tPA litigation was indeed because of potential complications of tPA use or the failure or delay to give it in the first place as we hypothesized. Patients who perceive that they have suffered pain or affliction owing to negligence, lack of responsibility, or indecision on the practicing physician’s part are able to file malpractice claims that can trend upwards of millions of dollars.

2 | METHODS

2.1 | Data source

We compiled our case data set from the online legal research database, Westlaw. Westlaw is a proprietary database that can be searched online and contains more 40,000 records of case law, state and federal statutes, administrative codes, newspaper and magazine articles, public records, as well as law journals, law reviews, treatises, legal forms, and other information resources. Most legal documents on Westlaw are indexed to the West Key Number System, which is West’s master classification system of US law. Attorneys for each case generally delineate a synopsis, judgment materials, statement of facts, the parties involved, the date of adjudication, state, and the judge’s ruling for each hearing.

2.2 | Search strategy

The a priori search criteria included the following case definition: adults aged 18 years and older who suffered an acute stroke for which where there was an allegation of medical malpractice. The search was conducted within “jury verdicts and settlements,” encompassing all federal and state cases. Within these parameters, the terms “stroke” AND “medical malpractice” were searched. These results were then narrowed down to the terms “tissue plasminogen activator” OR “tPA” OR “alteplase.” The search time frame spanned the years 1996–2021, given that tPA was approved in 1996. Stroke cases not related to tPA, including complications with social security plans, disability plans, the legitimacy of the pharmaceutical itself, intraarterial tPA, and thrombolytic therapy for myocardial infarction or pulmonary embolism were excluded.

In order to make sure lawsuits for complications related to tPA were captured, the search was redone using “tPA” OR “tissue plasminogen activator” AND “medical malpractice.”

2.3 | Measures

Information abstracted from Westlaw included case name, year, alleged complaint, sex and age of plaintiff, US state, who won—plaintiff or defendant, outcome of case, and amount of award if specified.

2.4 | Data analysis

Abstracted data were entered into a spreadsheet. Statistical analyses were performed in JMP 14.0 for the Mac. This study was considered exempt by our institutional review board. HCA Centralized Algorithms for Research Rules on IRB [Institutional Review Board] Exemptions (CARRIE)/IRB manager issued exemption 2021–206.

3 | RESULTS

Results from the search are summarized in Figure 1. A total of 66 cases related to tPA treatment for patients with acute ischemic stroke were retrieved from the Westlaw database over the last 25 years. The percentage of total cases during each year ranged from 2% to 15%, with year 2016 having the highest percentage (15%). There was otherwise no temporal trend. Of the cases, 58% were male and 42% were female. The median age was 53 years, with an interquartile range of 44–68 years and a range of 26–102 years. Cases took place in 23 states, with New York State having the highest number (14), followed by California (9) and Florida (6) [Figure 2].

In all 66 cases, the plaintiff claimed that the physician failed to offer or treat the patient with tPA and, of those cases, 15 were a result of a failure to diagnose the stroke, and three were a result of the hospital or physician violating the Emergency Medical Treatment and Labor Act. There was 1 case of intracerebral hemorrhage related to tPA administration after stroke; but even in this case, the allegation was brought owing to delay in giving the tPA, which allegedly led to the subsequent bleed, rather than the occurrence of the bleed itself.

Judgment was rendered in favor of the defendant in 77% of cases. In the 23% of cases where the verdict was in favor of the plaintiff,
awards ranged from $421,500 to $5.2 million, with a median award of $2.5 million.

In terms of defendants, 38% (N = 25) involved the emergency physician, 24% (N = 16) involved the hospital, 23% (N = 15) involved the internist, 18% (N = 12) involved the neurologist, 2% (N = 1) involved nurses, 2% (N = 1) involved physician assistants, and 2% (N = 1) involved the radiologist. Four percent of the cases did not clearly specify each defendant involved.

4 | LIMITATIONS

An important limitation of this study is the uncertain representativeness of the Westlaw database relative to all US lawsuits. Given that Westlaw is a proprietary database, it is not clear as to how cases get included and what proportion of cases one would expect to be included. Also, other databases, such as LexisNexis, VerdictSearch, and BloombergLaw, were not accessed, and some relevant cases may have been missed.

5 | DISCUSSION

Our study supports the premise that tPA administration should not be withheld or delayed on account of fear of litigation. One hundred percent of cases in our investigation were brought from a failure to treat with tPA or a delay in tPA treatment. Even in the one case that involved a complication (intracerebral hemorrhage [ICH]) of tPA administration, this was brought forward owing to delay in giving tPA, which then allegedly resulted in the ICH. This single case was ruled in favor of the defendant. Despite the widely held fear of legal consequence because of bleeding secondary to tPA administration for acute ischemic stroke, this is in fact a very rare occurrence. A 2013 systematic review7 structured similarly to ours examined 38 cases and failure to treat with tPA...
was the alleged complaint 70% of the time. This was also confirmed in a 2019 systematic review where the majority of malpractice lawsuits related to the emergency management of stroke alleged a failure to diagnose and failure to treat. Interestingly, the emergency physician was the one who was most often named as the defendant, almost a third of the time. By contrast, the neurologist was named at only about half that frequency, underscoring the fact that emergency physicians bear the brunt of lawsuits related to stroke and tPA. Further study could evaluate the level of communication that is documented in the emergency department record between emergency physicians and neurologists’ joint decisions for opting not to give tPA or for delays in doing so, to shed light on what could make emergency physicians less likely to take the burden of the defense.

Fortunately, the defendant (physician) prevailed most of the time. A number of factors can help the plaintiff or defendant prevail. Factors favoring the defendant include documentation of contraindications (such as patient arrival outside time window); documentation of discussion with patient and/or family; existence of an acute stroke protocol in the hospital; documentation of reasons for delay, if applicable; lack of tPA in the hospital; and timely transfer to another hospital if appropriate. Factors favoring the plaintiff include delay in being seen by a physician; failure to diagnose stroke; failure to give tPA (if eligible); delay in giving tPA, and/or obtaining necessary studies such as computed tomography (CT) or bloodwork; and delay in transferring a tPA eligible patient to an appropriate center if tPA not available.

Not giving tPA for eligible patients is most often due to not recognizing that the patient is having a stroke, rather than the physician not offering it at all. Prehospital stroke recognition aids in expediting tPA administration, and rapid prehospital stroke triage is being explored across the country. Delays in giving tPA for stroke, on the other hand, are multifactorial. They include local logistics, such as obtaining CT and lab work, drawing up the medication, and determining time last known well. The most physician-centric delay comes from the fact there is still uncertainty about both the benefit and the harm of thrombolytics for stroke, despite it being in the ASA guidelines. The original National Institute of Neurological Disorders and Stroke (NINDS) study reports that patients given tPA within 3 hours were 30% less likely to have an unfavorable outcome or disability at 3 months, with an odds ratio of 1.7 toward a favorable outcome. Number needed to treat analyses based on the NINDS data report that for every 100 patients with acute stroke treated with tPA, ∼32 have a better final outcome and 3 have a worse final outcome as a result of treatment.

However, it has been argued that baseline imbalances in the cohorts may have biased the results and thus these number-needed-to-treat calculations. Reanalyses of the NINDS data both support and refute the results. A 2012 meta-analysis showed that intravenous tPA administration up to 6 hours post-incident consistently resulted in favorable outcomes (being alive and independent at final follow-up), an effect that was even more pronounced if tPA was administered within 3 hours.

This underscores the importance of communicating every step of the physician’s treatment plan to the patient or patient’s caregiver. The standard of care per the ASA guidelines for ischemic stroke includes tPA for eligible patients within 4.5 hours of symptoms. However, 61% of the cases in our review were initiated because of physician failure to give tPA for various reasons. In such cases where other contraindications besides time are present, it is especially important for the physician to communicate and document clearly the reason the patient is not a candidate for tPA.

ACKNOWLEDGMENTS
This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily
represent the official views of HCA Healthcare or any of its affiliated entities. No funding was received for this work.

ETHICS APPROVAL
This study was considered exempt by our institutional review board. HCA Centralized Algorithms for Research Rules on IRB Exemptions (CARRIE)/IRB manager issued exemption 2021–206.

CONFLICTS OF INTEREST
None of the authors have any conflict of interest to disclose. The manuscript is original and is not currently under revision with another journal.

AUTHOR CONTRIBUTIONS
Latha Ganti conceived and designed the study, and developed the search strategy. Bryan Kwon conducted the literature search and compiled the tables. Andrew George and Thor Shiva Stead analyzed the results and designed the figures. Latha Ganti, Bryan Kwon, Andrew George, Thor Shiva Stead, Cherian I. Plamoottil, and Paul Banerjee drafted the manuscript, and all authors contributed substantially to its revision.

ORCID
Latha Ganti MD, MBA https://orcid.org/0000-0001-7717-3864
Bryan Kwon https://orcid.org/0000-0002-1226-1107
Andrew George https://orcid.org/0000-0002-6261-6711
Thor Stead ScB https://orcid.org/0000-0003-3602-6387
Cherian Plamoottil DO https://orcid.org/0000-0002-9971-7030
Paul Banerjee DO https://orcid.org/0000-0001-8971-3362

REFERENCES
1. Marler J. Tissue plasminogen activator for acute ischemic stroke. New Engl J Med. 1995;333(24):1581–1588.
2. Dewar B, Shamy M. tPA for acute ischemic stroke and its controversies: a review. Neurohospitalist. 2020;10(1):5–10.
3. Mosley M, MD. Is tPA study intentionally deceptive? Emerg Med News. 2009;31(8):5–6.
4. Mandrola JM. The case against thrombolytic therapy in stroke—Medscape—Apr 13, 2018. Group, G. Thromblytics For Stroke – Thennt. ThennNT; 2020.
5. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344–e418.
6. Moore MJ, Stuart J, Humphreys A, Pfaff JA. To tPA or not to tPA: two medical-legal misadventures of diagnosing a cerebrovascular accident as a stroke mimic. Clin Pract Cases Emerg Med. 2019;3(3):194–198.
7. Bhatt A, Safdar A, Chaudhari D, et al. Medicolegal considerations with intravenous tissue plasminogen activator in stroke: a systematic review. Stroke Res Treat. 2013:2013:562564.
8. Haslett JJ, Genadry L, Zhang X, et al. Systematic review of malpractice litigation in the diagnosis and treatment of acute stroke. Stroke. 2019;50(10):2858–2864.
9. Kass JS, Rose RV. Legal liability associated with rtPA administration and surrogate decision makers. Continuum (Minneap Minn). 2020;26(2):499–505.
10. McDermott M, Skolarus LE, Burke JF. A systematic review and meta-analysis of interventions to increase stroke thrombolysis. BMC Neurol. 2019;19:86.
11. Stead TG, Banerjee P, Ganti L. Real-world field performance of the Los Angeles motor scale as a large vessel occlusion screen: a prospective multicentre study. Cerebrovasc Dis. 2021;50:543–550.
12. Saver JL. Number needed to treat estimates incorporating effects over the entire range of clinical outcomes: novel derivation method and application to thrombolytic therapy for acute stroke. Arch Neurol. 2004;61(7):1066–1070.
13. Kwiatkowski T, Libman R, Tilley BC, et al. The impact of imbalances in baseline stroke severity on outcome in the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study. Ann Emerg Med. 2005;45(4):377–384.
14. Ingall TJ, O’Fallon WM, Asplund K, et al. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. Stroke. 2004;35(10):2418–2424.
15. Hoffman JR, Schriger DL. A graphic reanalysis of the NINDS trial. Ann Emerg Med. 2009;54(3):329–336, 336.e1-35.
16. Alper BS, Foster G, Thabane L, Rae-Grant A, Malone-Moses M, Manheimer E. Thrombolysis with alteplase 3–4.5 hours after acute ischaemic stroke: trial reanalysis adjusted for baseline imbalances. BMJ EBM. 2020;25(5):168–171.
17. Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. Lancet. 2012;379(9834):2364–2372.

AUTHOR BIOGRAPHY
Latha Ganti, MD, MBA is a professor of Emergency Medicine and Neurology at the University of Central Florida and Vice Chair for Research and Academic Affairs for the UCF Emergency Medicine Residency Program in Orlando, Florida.

How to cite this article: Ganti L, Kwon B, George A, Stead T, Plamoottil C, Banerjee P. Tissue plasminogen activator and patients with acute ischemic stroke: The litigation landscape. JACEP Open. 2022;3:12646. https://doi.org/10.1002/emp2.12646