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Reframing outcome measures for thrombolytics in acute ischemic stroke

Brandon Baker
DMC-Sinai Grace Hospital Emergency Medicine Residency, brbaker@med.wayne.edu

Charles W. Kropf
University of Michigan Emergency Medicine Residency, cwkropf@med.umich.edu

Nicholus Yee
Oakwood Annapolis Hospital Family Medicine Residency, nicholus.h@gmail.com

James Peter Meza
Wayne State University School of Medicine, jmeza@med.wayne.edu

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INFORMED CONSENT:

Reframing outcome measures for thrombolytics in acute ischemic stroke

BRANDON J. BAKER, MD, Detroit Medical Center-Sinai Grace Hospital, brbaker@med.wayne.edu
CHARLES W. KROPF, MD, Michigan Medicine, cwkropf@med.wayne.edu
NICHOLUS H. YEE, MD, Oakwood Annapolis Family Medicine Residency Program, Beaumont Health, nicholus.h@gmail.com
JAMES P. MEZA, MD, PhD, Wayne State University School of Medicine, jmeza@med.wayne.edu

ABSTRACT An informed consent conversation examining relevant research and discussing the potential benefits and harms of thrombolytic therapy in acute stroke.

Keywords: *stroke, t-PA, thrombolytic, alteplase*

Clinical Context

JS is a 58-year-old male, with a past medical history of controlled hypertension. He presented to the emergency department with his family for altered mental status that began 30 minutes prior to arrival. The patient's family reports that the patient became aphasic, developed a right-sided facial droop, and right upper and lower extremity weakness. In the emergency department, his vital signs were within normal limits, except for a blood pressure of 167/94. His National Institute of Health Stroke Scale (NIHSS) was 15/42, indicating stroke symptoms of moderate severity. The patient was then taken for a non-contrast head CT. While at the CT scanner, a discussion was had with his family members about the use of tissue plasminogen activator (t-PA) in acute stroke if it turned out to be ischemic in nature. It was explained that this is the standard of care in eligible patients, but is generally acknowledged to be a high-risk medical intervention. The patient did not exhibit any contraindications and presented well within the three-hour window advocated for by the American Heart Association (AHA) and American Stroke Association (ASA), so he was a prime candidate for treatment with t-PA[1].

Clinical Question

Your family calls you for advice about Uncle Joe:

"I'm scared. Uncle Joe had a stroke and he's here in the emergency room. They want me to sign papers to give him a clot-busting medicine, but they told me the medicine can cause bleeding into the brain. I want to try everything, but I don't want to hurt him. You're a doctor; what do I do?"

BRANDON J. BAKER, M.D. is an Emergency Medicine resident at Detroit Medical Center-Sinai Grace Hospital. CHARLES W. KROPF, M.D. is an Emergency Medicine resident at Michigan Medicine. NICHOLUS H. YEE, M.D. is Director of Inpatient Medicine at Oakwood Annapolis Family Medicine Residency Program, Beaumont Health. Clinical Research in Practice *Editor JAMES P. MEZA, MD, PhD teaches Translational Medicine and Evidence Based Practice at Wayne State University School of Medicine. He is also the Director of Research at Oakwood Annapolis Hospital Family Medicine Residency.*

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Related Literature

To prepare for this informed consent, we used the following search strategy and analysis of trials found.

A literature review was initiated using a Google Scholar search with the keywords "management of ischemic stroke t-PA review." This generated a list of recent review articles, in addition to a recent clinical trial on the use of t-PA outside of the traditional three-hour window.[3] Using the references found in this article, we located many of the original clinical trials of t-PA. Additionally, further evaluation was made utilizing thennt.com using the "Therapy (NNT) Reviews" section under the heading "Thrombolytics for Stroke." We read and analyzed ten high quality trials spanning the period of 1995-2012.[2-11]

We believe that the patient-oriented outcome measure of interest is long-term death and disability. Many doctors are concerned about the early risk of intracranial hemorrhage. Much of the debate on this topic centers on increased incidence of intracranial hemorrhage as the main risk of thrombolytic therapy. Not all intracranial hemorrhages result in permanent complications, so this is a disease-oriented outcome. When we measure long-term death and disability, this encompasses all of the major complications of ischemic and hemorrhagic stroke. Therefore, it is the most relevant measure of both efficacy and safety.

Upon examination of the trials performed during this time period, a mixture of positive, negative, and inconclusive conclusions of thrombolysis for acute ischemic stroke were reported. The first two trials (ECASS[2], MAST-I[9]) demonstrated no benefit of thrombolysis over placebo in terms of mortality or disability at 90 days. The first positive study was part 2 of the NINDS trial[3], which demonstrated benefit of t-PA vs. placebo at 90 days only if administered within 180 minutes of onset. Two trials (ASK[5], MAST-E[4]) published the following year using streptokinase showed no significant difference in terms of combined death/disability at three months or six months. These were stopped early due to a statistically significant increase in intracerebral hemorrhages (ICH) and a non-statistically significant increase in early death. However, by 90 days this was offset by an increased risk of death or disability from untreated ischemic stroke. The ECASS II trial[6] demonstrated no statistical benefit over placebo for t-PA administration at 0-6 hours after symptom onset, but showed a trend favoring t-PA.

The ATLANTIS study[7] in two parts showed increased ICH mortality at 3 months and no increase in favorable neurological outcome at 90 days, and enrollment was again prematurely ended. However, they stopped recruiting patients in the 0-3 hour window due to benefits demonstrated by NINDS. The vast majority of these patients received therapy 3 to 5 hours after symptom onset. The DIAS-II study[11] of desmoteplase given 3-9 hours after symptom onset failed to demonstrate a difference in terms of clinical response in NIHSS at 90 days.[11] A safety study conducted in patients receiving alteplase at between 3.5 and 5 hours after symptom onset did demonstrate a benefit over placebo, measured as a favorable outcome (0 or 1) on the modified Rankin scale of disability after stroke measured at 90 days.[10] Finally, in 2012, the IST-3 study[8] of the benefit of t-PA at anywhere from 0-6 hours after symptom onset showed a nonsignificant trend in the proportion of patients alive and independent at 6 months as measured by an Oxford Handicap Score of 0-2. This study did find an increase in mortality within 7 days in the t-PA group but this was again shown to be offset by a delayed mortality at 90 days from untreated ischemic stroke.[8]

Overall, two trials indicated worse outcomes with thrombolytics. Both of these trials use streptokinase outside of the 3-hour window. All of the remaining studies indicated significant benefit, nonsignificant trend, or no increase in overall harm from thrombolytic therapy, especially if given within three hours.

Effectiveness trials in a community hospital show that the protocol is hard to follow.[12,13]

Guidelines from the AHA/ASA[1] and American College of Emergency Physicians (ACEP)[14] recommend the use of t-PA. These guidelines are endorsed by the American Academy of Neurology and American Academy of Neurosurgery. Statements from the American Academy of Emergency Medicine (AAEM)[15] does not recommend for or against its use.

Strength of recommendation: B (based on inconsistent, limited randomized trials)[16]

Informed Consent

Flesch-Kincaid Grade Level for the following passage is 5.0.

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"I'm sorry to hear about Uncle Joe. How are you doing?

"You're asking a hard question. Different doctors would advise doing different things. This is because there's not a lot of good research studies.

"I have read all the original research studies. It turns out that (six) of the papers allowed patients to get this medicine up to six hours after their stroke. We don't do that anymore. People that get the medication after a longer period of time do worse. Luckily, Uncle Joe had his stroke only a half hour ago. He can get the treatment very quickly.

"The Food and Drug Administration approved this medicine based on a single study. That study showed that patients did better if they were treated within three hours. After three months, they were less likely to die or be disabled. However, some patients will die or be disabled, even if they did get the medication. If Uncle Joe gets the medication, it doesn't mean he will get better. He will just be less likely to be disabled.

"The medication can cause him to bleed. If he bleeds in his brain, that can be dangerous. Not all bleeds cause permanent complications, though. With the medication, he is at higher risk of having a bleed. He could have complications. However, in the long-term, we think he is more likely to be alive and functioning if he gets the medication.

"The other papers support this benefit, but are not conclusive. However, doctors have more confidence if we see it work well multiple times, in different places. That is not the case here.

"Another problem is that in a study, nurses and extra personnel help to make sure everything was done correctly. For Uncle Joe, we would have to use the treatment outside of the research setting. When this happens, there are more barriers to using it correctly. Many things can go wrong. The CT scan can be read incorrectly. The dose can be mixed wrong. Most importantly, they can give the medication after the time when it works the best. I think that probably won't happen with Uncle Joe. He can still get the medicine quickly. However, we know these things can happen.

"You asked my honest opinion. I find the evidence confusing and hard to interpret. Some days, I don't know if this treatment is a good idea. I also know that you have to make a decision right now. I can only give you an educated guess. Because this happened such a short time ago, I would tell them to give him the medicine. We have to remember it isn't guaranteed to help. It only makes it more likely.

"I wish I could give you a more confident answer. They asked you to make a decision. There is no right or wrong answer. This is a very hard decision to make. No one is allowed to second-guess you. I think that Uncle Joe is more likely to do better if he gets the medication.

"My thoughts are with you. Please keep me updated on how he's doing."

Take home points:

1.) The decision to give t-PA should be made by both the physician and the patient, or patient's family, on a case-by-case basis, using shared decision making.
2.) Confirmatory trials are needed to determine if patients benefit from thrombolytics in acute ischemic stroke, as demonstrated in NINDS.
3.) Any contraindication to thrombolytic use, even relative contraindications, should be taken seriously.
4.) As physicians, we want to do what is best for our patients. Doing something feels better than doing nothing, especially when confronted with a critically ill patient. However, we need to evaluate the available research to determine if what we are doing has been shown to improve patient outcomes.

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