

Journal Club Synopsis - Block 3
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Are tissue plasminogen activator therapy (TPA) and/or endovascular therapy safe and effective therapy for stroke and which patients should receive these therapies?

Clinical Scenario: You are working a shift at Kettering Medical Center and Kettering EMS calls to say they are bringing in a possible stroke. 65 y/o Caucasian male with no previous history of stroke whose wife noticed he developed garbled speech and right-sided weakness while getting ready for lunch. Symptoms onset was 30 minutes ago and symptoms are persistent with no improvement. Glucose in the ambulance is 130. VS are BP 170/95, P 85, R 16, SpO2 98% on room air. No previous history of stroke. History of hypertension on HCTZ and lisinopril, no anticoagulants besides a baby ASA that his wife states he takes every morning with his medications. On arrival patient is stable, protecting his airway but with unintelligible speech and unable to raise left arm or raise right leg off the cot. The patient goes straight to CT and stroke alert is placed. You discuss the case with the neurologist who agrees that the patient sounds like an excellent TPA candidate. Radiology calls with a non-acute head CT. You remember reading the 2012 AHA/ASA guidelines and begin running the TPA checklist with nursing staff awaiting the neurologist's arrival. No contraindications and stroke scale is 13. However you also remember the significant risk of intracranial hemorrhage but cannot recall the exact statistics.

Should this patient be offered TPA? Is he likely to benefit? What are the risks and benefits to discuss with patient and wife? What if he presented at 4 hours since onset? What if he had more symptoms; less symptoms? What if his symptoms are slightly improved when neurology arrives but not anywhere near completely resolved? The wife asks you, "If this was your father would you give him TPA?"

Introduction: The scenario is based on similar encounters experienced daily in the emergency departments across the country. The topic has generated extensive debate for the past 20 years since the initial FDA recommendation of TPA for stroke occurred. The topic has been so heated in the EM community it has led some to label it "the biggest, baddest controversy in our field." The most recent ACEP policy has a Grade A recommendation for TPA to be considered in those patients meeting current AHA/ASA guidelines for use of TPA in acute stroke. Though several studies show benefit, the risk of harm of a catastrophic nature is very real with TPA especially with regard to intracranial hemorrhage. Controversy regarding the efficacy of TPA aside, some recent topics of research and debate focus on the timing of TPA, and could focal TPA or other interventional therapies be of benefit in the acute stroke patient. These two areas were the focus of this journal club.

Article 1: Broderick, Joseph P, Yuko Y Palesch, Andrew M Demchuk, et al. "Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke." New England Journal of Medicine. 368.10 (2013)

A randomized, open-label clinical trial with a blinded outcome, to test the approach of intravenous t-PA followed by protocol-approved endovascular treatment, as compared with standard intravenous t-PA. Intravenous t-PA was started within 3 hours after symptom onset in both groups. At onset of the trial only one endovascular device was approved, however as further devices were cleared by the FDA, the study protocol did allow their introduction to keep the study maximally relevant to evolving therapies. Strokes in the endovascular group went to CTA for confirmation of stroke amenable to endovascular therapy. The primary outcome measure was a modified Rankin scale score of 2 or less (indicating functional independence) at 90 days. A total of 656 participants underwent randomization (434 participants to endovascular therapy and 222 to intravenous t-PA alone) at 58 study centers. **The trial was stopped early because of futility by predefined criteria. There was no significant difference between the endovascular therapy and intravenous t-PA groups in the overall proportion of participants with a modified Rankin score of 2 or less.** There were no significant differences in mortality at 7 days or 90 days, in the rate of symptomatic intracerebral hemorrhage, or in the rate of parenchymal hematoma, although the rate of asymptomatic intracerebral hemorrhage was higher in the endovascular-therapy group than in the intravenous t-PA group.

One of the key observations in the study was that although the endovascular group achieved almost twice the percentage of revascularization compared to tPA, no benefit was seen clinically. This highlights that revascularization is not the sole key to the therapy of either intervention and likely time to treatment as well as characteristics of the penumbra may be more important characteristics. One of the primary limitations of the study was the use of multiple devices preventing any one devices benefits from standing out. There were no increased adverse outcomes so long as protocols were adhered to. Discussion centered around the idea that though the method for both tPA and endovascular therapy make sense for restoring blood flow, the study results highlight that this isn't the most critical factor for a positive clinical outcome. Again what is needed is likely a better way to identify the patients that stand to benefit from these therapies before treatment is initiated. This trial does not rule out endovascular therapy but clearly points to the need for further trials before it goes into general use.

Article 2: Hacke, Werner, Markku Kaste, Erich Bluhmki, et al. "Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke." New England Journal of Medicine. 359.13 (2008): 1317-1329.

A double blinded, randomized, placebo controlled study conducted to examine the safety and efficacy of alteplase administered for acute stroke in the 3 to 4.5 hour time range. The primary end point was disability at 90 days, dichotomized as a

favorable outcome (a score of 0 or 1 on the modified Rankin scale) or unfavorable outcome (Rankin score 2 to 6). The secondary end point was a global outcome analysis of four neurologic and disability scores combined. Safety end points included death, symptomatic intracranial hemorrhage, and other serious adverse events. There were a total of 821 patients in the study and randomly assigned 418 to the alteplase group and 403 to the placebo group. The median time for the administration of alteplase was 3 hours 59 minutes. **More patients had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% confidence interval 1.02 to 1.76; (P = 0.04). The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 27.0% vs. 17.6%; P = 0.001; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%; P = 0.008). Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; P = 0.68).** There was no significant difference in the rate of other serious adverse events.

Though the study showed a statistical and Rankin score clinical benefit, it did come with more stringent restrictions on the use of tPA. The two most prominent were stroke severity and age. Both these restrictions were placed to mitigate the risk of hemorrhage but do limit the population to which the results can be extrapolated. Both these limitations too could lend towards a more demonstrable effect since less severe strokes may be more likely to respond favorably given a smaller penumbra. This also highlights a limitation of the study in relying on clinical diagnosis of stroke rather than MRI confirmation. This leaves open the possibility of stroke mimics that “resolve” with tPA falsely elevating the efficacy. Randomization would hopefully account for this as mimics should end up in both treatment and placebo groups. Discussion largely focused on ensuring proper patient selection to apply the extended window in clinical practice and on the lower severity of strokes creating possible bias. A final point of discussion centered around the fact that there does appear to be a sub-group of strokes that clearly benefits from tPA just as there is a subset that unfortunately hemorrhages. Identifying which group is which, possibly with earlier and faster MRI could help to maximize effect while minimizing risk.

Article 3 : Saver, Jeffrey L, Gregg C Fonarow, Eric E Smith, et al. "Time to Treatment With Intravenous Tissue Plasminogen Activator and Outcome From Acute Ischemic Stroke." Journal of the American Medical Association. 309.23 (2013): 2480-2488.

A retrospective cohort chart review study conducted to identify the impact of timing on outcomes in stroke patients receiving TPA. Primary outcomes of interest were relationship between administration time and in-hospital mortality, symptomatic intracranial hemorrhage, ambulatory status at discharge, and discharge destination. The U.S. national Get With The Guidelines–Stroke (GWTG-Stroke) registry was analyzed. Both multivariable binary and ordinal logistic regression analyses were performed to explore the relationship between administration time and clinical outcome measures, including in-hospital mortality, discharge status (ordinal: home, acute rehabilitation, skilled nursing facility, or dead; and binary: home vs. other),

and ambulatory status at discharge (ordinal: ambulatory without another person's assistance, ambulatory only with another person's assistance, non-ambulatory, or dead; and binary: ambulatory without another person's assistance vs. other). Additionally all tPA complications in the first 36 hours were analyzed. 58,353 patients from 1,395 sites treated after emergency department arrival with IV tPA within 4.5 hours of symptom onset, concordant with current national guideline recommendations, made up the study population. **The study confirmed the hypotheses that earlier treatment was associated with reduced mortality and intracranial hemorrhage and increased achievement of independent ambulation at discharge. For every 100 patients treated with tPA, for every 10-minute delay in patients treated within 4.5 hours of onset, 1.2 fewer had better ambulation at discharge and 0.8 fewer had a more independent discharge destination. Earlier time to treatment was clearly associated with a reduction in the occurrence of symptomatic intracranial hemorrhage.**

Limitations include it was a retrospective registry analyses relying on the accuracy of the reporters for timing which is susceptible to reporter errors. The study was also very short term with only 72-hour follow-up data considered. Discussion focused largely on the study making "physiologic sense" since breaking clot and getting the brain oxygen sooner should result in a better outcome and that outcome should be at least somewhat apparent in the very short term. The study also places ever-increasing emphasis on time to treatment, having a streamlined system, and making every minute count.

Overall Summary: Despite several studies subsequent to the NINDS trial demonstrating no clinical benefit of tPA over placebo, recently several well-powered and randomized trials have shown that some patients do benefit from tPA in acute stroke. Current limitations center on identifying which patients these are, and the equally important task of identifying which patients are likely to bleed from tPA. Despite good reperfusion rates, the IMTS III trial showed that time and other factors are more important for achieving good clinical outcomes in reperfusion. This places endovascular therapy in the unproven category for stroke and necessitates further research. Patients that meet inclusion criteria should be offered tPA up to 4.5 hours after onset but emphasis should always be on tPA administration ASAP as both second and third trials showed earlier intervention had better outcomes and less bleeding. Whether a believer in tPA or not, it appears to be here to stay for now after over 20 years of research since NINDS as there does appear to be a subgroup with unidentified characteristics that lead to better clinical outcomes from intervention. The hope is that future studies and technology can serve to identify which patients are likely to benefit and which are likely to have no benefit or harm from either tPA or interventional therapies.