MAINE MEDICAL CENTER
DEPARTMENT OF EMERGENCY MEDICINE

Journal Club / Research Article Summary - (Adapted from Schultz Table)

Date: ___11/20/14_________
Presenter: _____Janessa Leger___________

ARTICLE:
- Citation: tPA for acute ischemic stroke, conducted by the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, December 14, 1995, NEJM
- Country: USA
- Funding Sources: Genentech supplied and distributed both the tPA and the placebo and monitored the clinical sites

PURPOSE:
- Research Question(s): What is / are the primary questions being addressed by this study? Usually found just before the methods.
- Test whether tPA has clinical activity and improves clinical outcome in patients with acute ischemic stroke
- Hypothesis: What is the anticipated outcome or alternatively, the null hypothesis (there will be no difference between groups).
- Hypothesis was that there would be difference in tPA and placebo groups in terms of proportion of patients who recovered with minimal or no deficits at 3 months

DESIGN:
- Study Design: Randomized double-blind trial
  - Major types of quantitative designs: Descriptive (case / series) Correlational (prospective / restrospective cohort), Quasi-Experimental, and Experimental (Randomized Controlled).
  - ? prospective vs. restrospective.
  - ? blinding
- Dependent / outcome Variable(s): What is the variable of interest / outcome being studied. Part 1; improvement in NIHSS by 4 or more points 24 hours after onset of stroke or resolution of symptoms; Part 2; Four outcome measures; NIHSS, Modified Rankin Scale, Glasgow Outcome Scale, and Barthel Index
- Independent / research Variable: What is the variable that is modified among groups? tPA given at 0.9 mg/kg max dose 90 mg vs. placebo given within 180 minutes of onset of stroke symptoms
They also studied safety by monitoring adverse events including intracranial hemorrhage, serious systemic bleeding, death, and new stroke.

**SETTING / SUBJECTS:**

- **Research Setting:** Inpatient / outpatient, rural / urban, academic / community, EM / non-em, etc. Research setting was multiple academic institutions including University of Cincinnati, UCSD, Univ. of Texas, Houston, Long Island Jewish Medical Center, Henry Ford Hospital, Emory University, University of Virginia, University of Tennessee, Henry Ford Health Sciences Center

- **Subjects:**
  - **Study population:** Who was studied (eg: all adults presenting with chest pain, all children with wheezing, etc). **Patients with ischemic stroke with clearly defined time of onset, deficit measurable on NIHSS, and baseline CT showing no ICH.**
  - **Inclusion / Exclusion criteria:** Are there any important inclusion or exclusion criteria, especially those that may affect generalizability. Exclusion criteria; another stroke or serious head trauma within preceding 3 months; major surgery within 14 days, history of ICH; systolic BP greater than 185 or diastolic above 110; rapidly improving symptoms; symptoms suggestive of SAH; GI hemorrhage or urinary tract hemorrhage within previous 21 days; arterial puncture at non-compressible site within previous 7 days; or had seizure with onset of stroke. Patients taking anticoagulants or had elevated PTT, or PT greater than 15 sec, plt less than 100, glucose less than 50 or above 400, or if aggressive treatment of BP required.
  - **Number (control / intervention groups):** Number of subjects in each group. Table 3: 624 patients total; for part 1: 71 in 0-90 min group, 73 in 91-180 min group that received tPA. 68 in 0-90 that received placebo, 79 in 91-180 min group that received placebo. For part 2: 86 patients in 0-90 got tPA, 82 within 91-180. 77 within 0-90 got placebo, 88 within 91-80 got placebo.
  - **Demographics:** Age, sex, race, etc. Table 2: included age, sex, race, weight, NIHSS, stroke subtype, BP, fibrinogen, glucose, CT findings (edema, mass effect)
  - **Attrition:** Did patients exit the study or were patients lost to follow up. In Part 1, 1 patient’s data was missing for primary outcome. In part 2, 4 patients data was missing for primary outcome. In part 1, 90% tPA group and 92% placebo group got full dose, in part 2 93% both groups got full dose.
METHODS:

- **Interventions:** What, if any, interventions were performed among the study groups. Control group got placebo, intervention group got .9mg/kg of tPA, with 10% dose as bolus and 90% as infusion over 60 minutes.

- **Study Groups:** What were the various study groups (eg: control / placebo, intervention 1, intervention 2, etc). Study groups were control group which got placebo within 0-90 and 91-180 minutes, and intervention group which got 0.9 mg/kg tPA at 0-90 and 91-180 minutes.

- **Instruments:** What devices, special equipment, surveys, rating scales, etc. were utilized. They used 4 outcome scales to evaluate outcome at 3 months which included NIHSS, Glasgow Outcome Scale, Barthel Index, and modified Rankin scale. They used third and fourth generation CT scanners whose quality standards were established before the trial started.

- **Data Collection:** Who collected data? What was their training? Was there consistency among data collectors? Were there changes to data collection / study protocol during the period of the study. Data was collected by “certified examiners who had not performed the base-line exam and had not been present during the initial treatment.” Don’t say if they were neurologists, residents, attendings, etc. CT scans were reviewed by radiologist blinded to all clinical information including treatment group.

DATA ANALYSIS:

- **Level of Data:** Categorical (two or more categories without order, (ie: male / female)  Ordinal (hierarchical categories without set spacing, (ie: education level, death / discharge)  Interval (continuous data with set spacing, (ie: age, weight, hemoglobin)  Categorical

- **Statistics Used:** What type of statistical tests were utilized (eg: T-test, ANOVA, regression analysis). Part 1 used Mantel-Haenszel tests to compare proportion of patients with improvement at 24 hours. Part 2 used global statistic (wald test) derived from a general linear model with logit-link function, computed with use of generalized estimating questions. Global test statistic simultaneously tests for effect in all four outcome measures specified. If patient died; worst possible score given. If survived but missing outcome data; used one closest to that time, otherwise worst score given. Mantel-Haenszel tests compared differences in each of the 4 measures only if global test results were significant at 0.05 level.

- **What, if any, variables were controlled for?** Do the results adjust for confounding variables? There was no adjustment in part 1 since the three hypotheses were pre-specified. In part 2, see above.

RESULTS:

- **Brief answers to research questions:** What were the conclusions made by the authors? Do they answer the original research questions? Do you think their conclusions are valid based on the data reported? Conclusion was that there was benefit to giving tPA within 3 hours of stroke onset. Table 3 and Table 4
outline the primary outcomes for each part 1 and part 2. For part 1; % of
patients with improvement in NIHSS at 24 hours both at 0-90 and 91-180;
there was no statistically significant difference. Post-hoc comparisons of
median NIHSS scores showed improvement in condition of patients treated
with tPA compared with placebo in most time strata in parts 1 and 2 in the
combined analysis. In part 2; number of patients with favorable outcome for
each of the 4 outcome measures at 3 months was higher in the tPA than in
the placebo group. Odds ratio for favorable outcome in tPA group 1.7
(confidence interval 1.2-2.6). 12% absolute increase in number of patients
with minimal or no disability in tPA group. 11% absolute increase in
number of patients with NIHSS 0-1. Similar effect seen with modified
Rankin and Glasgow outcome scales. No difference in mortality.

- **Additional findings:** An any additional findings other than the primary research
  questions discussed? Were these expected or unexpected based on the study
design? ICH within 36 hours more common in tPA group, and happened in
pts with higher NIHSS at baseline (median 20). 9% of them had evidence of
  cerebral edema at baseline. Another 6 patients had symptomatic ICH after
  36 hours. 11 deaths from ICH. 17/28 pts with symptomatic ICH at 3 months
died (61%). Similar rate of asymptomatic ICH. Serious systemic bleeding
  similar in part 1 and part 2 between the two groups. More common to have
  minor external bleeding in first 10 days with tPA. New ischemic strokes in
  8% with tPA and 7% with placebo in part 1, 4% in both in part 2.

- **Other possible explanation for findings:** Are their other possible / probable
  explanations for the results other than those presented by the authors? Do the
  results correspond with the purpose of the study? Consider: sample size issues,
  measurement issues (did they measure the right outcomes?), attrition, treatment integrity
  (was the intervention always delivered exactly the same way?), and other issues you
  identify. Results do correspond to purpose of the study. There were baseline
differences in the study groups (aspirin therapy, stroke subtype, age, weight,
  smoking, etc) which could have contributed to results. Not all patients got
  full dose of tPA (10% didn’t in part 1 and 7% in part 2).

- **Limitations:** Are their important limitations identified by the authors? Do you see
  any other important limitations? Do these limitations significantly alter the
  conclusion or the applicability of the study?
  Seems like they did two parts to the study because part 1 showed no
difference. Changed primary outcome halfway through the study.
  Study funded by Genentech who makes the tPA and monitored the clinical
  sites.
  Differences in baseline patient characteristics and stroke subtypes.
  Half patients given treatment within 90 minutes which may not be feasible in
  more rural areas or in real life.
IMPLICATIONS FOR PRACTICE:

- **Applicable to this clinical practice:** Is the study population generalizable to the population likely to be affected by this intervention / outcome in your clinical practice? If not, what setting may this be applicable to?

- **Applicable to our practice:** we are a stroke center, ACEP guidelines say Level 1 recommendation, really have to defend if you’re not going to use tPA when it could potentially be indicated

- **Feasible (cost, resources, etc):** Is this an intervention that would be reasonable to institute in clinical practice? Are instruments / medications available? Does the study adequately assess risks and unforeseen outcomes? Is the intervention cost / resource effective? Does the study account for cost / benefit? Are there more effective treatments available? **More difficult in rural areas to treat patients within 90 minutes or even 180. tPA is available at our hospital.**

- **Clinically Relevant:** Is this intervention likely to make a clinically significant impact on your patients if instituted? That is, some interventions may show statistically significant changes without making an impact that is clinically important. **Definitely makes clinically significant impact; risk of ICH after tPA has implications for outcomes. This intervention can potentially improve outcomes in a patient population with significant disability following their stroke.**

LEVEL OF EVIDENCE / DECISION FOR USE:

- **Background**  
  **Consider Replication**  
  **Ready for use**

- **Level of Evidence:**
  - Ia Evidence obtained from meta-analysis of randomized controlled trials
  - Ib Evidence obtained from at least one RCT
  - IIa Evidence obtained from at least one well-designed controlled study without randomization
  - IIb Evidence obtained from at least one other type of well-designed quasi-experimental study
  - III Well-designed non-experimental studies
  - IV Expert committee reports, opinions of experts