Prior Use of Intravenous rt-PA Improves Outcome in Endovascular Stent Retriever Trials for Acute Large Vessel Ischemic Stroke

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Background: Results of randomized clinical trials (RCTs) of endovascular stent-retriever (ESR) trials have mostly shown improved outcomes. However, inclusion and exclusion criteria for these trials and the individual case series that preceded them differ considerably. A major difference between these trials was the extent of intravenous thrombolysis (IVT) with rt-PA prior to endovascular intervention. We therefore applied a method we developed for clinical trial analysis (pPREDICTS, pooled Placebo Response Dictates Treatment Success) associating baseline factors with outcome from an aggregation of the placebo arms of RCTs to generate a pPREDICTS model from trial arms based on different percentages of rt-PA use. We show the successful generation of a pPREDICTS model correlating baseline NIHSS and % utilization of rt-PA with good functional outcome (modified Rankin Scale 0-2) and mortality. We take advantage of this arm to arm to generate plots of ESR trials to determine the best and worst performers compared to this “pseudo-control” arm.

Methods: We employed our previously published method (Mandava and Kent, Stroke ’09) to develop a model based on 55 RCTS representing >11000 subjects that included various percentage of patients receiving IV rt-PA and their baseline NIHSS. We generated multi-dimensional “prediction” intervals (p=0.05) to assess difference from predicted outcomes. We compared case series (n=15) of stent retrievers and recently completed stent retriever trials (n=6) against the model directly and through funnel plots (Duval and Tweedie, ’02) of case series vs. the pooled control arm. We evaluate this model to determine the best and worst performing trials and adjust for publication bias in meta-analysis.

Results: Figs 1 shows the outcome model for mRS0-2 and mortality (r²=0.83/0.65 respectively; p<.001). The middle surface is outcome model correlating baseline NIHSS and % rt-PA use (x axis). r²=0.12; Figure not shown). Fig 3a: Best fit exponential model for odds ratio of good outcome (y axis) showed a significant relationship to increasing rt-PA use (x axis), r²=0.22, p=.003. The exponential fit for time to recanalization vs good outcome was not robust (r²<.012; Figure not shown). Fig 3b: Best fit exponential model for odds ratio of mortality vs. percent rt-PA (r²=0.28, p=.014). The fit for time to recanalization and mortality was also significant (r²=.021; p=.03; Figure not shown).

Conclusions: 1. Our analysis supports that all 7 RCTs of stent retriever intervention show benefit in terms of improved good functional outcome compared to control arms at their baseline NIHSS and % rt-PA usage. The trial with higher than expected mortality had among the lower %s of IV rt-PA. 2. Seven stent retriever RCTs and 14 case series showed a greater chance of good outcome the higher the percent use of IV rt-PA prior to intervention. 3. Time to recanalization was not significantly correlated with good outcome but showed increasing mortality with increasing time to recanalization. 4. It is not clear whether this striking relationship of good outcome to IV rt-PA is due to specific inclusion criteria, but our results suggest strongly that timely IV rt-PA administration should not be sacrificed in order to go directly to endovascular intervention.