DEM Journal Club

Article Appraisal

Article: Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke (ENCHANTED)

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Background and Study Objective(s):

Intravenous tissue plasminogen activator (tPA) in acute ischemic stroke has been studied numerous times over the past two decades. Currently, per the 2015 CAEP recommendations, IV tPA has a "strong recommendation with high quality evidence" for offering it within 3 hours, and not routinely offered after 3 hours with "weak recommendation, moderate quality evidence."
Previous trials and registry studies have suggested a lower dose of IV tPA (0.6mg/kg instead of the standard 0.9mg/kg) may have equivalent clinical outcomes with decreased risk of symptomatic intracerebral hemorrhage in Asian populations.
The Enhanced control of Hypertension and Thrombolysis Stroke study (ENCHANTED) was designed to compare low-dose tPA vs standard-dose tPA (and in a separate study, yet to be released, low target and standard target blood pressure control) in acute ischemic stroke.

Study Design:

Randomized, open-label, trial with a quasi-factorial design comparing two doses of IV tPA as well as two blood pressure targets at 111 clinical centers in 13 countries. Recruitment occurred between March 2012 and August 2015. Inclusion criteria was consistent with previous ischemic stroke studies, including time of onset up to 4.5 hrs. Exclusion criteria primarily focused on those unlikely to benefit from therapy secondary to pre-existing disability or very high likelihood of death within 24 hours. Eligible patients were randomized centrally at the George Institute for Global Health into the low-dose (0.6mg/kg) and standard-dose (0.9mg/kg) groups. The primary endpoint was a composite endpoint of death or disability (as defined by modified Rankin score of 2-6) at 90 days. There were several secondary and tertiary outcomes, but most importantly their main secondary outcome (and key safety outcome) was symptomatic intracerebral hemorrhage within 36 hours.

Results:

1654 patients were randomized to the low-dose group with 1643 to the standard-dose group. The patient demographics were equivalent in the two groups, and, of note, had a large Asian cohort.
The primary outcome occurred in 53.2% in the low-dose group and 51.1% in the standard-dose group with an odds ratio of 1.09 (95% CI 0.95 to 1.25), which is higher than the pre-defined endpoint of 1.14, which fails to show non-inferiority. The secondary (safety) endpoint occurred in 1.0% in the low-dose group and 2.1% in the standard-dose

group with an odds ratio of 0.48 (95% CI 0.27-0.86). Mortality at 7 days was also reduced in the low-dose group: 3.6% vs 5.3% (P=0.02). At 90 days there was a trend towards decreased mortality in the low-dose group (P=0.07).

Validity of Results:

This large trial attempted to validate previous trends seen in the ischemic stroke literature. The odds ratio for the primary endpoint crossed the pre-defined value for non-inferiority, essentially making this a negative trial.
Though an open label trial with significant risk for bias, we thought the authors utilized multiple mechanisms to minimize this bias. We furthermore recognized that the authors did an excellent job attempting to find a difference between the two groups, including multiple subgroup analyses, but their detailed statistical assessment also detracted from any "positive" results that were found.

Generalizability of Results:

The ENCHANTED (tPA) trial was performed in multiple departments in several countries, though none of them North American, potentially limiting the generalizability. The trial included a large cohort of Asian patients, which could have a role in the Vancouver population.
We recognized that this is trial is unlikely to be reproduced, leading our discussion towards the difference between failing non-inferiority and true inferiority, and potential trends in the secondary outcome suggesting decreased mortality in the low-dose group. Furthermore, as this trial is unlikely to be reproduced, inferences to the secondary outcome are limited.

The Bottom Line:

The ENCHANTED (tPA) trial adds a modicum of evidence to the tPA in ischemic stroke literature, comparing a low-dose (0.6mg/kg) to standard-dose (0.9mg/kg) protocol. Given the inability to achieve non-inferiority in the trial it is unlikely that it will change stroke neurologist practice towards low-dose tPA, and has limited utility for emergency department physicians in Canada.