Need to Know: CJEM Journal Club

Extending the window for thrombolysis in acute ischemic stroke?

Ariel Hendin, MD*; Matthew Lipinski, MD*

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INTRODUCTION

Background

Advances in imaging technology have facilitated the identification of stroke patients with potentially salvageable penumbra, sparking interest in whether these patients could benefit from intravenous thrombolysis beyond the accepted time window of 4.5 hours.

Objectives

Ma and colleagues sought to identify whether intravenous thrombolysis, administered between 4.5 and 9 hours after symptom onset, would improve neurological outcomes in select patients with ischemic stroke.

METHODS

Design

Double-blind, randomized controlled trial that compared intravenous alteplase (tPA) and placebo in ischemic stroke patients with potentially salvageable tissue based on perfusion imaging.

Setting

International multicentre study at 16 centres in 4 countries.

Subjects

Included patients presented between 4.5 and 9 hours after stroke symptom onset and had a region of potentially salvageable hypo-perfused brain tissue on perfusion imaging.

Outcomes

The primary outcome was a modified Rankin scale (mRS) score of 0–1 at 90 days. Secondary outcomes included ordinal mRS at 90 days, percentage of reperfusion at 24 hours on imaging, and safety outcomes including death and symptomatic intracranial hemorrhage (ICH).

RESULTS

Over an eight-year period, 225 patients were enrolled, after which the study was terminated early because of "loss of equipoise" from the results of a similar trial.[1] Of the 225 patients studied, 113 were allocated to the tPA group and 112 to the placebo group. The primary outcome of an mRS of 0–1 at 90 days occurred in 40 (35.4%) of the patients who were administered tPA versus 33 (29.5%) of the placebo group (CI 1.01–2.06, $p = 0.04$). The adjusted risk ratio for a good neurological

From *University of Ottawa Department of Emergency Medicine, Ottawa, ON.

Correspondence to: Dr. Ariel Hendin, Box 254, Emergency Physicians Associates, The Ottawa Hospital, 1053 Carling Avenue, Ottawa, ON K1Y 4E9; Email: ahendin@toh.ca

outcome among patients administered tPA was 1.44 (95% CI 1.06–2.06, $p = 0.04$). There was no significant difference between groups in the secondary ordinal analysis of mRS scores. Six patients who were administered tPA had ICH (6.2% v. 1 patient (0.9%) in the placebo group, $p = 0.05$). The number needed to treat to produce a good neurological outcome with tPA was 17, and the number needed to cause one symptomatic ICH was 19.

APPRAISAL

Strengths

- Makes use of advances in imaging technology to identify whether patients might benefit from extended stroke therapy windows
- Well-designed study: Multicentre, randomized, and placebo-controlled trial
- Zero loss to follow-up
- Intention-to-treat analysis
- Patient-oriented primary and safety outcomes studied

Limitations

- Small number of patients enrolled over multiple years: an average of 1.8 patients enrolled per centre per year, highlighting the difficulty in selecting patients who are eligible for this
- Enrolment terminated early that might have increased the likelihood of overestimating the treatment benefit
- Perfusion imaging software used in this study may not be available at all centres
- Although the investigators found a significant difference in their primary outcome, this was underpowered for a difference of 15% that they expected to find

CONTEXT

Recent studies of endovascular therapy in stroke have demonstrated that select patients with a small infarct core and salvageable penumbra benefit from endovascular therapy up to 24 hours after stroke symptom onset.[2,3]

In WAKE-UP, published in May 2018, Thomalla and colleagues assessed the effect of tPA versus placebo among patients with an unknown time of symptom onset, but for whom MRI diffusion-weighted imaging indicated a stroke within 4.5 hours.[4] This study was stopped early for lack of funding but found that the patients who were administered tPA had improved neurological outcomes. This prompted the early stoppage of the EXTEND trial.

BOTTOM LINE

This was a well-designed trial of intravenous tPA in patients with stroke who presented 4.5–9 hours after symptom onset and who had salvageable penumbra tissue on perfusion imaging. More patients in the tPA group had complete functional independence at 90 days versus those who received placebo (35.4% v. 29.5%, respectively); however, rates of symptomatic ICH were also higher in the tPA group (6.2% v. 0.9%, respectively). Major limitations include early stoppage of the trial, and the study population was selected using perfusion software that is not currently available in many centres. Emergency physicians who administer tPA for acute ischemic stroke should not modify therapy based on this study.

Keywords: Neurology, stroke, thrombolysis

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