



Thrombolysis and Beyond: New Therapeutic Horizons for Acute Ischemic Stroke Patients

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Case Presentation

A 76 year old male acutely developed aphasia and right sided weakness while eating at home. He had been left to have his lunch by a daughter who was doing errands. She returned 2 hours after leaving him and found him on the floor. EMS was called and the patient arrived 2 hours and 25 minutes after the onset time. The cranial CT was read as normal 3 hours and 35 minutes after the time of stroke onset.

The EM physician wonders if there are any therapies that would help his patient since he is outside the IV thrombolytic window of 3 hours.

What issues exist in the use of IV thrombolytics in ischemic stroke patients?

Is the data regarding thrombolytics any clearer with the NINDS reanalysis?

Does intra-arterial thrombolysis extend the window of therapy beyond three hours?

What new therapeutic modalities are on the horizon?

What will the treatment of ischemic stroke look like in 10 to 15 years?

Key Clinical Questions and Learning Points

What issues exist in the use of IV thrombolytics in ischemic stroke patients?

Intravenous thrombolytics have been available for 10 years. In that time many EM physicians have been uncomfortable with using this therapy in ischemic stroke patients. There is concern about causing an intracerebral hemorrhage and concern over whether or not the therapy actually works. Brown published a survey of EM physicians in 2005 which found that 40% do not use thrombolysis in their practice. Of this group 65% cited ICH as the cause of their decision, 23% cited lack of benefit and 12% cited both. This concern has been seen in policy statements by ACEP, AAEM and SAEM which do not fully endorse the therapeutic benefit of thrombolysis and one even calls into question whether or not it should be considered the standard of care.

Is the data on the use of thrombolytics any clearer with the NINDS reanalysis?

NINDS commissioned an independent panel to review all of the data from the original NINDS trial. They were asked to determine if the fact that the lysis group had more minor strokes (NIHSS 1-5) unfairly biased the results, did the benefit hold on recalculation of the data, could the BP recommendations be verified. They found that though there were more minor strokes in the lysis group this did not bias the data because these patients invariably did well and so would not have benefited either the placebo or the lysis group. The odds ratio for having a minimal or no neurological deficit with thrombolysis in the original trial was 1.7. In the reanalysis this actually increased to 2.1. The commission was unable to make a recommendation regarding BP because the data was inconsistent. Other information to come out of the reanalysis is that glucose management may be key to improving the outcome of ischemic stroke patients. In addition, in stratifying the risk of ICH four risk factors became apparent, NIHSS >20, age >70, ischemic changes on CT scan and glucose >300 mg/dl. No risk factors gave a risk of ICH of 1.8%, one risk factor increased the risk to 4.9%, and two or more risk factors increased the risk to 21.2%. The commission concluded that thrombolysis is of benefit to ischemic stroke patients when used within the protocol and in the proper patients.

Does intra-arterial thrombolysis extend the window of therapy beyond three hours?

Intra-arterial thrombolysis allows for a much smaller dose of TPA to be used by aiming it directly at the clot. This theoretically decreases the risk of ICH and may extend the window of opportunity for treating ischemic stroke patients. Two small randomized trials – PROACT 1 & 2 have been conducted which tested prourokinase vs. heparin within a 6 hour window. They did these on MCA occlusions only. They found that recanalization improved with IA and that mortality identical. The relative risk reduction for improved outcome was 60%. Intra-arterial thrombolysis is not available at most hospitals but perhaps transferring the patient to a tertiary care center that provided IA may be warranted in the patient who falls in the 3 to 6 hour time window. Anecdotal reports have been published of successes with IA up to 12 hours out from initial symptoms but there has not been any prospective study of this time window.

What new therapeutic modalities are on the horizon?

The first tested neuroprotectants were all a bust either because of lack of clinical improvement or because of adverse effects. This month the first neuroprotectant to show a therapeutic benefit was published in the New England Journal of Medicine. The SAINT I trial studied NXY-059 which is a free radical sink that was found to improve outcomes in ischemic stroke patients as measured on the Modified Rankin scale. Comparing NXY-059 to placebo there was a 4.4% absolute improvement in achieving a Modified Rankin score of 0 (no disability). The adverse events profile was favorable. SAINT II, the confirmatory trial is underway. There are other second generation neuroprotectants about to enter clinical trials. These focus on the NMDA receptor and the glutamate/calcium cascade. Hypothermia continues to be studied with modest improvements in outcome. Technical issues such as timing and maintaining a consistent temperature make this therapy difficult to implement.

What will the treatment of ischemic stroke look like in 10 to 15 years?

As new therapies become available EM physicians will have the ability to customize their practice to that which best serves their patients and maximizes their resources. Thrombolytics will likely remain a part of the therapeutic armamentarium for the treatment of ischemic stroke but may be coupled with neuroprotectants that will either improve outcomes or extend the window for implementing other therapeutic interventions such as thrombolytics or mechanical clot removers. Stroke centers will provide a variety of therapies for the treatment of ischemic stroke with various time windows for implementation. Non-stroke center hospitals may develop transfer protocols to tertiary centers in order to maximize the outcomes of ischemic stroke patients. Many things are likely to change in the next 10-15 years in the management ischemic stroke patients and EM physicians will be at the forefront of these changes.