May 2015

Washington University Emergency Medicine Journal Club
Endovascular Stroke Treatment

Vignette

A 67 year old white female presents to a moderate sized community hospital (also a Primary Stroke Center) 90 minutes after the onset of right-arm and leg hemiplegia as well as aphasia. The initial NIH Stroke Scale (NIHSS) is 13. A non-contrast head CT is negative, though there is a possible hyperdense "MCA sign" per the preliminary read. All labs are unremarkable and no contraindications to IV thrombolysis were elicited. The local emergency physician and neurologist agree that the patient is a good candidate for IV tPA. The risk and benefits are discussed but the family had some excellent questions. As the expert at the regional Comprehensive Stroke Center, you are contacted for your opinion. The patient's son happens to be a family practitioner and has heard about some new interventional therapies that have been studied, including several studies recently published in the New England Journal of Emergency Medicine.

The family poses the following questions:

1. Are the new endovascular studies now the new standard of care for acute stroke care?
2. Does the patient really need to get IV tPA locally? Can she just be transported to the regional stroke center for endovascular therapy?
3. How do you know which patients will benefit from endovascular therapy? Can you predict who will do well?
4. Can every stroke center perform this therapy? Why does she need to go to a larger center?
5. How much better are these new therapies compared with standard IV therapy?

PICO Question
Population: Adult patients with acute ischemic stroke
Intervention: Intra-arterial clot retrieval or intra-arterial thrombolysis
Comparison: Standard of care
Outcome: Functional status, mortality, quality of life

Search Strategy

No formal search was conducted. Three recent positive articles and one negative article from 2013 were selected by Dr. Peter Panagos, an expert in neurologic emergencies.

Article 1: Goyal M, Demchuk AM, Menon BK, et al. ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015 Mar 12;372(11):1019-30. Answer Key.

Article 2: Broderick JP, Palesch YY, Demchuk AM, et al; Interventional Management of Stroke (IMS) III Investigators. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med. 2013 Mar 7;368(10):893-903. Answer Key.

Article 3: Berkhemer OA, Fransen PS, Beumer D, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015 Jan 1;372(1):11-20. Answer Key.

Article 4: Saver JL, Goyal M, Bonafe A, et al; SWIFT PRIME Investigators. Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke. N Engl J Med. 2015 Apr 17. Answer Key.

Bottom Line

In 2013, the stroke world was turned on its ear by the publication of three articles - all in the same issue of the New England Journal of Medicine - that showed no benefit to endovascular therapy in the treatment of acute stroke (IMS-III, SYNTHESIS, and MR RESCUE). While some felt this to be the final nail in the coffin for endovascular treatment, others felt that issues with inclusion criteria and treatment strategies may have negated any potential benefit of treatment.

In the SYNTHESIS trial, patients were randomized to either endovascular treatment or intravenous (IV) t-PA, rather than being eligible to receive both therapies. In both SYNTHESIS and IMS-III, patients were selected based solely on clinical data, and no radiologic assessment was made to verify large vessel occlusion. Finally, MR RESCUE excluded patients who were eligible for IV t-PA and also extended eligibility to 8 hours from symptom onset.

As a result of these proposed limitations (lack of proper confirmation of large vessel occlusion using either CT angiogram or MR angiogram, exclusion of patients eligible for IV t-PA, and inclusion of patients with prolonged symptoms) further research was planned and has been conducted to attempt to identify an appropriate subset of patients for endovascular therapy.

Three positive studies were published earlier this year. All three trials included only patients with imaging-confirmed occlusion of a large artery in the anterior cerebral circulation.

- The first of these was MR CLEAN, which was conducted in the Netherlands and included patients who could receive endovascular treatment within 6 hours of symptom onset. The result was a favorable shift in the distribution of the modified Rankin scale in favor of endovascular treatment, with an adjusted odds ratio of 1.67 (95% CI 1.21 to 2.30).

- The second article, ESCAPE, placed an emphasis on "fast treatment times and efficient work-flow." This trial was stopped early for a perceived benefit, demonstrating a common odds ratio of 2.6 (95% CI 1.7-3.8) for an improvement of 1 point on the modified Rankin scale, favoring the intervention.

- The third trial, SWIFT PRIME, was also stopped early for perceived benefit. Patients were eligible if endovascular therapy could be initiated within 6 hours of the time they were last seen normal. This study demonstrated a shift towards more favorable outcomes on the modified Rankin scale associated with endovascular treatment ($p < 0.001$). The calculated number needed to treat to have one patient have a "less-disabled outcome" was 2.6.

Two additional studies have been published in the last year: REVASCAT and EXTEND-IA. These studies also required imaging-confirmed large proximal vessel occlusion in the anterior circulation for enrollment. Both studies were also stopped early for perceived benefit, and both demonstrated improved functional outcomes at 90 days.

Finally, two additional studies have been completed, but have not yet been published. The THRACE trial had positive results, while the THERAPY trial resulted in clinical equipoise. Both of these trials were halted early based on the results of MR CLEAN.

Despite the rousing success of these more recent trials, there is still a great deal of controversy surrounding endovascular treatment. Some argue that the prior negative results simply can not be ignored, pointing out that previous negative studies raise the bar for statistical success in subsequent trials. Others have argued that the use of an ordinal analysis of the modified Rankin scale in many of these subsequent studies raises the possibility of erroneously detecting a benefit when one does not truly exist, given the limited reliability of the scale. Finally, two of these more recent studies were stopped early for benefit at unplanned interim analyses, raising the possibility that benefit was detected that would not have been found had the studies been completed.

On the other hand, proponents of endovascular therapy point out that the more recent studies used more strict inclusion criteria and protocols - including more timely intervention - than the original studies. It should also be pointed out that the largest of these trials (MR CLEAN) was not stopped early. Finally, ordinal analysis has become a common statistical tool in stroke trials, and has been accepted as a means of identifying smaller (but clinically significant) differences in outcomes than using a dichotomous cutoff for the modified Rankin scale.

Both sides in the debate over endovascular therapy for stroke make salient points. The current tide, however, seems to be in favor of its proponents. Many institutions have begun to perform endovascular procedures, with strict protocols guiding eligibility, including imaging-confirmation of large vessel occlusion. This practice will have far-reaching implications, including an impact on EMS transport and inter-hospital transfer to stroke centers. The data will need to be carefully considered, not only with respect to the treatment of individual patients, but also the broader impact on our healthcare system.