



## **Stroke Care Beyond the 3 Hour Window for IV tPA Use: What are the Diagnostic and Treatment Options, and How Can They be Accessed?**

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### **Case Presentation**

A 28 year old male presents to the ED as a possible seizure and altered mental status. His symptoms were first noticed about 3 hours ago. His friends thought he was playing around so delayed transport until he became unresponsive. He was able to open his eyes, but could only make guttural speech. He was not able to sit or stand, and seemed weak on his right side. Review of systems was positive for a mild head ache. His past medical history is essentially negative, he takes no medications, does not smoke, drink much alcohol, or use street drugs. Family history was non-contributory.

Physical examination showed a well developed male with normal vital signs. His eyes are open, though he intermittently has disconjugate gaze. He could follow examiner with eyes, his speech was garbled though appropriate. He had a weak gag reflex, clear breath sounds, regular heart rhythm without murmurs or gallops, normal abdominal and extremity exam. On neurological exam he had profound weakness of his entire right side (1/5). He has complete paralysis of his lower right face, and can move but not lift his right arm or leg off the stretcher. He has diminished sensation on the right side as well. There are no visual field deficits.

His coordination in his left arm and leg is poor, and can not be assessed on the right.

His initial head CT was normal, as were his ECG and blood-work (CBC, chem.-7, drug screen and alcohol). His respiratory status deteriorated requiring intubation and ventilation. Chest X-ray showed good tube placement and was otherwise normal. He was sent for emergency MRA/MRI. His MRI showed a basilar artery thrombosis with early infarction of the pons, left midbrain, and right superior cerebellum. He is outside the 3 hour window.

What do you do???

## **Key Clinical Questions and Learning Points**

### **What therapies are approved for use in treating ED ischemic stroke patients beyond the three hour IV tPA window?**

Intra-arterial thrombolytics (tPA) may be provided up to 6 hours following onset of symptoms for an acute ischemic stroke, and up to 24 hours following a basilar artery infarct. There are many methods of mechanical removal of an embolus including embolectomy with the “*MERCI*” retriever, guide wire maceration combined with lytics, direct thrombectomy (craniotomy), balloon angioplasty, snare, photoacoustic assisted thrombolysis (EPAR), ultrasonic intravascular assisted thrombolysis (EKOS). However, of these only the *MERCI* retriever is an FDA approved device. However guide wire maceration of the clot followed by lytics is also technique that is probably often used when administering IA thrombolytics. All others are experimental or non-FDA approved.

## **What neuroimaging is available beyond non-contrast cranial CT, and how might it enhance understanding of the ischemic penumbra and acute care strategies?**

In brain imaging of patients with acute ischemic stroke there are four questions to be answered. 1. Is there a bleed? 2. How much of the brain is irreversibly injured? 3. Is the vessel occlusion large or small? and 4. Is there a clinically relevant “ischemic penumbra” (at risk, but viable, brain)? Traditional CT imaging answers the first and maybe the second and third question, but not the fourth. MRI can answer all four, but is not logistically available at most institutions. CT angiography (CTA) with CT perfusion is more likely to be available to the ED and is probably capable of answering all questions. In gauging the risk / benefit of thrombolysis, imaging the penumbra may in fact be a better gauge of benefit than time from symptom onset. Perfusion imaging plays a greater role in patients that present 3 to 6 hour window following stroke onset in deciding which patients are optimal candidates for intra-arterial (IA) thrombolysis. If the entire infarcted brain is “dead” with less than half remaining viable brain, the risk of IA thrombolysis is greater than the benefit.

## **Is there data to suggest that all ischemic stroke patients should receive advanced neuroimaging and interventional radiological techniques, regardless of time from symptom onset and IV tPA use?**

Regarding interventional techniques - in the first 3 hours, there is not conclusive data which suggests that intra-arterial reperfusion techniques are superior to systemic lytics. However, there is data showing that with systemic lytics 39% of patients will never reperfuse, and 18% will take more than one hour to reperfuse as documented on trans-cranial doppler. This begs the question – if both treatment options are available at the same time, will IA be a better option.

Regarding advanced neuro-imaging, again traditional head CT remains the primary imaging modality. However, there is also data which shows that perfusion imaging of the ischemic “penumbra” may be a better marker of a patients’ reperfusion eligibility than time from symptom onset. In a study by Ribo, patients with documented viable “penumbra” tissue that were given IV tPA at 3 to 6 hours were as likely to have a modified Rankin score less than 2 at three months as those patients treated within 1 to 3 hours of infarct onset.

**What interventional radiographic techniques are available, and how might they enhance perfusion of the ischemic penumbra and enhance patient outcome?**

Interventional reperfusion can be broken down to intra-arterial (IA) thrombolysis, mechanical thrombectomy, or a combination of both. Regarding IA thrombolysis, Lisboa did a summary analysis of 27 studies comparing outcomes of IA thrombolysis with a control group (no lysis). IA patients were more likely to achieve a good clinical outcome (41% vs 23%, O.R. 2.4), and a lower mortality rate (27% vs 40%). While several mechanical reperfusion devices have been studied, only the MERCI thrombectomy coil is FDA approved. In the MERCI trial, this device achieved recanalization in 48% of patients, with 28% achieving a modified Rankin score less than 2 on follow-up. The IMS study showed that IV plus IA lytics have rates of intracranial bleeding that is comparable to patients treated with lytics alone (6.3%), with comparable improvements in three month outcomes relative to placebo (mRS of 0-2 of 43% vs 28%). The multi-MERCI trial showed similar results.

**Do any of the experimental protocols utilizing these advanced techniques suggest any modifications in current ED practice when managing acute ischemic stroke patients?**

Perfusion or “penumbra” imaging, MR diffusion / perfusion or CTA perfusion, might be considered in patients whose stroke is greater than 3 hours as long as it does not delay therapy.

**Given that there are FDA approved devices that promote reperfusion but no standard of care with regards to accessing these devices, what is the best approach of the emergency physician in 2006?**

If a stroke patient presents within 3 hours of symptom onset, traditional management with IV tPA is a very reasonable approach. The most compelling change to consider is that if an otherwise thrombolytic eligible patient misses the 3 hour treatment window, but is still less than 6 hours from stroke onset, and IA

thrombolysis is available within that timeframe – that might be best to pursue that option. Additionally, because basilar artery strokes are so devastating and have such a high mortality rate, the IA treatment timeframe can be extended up to 24 hours from symptom onset. These are “systems” and “resource” issues that the working emergency physician must consider - ideally before being confronted with the issue. The best approach is to work within one’s hospital to establish treatment protocols or transfer protocols.

### **Are there publications or clinical guidelines that provide a suggested approach to the use of stroke therapies beyond the three hour IV tPA window?**

In 2005 the Brain Attack coalition made recommendations for comprehensive stroke centers, which encompass what hospitals that provide these advanced therapies need to consider. This is a good guideline for such hospital systems. There are several strategies for organizing regional stroke interventional treatment strategies available – perhaps best summarized by Rymer et al.

### **Patient Case Hospital Course and Patient Outcome**

The patient was taken to the interventional radiology suite where a MERCI clot retrieval device was successfully used to remove his basilar artery thrombus. The patient was admitted to the ICU and showed much improvement. His hospital work-up demonstrated a patent foramen ovale and an underlying hypercoagulable condition. A PFO patch was placed he was placed on coumadin. Although he had mild remaining dysarthria, he was able to perform all functions of independent living on 30-day follow-up evaluation.

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