

STROKE INFARCTION: THROMBOLYSIS



“Perseus and the Sea Nymphs”, oil on canvas, 1884-85, Edward Burne-Jones.

Perseus was one of great heroes of ancient mythology. Like Heracles, Achilles, Theseus, and others he was a demigod, born of Zeus his father and the beautiful mortal, Danae, his mother. Perseus and his mother lived happily on the island of Seriphos until one day its king, Polydectes ordered Perseus to undertake an impossible suicide mission. The treacherous Polydectes lusted after Perseus' mother, Danae, and he wanted the watchful young man, who closely protected his mother, out of his way, so he could pursue her. He commanded Perseus to kill the monster, the gorgon Medusa. With hundreds of snakes sprouting from her head, her appearance was so horrible that no living thing could look her directly in the eye without being instantly turned into stone! King Polydectes was certain that Perseus would be killed by Medusa, however he perhaps didn't understand who Perseus' father was; many of the gods were outraged that a son of Zeus and a mortal wife of the great god could be so badly treated. The goddess Athena in particular took an intense interest in the plight of the young hero, as she held a special hatred for Medusa. Many years before Medusa had been a very beautiful but also very conceited woman. She had had sex with the god Poseidon in the Temple dedicated to Athena and so had earned the everlasting wrath of the powerful goddess. For this unforgivable insult, Athena turned Medusa, as well as her two sisters, into the horrible gorgons. She took Perseus under her personal protection. She went to him and gave him very careful instructions on how he could kill the gorgon. She instructed him to go to North Africa and seek out the Graeae, three horrible witches, who could give Perseus the knowledge to find Medusa.

Before Perseus set out for North Africa, Athena gave him a great bronze shield, so highly polished it could be used as a mirror. The god Hermes, then came to Perseus and gave him a magical sword. Finally Athena instructed Perseus to seek out a certain group of Sea Nymphs who would also help him. The Sea Nymphs supplied Perseus with a magical winged helmet, which could also make him invisible, as well as a pair of winged sandals, by which he could fly to North Africa and finally they gave him a special sack, the only object able to safely hold the head of the monster. Perseus flew to North Africa on his winged sandals and found the three witches beside the great Ocean that surrounds the Earth. They were terrifying old crones, who only had one eye between them, which they would have to pass between themselves in turn and place it in their face in order to see. At first they refused to provide the location of Medusa but as they were passing the eye around, Perseus grabbed it from them and warned them that he would not return it unless they told him what he needed to know. Reluctantly, they gave him the information he desired upon which to the crones' great distress; he flung the eye into the sea - perhaps not one of the Perseus' finest moments! Swiftly then Perseus flew on his winged sandals to the land where the terrible Medusa and her two sisters dwelt. He found the three of them sleeping. Barely able to breathe he inched forward towards Medusa using his bronze shield as a great mirror to see his way and to avoid her direct eye, lest he be instantly turned into stone. When he was close enough, with one mighty blow from his sword, he severed Medusa's monstrous snake-covered head from her body. Poisoned blood spewed forth in abundance, and from it sprang to life two magical creatures, one a monster of the essence of her current form - the Chrysaor, the other of the essence of her former beauty - the magnificent winged horse, Pegasus. Ancient sources record that he then flew away on his winged sandals carrying Medusa's head in the sack given to him by the Sea Nymphs, but later artistic Renaissance traditions have him mount the winged horse Pegasus to make good his escape. On his flight back to Seriphos, Perseus catches sight of the beautiful Andromeda chained to the rocks for sacrifice to a sea monster, the

Kraken. He instantly falls in love with Andromeda and swoops down on his winged horse to rescue her. He does battle with the Kraken, having difficulty in fighting it off with his sword, but eventually manages to extract Medusa's head from its sack, and without looking at it directly points it at the Kraken and turns it to stone. After many other adventures, he eventually arrives back at Seriphos to find to his horror that his mother has sought sanctuary in a temple to avoid the lecherous advances of King Polydectes. The king is stunned to see that Perseus has not only survived his encounter with Medusa, but has also managed to kill her and bring back her head, as he had commanded. Perseus, outraged at King Polydectes' treatment of his mother, points Medusa's head at him and turns him into "bloodless stone". Perseus and Andromeda then live long happy lives together and have many children. When they die a grateful Athena places them both, alongside with Pegasus, among the Constellations of the heavens.

When we are faced with a difficult mission it is vital that we have at our disposal the necessary implements to ensure its success. When we contemplate stroke thrombolysis, we must, as Perseus had, have the appropriate implements on hand. Sadly we do not have magical gifts of the gods to assist us, but we do have the wondrous technology of the 21st Century - in the form of CT angiography and the CT perfusion scan.



*"Perseus", in bronze,
Benvenuto Cellini, 1545,
Loggia dei Lanzi, Florence,
(author's photograph, 2011)*

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Introduction

Patients with some types of acute ischaemic stroke can benefit from intravenous Alteplase (recombinant tissue plasminogen activator, rtPA) thrombolytic treatment given as soon as possible and within **4.5 hours of symptom onset**.

Patients who receive thrombolysis have, on average, a 30% reduction in the risk of developing moderate to severe disability as a consequence of the stroke.

Stroke thrombolysis therapy has therefore become an important treatment option for acute ischaemic stroke patients.

This treatment is complex and requires specific hospital systems protocols, and imaging capabilities run under the expert supervision of clinicians and radiologists experienced in this treatment. Institutions that cannot provide these should not initiate this treatment.

Each institution must have its own dedicated protocols that take into account local expertise, practice and resources.

The following is a general educational discussion only on the principles of this treatment and does not replace the need for local protocols.

Pathophysiology

Once a cerebral artery is occluded a variable central **core** of tissue quickly infarcted and dies within a matter of minutes.

Surrounding the central infarcted core however is a variable region of partially perfused tissue which may remain viable providing arterial blood flow can be fully re-established within 4.5 hours. The earlier flow can be re-established to this region, the greater the chance of survival of this tissue. This region of potentially salvageable tissue is known as the **ischaemic penumbra**.

Early stroke management aims at identifying the region of ischaemic penumbra where possible and re-establishing arterial flow as soon as possible.

Systems

Thrombolysis should only be undertaken in well equipped and skilled EDs that have adequate expertise and infrastructure for the monitoring, rapid assessment and investigation of acute stroke patients.

It should only be given under the authority of a physician trained and experienced in stroke management.

Local prehospital early warning systems should be in place to alert receiving Emergency Departments of incoming stroke patients

Local systems should be in place for an Emergency **Code Stroke protocol**, once the patient arrives in the ED, in order to alert and mobilize all necessary staff involved in the treatment of acute ischaemic stroke.

Local practice varies, but commonly ED physicians will perform an initial assessment and stabilization of the patient, and initiate urgent investigation. Radiologists in conjunction with Neurologists will assess the radiological images, and the consultant Neurologist will usually make the final decision to thrombolyse the patient. ICU staff also need to be alerted, as they will generally assist in the immediate post thrombolysis period.

Criteria

Inclusion Criteria

1. **Within 4.5 hours of symptom onset, but the earlier treatment is initiated (< 90 minutes in particular), the better.**
 - *For patients who woke up with stroke symptoms, the time of onset must be assumed to be the time they were last seen well.*
2. Patients must have clear clinical signs of a stroke with measurable neurological deficit (impaired language, motor function, cognition, vision, gaze, and/or sensory function including, inattention).
3. A grading NIHSS greater than 4.
4. CT brain excludes intracerebral haemorrhages and other stroke mimics (e.g. space occupying lesions).
5. Patient aged 18 years or over.
 - Age over 80 is considered a relative contraindication in the 3.0 - 4.5 hour window.

Exclusion Criteria

1. Stroke of minor degree:
 - NIHSS 4 or less or resolving stroke
2. Stroke of very major degree:
 - Coma or severe obtundation with fixed eye deviation and complete hemiplegia

- CT showing signs of early infarction in >1/3 of one MCA territory
3. Significant pre-morbid disability:
 - Modified Rankin Score of 4 or more
 4. Clinical suspicion of septic embolism e.g. sub-acute bacterial endocarditis
 5. Possible stroke mimic:
 - Seizure at symptom onset
 - Blood glucose < 2.8 mmol/L or > 22 mmol/L
 - Suspicion of SAH, even if CT normal.
 6. Hypertension:
 - Blood pressure \geq 180/110
 7. Combination of diabetes and previous stroke, if in the 3.0 - 4.5 hour window.
 8. Pregnancy:
 - A strong relative contraindication.
 - Recent (< 10 days) childbirth.
 9. Other general contraindications to thrombolytic therapy including:
 - Coagulopathy including:
 - ♥ Warfarin treatment, with international normalized ratio (INR) 1.6 or greater

Or on oral anticoagulants (regardless of INR), in the 3-4.5 hour window.
 - ♥ Known bleeding diathesis of any cause (acquired or inherited).
 - ♥ Platelet count <100x10⁹/L.
 - Previous intracerebral haemorrhage, including subarachnoid haemorrhage, and/ or known intracerebral aneurysm, arteriovenous malformation or brain tumour
 - Ischaemic stroke in the previous 3 months.

- Myocardial infarction (risk of myocardial rupture) or pericarditis (risk of bleeding) in the last 30 days.
- Recent trauma:
 - ♥ Serious trauma or major surgery in the previous 30 days
 - ♥ Recent (< 10 days) prolonged or vigorous CPR.
- Active or recent systemic haemorrhage where recurrent bleeding would be unmanageable
- Recent (< months) ulcerative gastrointestinal disease or oesophageal varices.
- Hemorrhagic retinopathy

Investigations

Blood tests

- FBE
- U&Es/ glucose
 - ♥ Blood glucose needs to be optimized < 2.8 mmol/L and < 22 mmol/L
- LFTs
- Coagulation profile
- ESR/CRP
- Blood group and hold

Note that although blood tests are urgently requested, thrombolysis administration should not be unduly delayed whilst awaiting results (including the eGFR) *when there is no prior clinical suspicion* that an abnormality may be present.

ECG:

- 12 lead

Imaging

Urgent CT scanning of the brain.

Where there is not a contra-indication to IV contrast and where there will not be unacceptable delays to treatment, **CT angiography** and **CT perfusion scanning** are also desirable.

Management

Initial activation of the **Code Stroke Response**

1. Attend any immediate ABC issues
 - Gain two IV access points
 - Take blood for laboratory studies
2. Check blood glucose
3. 12 lead ECG
4. Control of blood pressure:

This must be kept to below **180/110**

Options include:

- IV Labetalol
 - IV GTN infusion
 - IV hydralazine
5. Alteplase (rt-PA):

After close consultation with radiologist and neurologist.

The possible risks and benefits of this therapy should be discussed with the patient (where possible) and/ or next of kin.

Dosing:

- Alteplase is given as an IV infusion.
- The total dose is given on a per weight basis:
 - ♥ **0.9mg/kg to a maximum total dose of 90mg.**
 - ♥ **The first 10% of the total dose given as a slow bolus over 1 minute and the final 90% of the dose is given IV over 60 minutes immediately following the initial bolus, (the half life of rtPA is only 5 minutes).**

6. A repeat CT brain is performed routinely within 24 to 36 hours after thrombolysis for exclusion of occult bleeding.
7. Aspirin (or other anti-platelet agents) and heparin infusion (or similar) must not be given within 24 hours of rtPA administration and ideally, these drugs should be withheld until the repeat CT brain scan is performed.
8. Definite neurological deterioration occurring during rtPA infusion or during the first 24 hours after treatment *should be assumed to be intracranial haemorrhage until proven otherwise. An urgent repeat CT scan must be done.*

Disposition

Patients should remain in the ED until the Alteplase has been given.

Admission should be to a monitored **High Dependency** or **Intensive Care Unit**.

References

1. **Clinical Guidelines for Acute Stroke Management National Stroke Foundation 2010**

Dr J. Hayes
February 2013