Poor clinical outcome despite successful arterial recanalization. What went wrong? How can we do better?

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In the treatment of hyperacute ischemic stroke, there is consensus regarding 1. Time is brain 2. Early recanalization helps [1]. It is also well known that, surrounding the core of infarcted brain, there is often salvageable tissue also known as penumbra. While there continues to be ongoing discussion regarding the best imaging modality to document the penumbra and use it to guide therapy, it is clear that penumbra is a dynamic state dependent on several factors [2]. Hence, any imaging modality even if perfectly accurate would document the state of penumbra at that instant and would not allow precise extrapolation into the future.

The NINDS study [3] established the role of IV therapy in the treatment of acute stroke. The effect size overall is quite small and rapidly diminishes with relatively delayed initiation of therapy. It is quite clear the IV approaches result in significant time saving compared to IA approaches and allow “drip and ship” strategies. However, if the IV approach achieves either no recanalization or recanalization after several hours, it may not necessarily provide any time savings. Unfortunately, we have no well-documented data on precise recanalization times with IV strategies. The PROACT-II [4] study showed benefit of intra-arterial (IA) thrombolysis in a highly select group of patients. Since that time, various neurointerventional centers involved in acute stroke procedures have anecdotally shown good outcomes in patients with large vessel occlusions using a variety of

chemical and mechanical means. Also, the ability of IV-tPA to recanalize large occluded vessels such as ICA or proximal MCA has been shown to be limited [5, 6]. This led to the various Interventional Management of Stroke (IMS) trials [7, 8]. The trial design is centered on starting the IV drug and then taking the patient to the angiography suite to recanalize the vessel using chemical or mechanical means when necessary. In IMS-III [9], there is randomization of IV therapy only against IV and IA approach. This trial is currently enrolling, and results are likely at least a few years away. Of note, in the IV only studies, there is no easy way to document precisely when recanalization and hence, restoration of blood flow to the penumbra takes place. In the IA studies, this documentation is easy but has not been systematically documented against the time of onset of symptoms or against the last imaging (that could potentially provide some insight into the salvageable tissue) study. The documentation often relates to the commencement of the therapy.

Recently, we have seen a dramatic advancement in the tools for achieving successful recanalization of occluded vessels using the IA approach [10]. The Multi-MERCI trial [11] demonstrated the results using the L5 retriever device. Interestingly, while there was an excellent recanalization rate (69.5%), favorable clinical outcomes occurred in only 36% with a mortality of 34%. The Penumbra study [12] demonstrated an 81.6% revascularization rate with only a 25% good outcome. In both the studies, patients in whom recanalization was achieved did better than those in whom it was not successful, providing further proof that recanalization helps.

The question still remains: why is there a poor rate of good clinical outcome in spite of recanalization?

At the expense of oversimplifying a complex problem, it makes intuitive sense and is supported by available

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literature that the likelihood of good outcome is dependent primarily on:

1. Good premorbid status and relatively small deficit at presentation;
2. Small infarct core (of course, the eloquence of involved brain would play a role);
3. Short-time interval between imaging and recanalization (to maximize the likelihood of salvaging the penumbra); and
4. Low complication rate related to the intervention (whether IV or IA; chemical or mechanical).

There are, in addition, several other factors that play an important role but are either not easily measurable or modifiable. Selective vulnerability of neurons is well known but is currently neither measurable nor modifiable. Collaterals are responsible for sustaining ischemic brain beyond the level of occlusion. Measurement of collateral flow, its variation over time, and intervention to augment collateral flow may prove to be quite useful in the not too distant future [13]. Separation of penumbra from benign oligemia remains a challenge. Persistence of penumbra, well beyond the traditional “time-window” for treatment, is well documented [14]. We are still not very good at predicting the rate of progression of penumbra to infarct. Also, we have no clear strategies to check if arterial recanalization does in fact result in reperfusion of brain tissue.

I feel that there should be a change in how we design and report acute stroke intervention studies. There should be more focus on documenting infarct core rather than penumbra [15]. In addition, all energies of the trial design and the stroke team should be focused on achieving quick recanalization in a safe fashion. Recanalization time should be precisely documented (this is clearly not an easy task for studies using IV treatment strategies but transcranial Doppler may play an important role in this regard). This data (infarct core and imaging to recanalization time) should be clearly reported. It is quite possible and likely that patients with low infarct volume at imaging and quick subsequent recanalization will show a good clinical outcome, while patients with a sizeable infarct core and in whom recanalization is delayed or results in complications shall be the ones with the bad clinical outcome. Presenting results in this way would have several positive implications:

1. If we are able to show that there is clear clinical benefit to early safe recanalization in patients with small core at presentation, we would be able to breakdown the process to look at various aspects of the patient’s care from the time the patient presents to the hospital to the time recanalization is achieved. As an example, we

could look at time taken from presentation to ER to start of imaging, time it takes to image, time of image interpretation, time to start of IV treatment (if applicable), time to reach angiography suite, time to groin puncture, time to reach the clot, and finally, time taken to achieve recanalization. Each part of the process could be analyzed independently with an attempt to reduce the total amount of time taken (please note that the time it takes to achieve recanalization once we are at the clot face is but a small part of the entire process that the patient must go through).

2. Hospitals would focus on creating the infrastructure to allow for quick, safe recanalization. Correspondingly, the industry would focus their resources on devices/drugs to reduce the time from puncture to recanalization.
3. Imaging protocols would focus on methodologies to efficiently and precisely document vessel occlusion and infarct core (as opposed to trying to document the penumbra not only in an imprecise fashion but also at one point in time that may be a couple of hours away from recanalization). Understanding the vascular anatomy and site of occlusion would allow for better planning of safe and efficient recanalization strategies.

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