A research roadmap of future endovascular stroke trials


The recent completion of the MR CLEAN trial and news of early stoppage of other stroke trials demonstrates the ability of the neurointerventional community to address a crucial question that has hindered the ability of intra-arterial therapy (IAT) to be offered more widely. The focus of future studies will now shift towards improving clinical outcomes in patients undergoing IAT.

PATIENT SELECTION

Imaging

There is currently no consensus regarding the optimal imaging strategy for the selection of patients for intervention. The modality must be efficient, accurate, available, and repeatable. Non-contrast CT using Alberta Stroke Program Early CT Score (ASPECTS) scoring, CT perfusion and MRI are all in widespread clinical usage at interventional stroke centers. A trial comparing different modes of imaging based patient selection would be valuable and currently does not exist. There are advantages and disadvantages to each technique with strong beliefs that each modality has its advantages.

The question is whether the widespread availability, ease of access and time savings justify using non-contrast CT (supplemented by ASPECTS) as ‘good enough’ to select patients when compared to advanced imaging modalities that may be more specific to detecting ischemia. Developing an educational pathway with ASPECTS scoring to reduce inter-rater variability along with a standardized CT perfusion algorithm that can be replicated across institutions can allow for a trial examining this question to occur. The current landscape would potentially also allow for an MRI comparative trial.

Selection scales

Another critical element of proper patient selection is the patient demographics. Clinical information such as time from stroke onset, nature of large vessel occlusion, admission National Institute of Health Stroke Scale (NIHSS), collateral grade, age and medical comorbidities contribute to outcomes after stroke. The Houston Intra-arterial Therapy (HIAT) scale and Total health risks in vascular events (THRIVE) score represent validated attempts at predicting outcomes in patients treated with IAT using readily available clinical information on admission. Such scales may allow for improved triage of patients being considered for inter-facility transfer or pre-hospital notification to an institution performing IAT and defining the optimal matching of appropriate scales with various clinical scenarios could be the goal of future trials.

FACILITATED REPERFUSION

A more controversial and challenging study design would be to test the hypothesis of if intravenous t-PA prior to IAT is beneficial to patients. Although the current evidence supports administration of t-PA to all patients who meet inclusion and exclusion criteria, it is not clear if this treatment offers additional benefit to patients undergoing IAT for large vessel occlusion. Patients presenting to an institution’s emergency room that offers endovascular treatments could be randomized to IV t-PA and IAT compared to IAT only. There is precedence with such a trial in the cardiac literature. For example a meta-analysis of ST-elevation myocardial infarction showed pre-percutaneous coronary intervention (PCI) thrombolysis was not beneficial and increased bleeding complications.

USE OF GENERAL ANESTHESIA

At many centers the sedation type used for acute stroke interventions has evolved from general anesthesia towards conscious sedation over several years. Several reports suggest patients have better outcomes with the latter. However, these data are derived from retrospective studies in unselected and non-randomized patient populations. A recent analysis by McDonald et al reviewing the Premier database indicates that adoption of conscious sedation is not widespread. Given the equipoise surrounding this question, a randomized trial of conscious sedation versus general anesthesia for patients amenable to intervention under either circumstance is feasible. This will allow centers to define and standardize pathways with their respective anesthesia departments with supportive evidence on how best to sedate patients prior to the most important variables in stroke intervention. Inter-facility transfers from a primary stroke center to an endovascular capable center has been fraught with delays potentially leading to worse clinical outcomes. Whether tissue plasminogen activator (t-PA) should be delivered rapidly with the patient then transferred versus directly taking the patient to an IAT ready center where there may be a delay in t-PA delivery but faster intervention is a crucial question. Such investigations are essential to the development of stroke systems of care.
intervention. There are logistical challenges to such a trial including the development of an experience curve and ensuring adequate hemodynamic parameters for each group. However, the ability to determine if there is a clear benefit, or absence of benefit, with a given management paradigm would standardize the treatment and provide benefit to patients.

PROCEDURAL TECHNIQUES

Device technology has rapidly evolved allowing interventionists to achieve high rates of reperfusion. Many retrospective analyses have shown times to reperfusion of various techniques, but the question that needs to be addressed is if one technique is superior to another. For instance, recent data suggests proximal balloon guide occlusion may improve reperfusion and outcomes.11 Evolution of techniques will allow for randomized comparisons such as balloon guide to regional aspiration with thrombectomy or aspiration alone to thrombectomy. Similarly, for patients presenting with proximal carotid artery occlusion/stenosis whether stenting/angioplasty should be performed and evaluating if anti-coagulants or anti-platelets are of benefit prior to or during IAT would all be interesting clinical questions. Standardization of procedural techniques with information gained through comparative trials will allow for clinicians to deliver optimal care going forward.

NEUROPROTECTION AND REPERFUSION INJURY

Many neuroprotective drugs have failed in clinical trials in ischemic stroke. The reasons for this are manifold. One reason is the availability of the medication prior to the onset of ischemia. There is a unique opportunity with the ability to deliver therapies prior to reperfusion that would potentially reduce the secondary injurious effects of reperfusion injury. Such trials may potentially begin in the pre-hospital phase similar to the FAST-MAG trial13 or in the hospital with novel therapeutic agents reducing the secondary effects of reperfusion that may harm patients. One such treatment is hypothermia that may have benefits due to its pleiotropic effects.13 The ReCCLAIM I study14 recently showed the feasibility and initial safety profile of employing hypothermia in conjunction with reperfusion therapy and the multi-center phase II study has just begun randomizing patients undergoing endovascular reperfusion therapy to hypothermia and normothermia.

EXTENDED TIME WINDOWS

As the recent data shows the benefits of IAT for large vessel occlusion up to 6 h from last known normal, there is the opportunity to best understand if patients achieve benefit from reperfusion treatment beyond this time point. Two ongoing trials POSITIVE13 and DAWN16 are currently enrolling patients to address this crucial question.

CONCLUSION

We have reached an exciting time point in the field of stroke where the clinical trials can be escalated to identify best practices for treating patients. In this commentary we have delineated a roadmap for future areas of study as the field continues to evolve. Exciting times indeed.

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