FRONTIERS OF MECHANICAL THROMBECTOMY IN ACUTE ISCHEMIC STROKE

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In 2015 five major trials established endovascular therapy with mechanical thrombectomy as standard of care in the treatment of acute ischemic stroke (AIS) due to emergent large vessel occlusion. These trials largely used retrievable stents, or “stent-retrievers” for mechanical thrombectomy of identified anterior circulation proximal occlusion within 12 hours of onset. A pooled analysis calculated that the number needed to treat (NNT) to reduce disability, as per shift in modified Rankin Scale (mRS), was 2.6. [1]

American Heart Association / American Stroke Association (AHA/ASA) and European practice guidelines for the early management of acute ischemic stroke were subsequently updated to include recommendations based on the positive trials of mechanical thrombectomy. [2, 3]

Major determinants of eligibility include time from symptom onset, identified target large vessel occlusion, size of core infarct, and anterior versus posterior circulation location. These variables represent the relative boundaries of endovascular therapy. [3] As technology in the field advances and experience accumulates, more opportunities for optimizing endovascular technique and broadening inclusion criteria will likely be identified. A discussion of this frontier for mechanical thrombectomy is pertinent.

<u>Prolonged time from symptom onset:</u>

An estimated 20% of all acute stoke admissions may be those who experienced the stroke during sleep to discover the symptoms only after waking. These so called “wake-up stroke” patients are not currently considered eligible under established guidelines of standard of care. A recent international survey of stroke experts reported a majority recommended recanalization treatment despite the time delay beyond 6 hours.[4]

Trials to study the potential benefit of mechanical thrombectomy in this group include the Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes (DAWN) and Endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE 3) trials, both actively enrolling patients.

DAWN is a prospective, multicenter, Phase II/III (feasibility/pivotal), randomized controlled trial designed to demonstrate that mechanical thrombectomy using a stent-retriever with medical management is superior to medical management alone in improving clinical outcomes at 90 days, in appropriately selected wake up and late presenting acute ischemic stroke subjects. [5]

DEFUSE 3 is a prospective, multicenter, Phase III randomized controlled trial of patients with acute ischemic anterior circulation strokes due to large artery occlusion treated between 6-16 hours of stroke onset with mechanical thrombectomy therapy versus control. [6]

<u>Treatment with intravenous (IV) tissue plasminogen activator (tPA) prior to mechanical thrombectomy:</u>

IV tPA in treatment of proximal vessel occlusion has low rates of acute recanalization and with current stent-retriever technology its use prior to thrombectomy may be of limited value, especially if rapid endovascular therapy is readily available. [7, 8]

A subgroup analysis of 6 randomized controlled trials studying the efficacy of mechanical thrombectomy for AIS showed that endovascular therapy was associated with a higher probability of improved functional outcome regardless of pretreatment with IV tPA. [9]

Recently a pooled analysis of 2 large, multicenter trials of stent-retriever thrombectomy in AIS also failed to show clinical benefit of IV tPA treatment before mechanical thrombectomy. [10]

A single center retrospective analysis compared outcomes and hospital costs for anterior circulation large vessel occlusion treated with either mechanical thrombectomy alone or in addition to pre-treatment with IV tPA. Combined therapy was associated with higher hospital costs than mechanical thrombectomy alone. [11]

It is important to note that IV tPA remains standard of care in AIS and can represent the only rapidly available treatment for some patients where there may be a delay in, or unavailability of, endovascular therapy. IV tPA may serve to aid in ease of thrombectomy and enhance distal reperfusion. A study employing an animal model of MCA occlusion with real-time imaging downstream of the occluded vessel showed that downstream microvascular thrombosis is an early phenomenon and preservation of cerebral microvascular perfusion with early administration of IV tPA, and before recanalization, was associated with reduced final infarct volume. [12]

Location of vessel occlusion:

Patients with M2 middle cerebral artery (MCA) segment occlusions are at risk for adverse outcomes, and occlusions often persist despite IV tPA treatment.[13]

In the major trials of endovascular therapy only 8% of patients studied had an occlusion of the M2 MCA; the ESCAPE, REVASCAT, and SWIFT PRIME trials did not include patients with isolated M2 occlusions. As such, thrombectomy is currently not considered the standard of care for patients with an M2 occlusion.[1, 2]

50 patients with isolated M2 compared to 249 proximal (M1) MCA occlusions pooled from 3 large prospective studies on stent-retriever thrombectomy in AIS showed feasibility of therapy in selected patients with M2 occlusions. No significant differences were found in recanalization rates, adverse events or 90 day good functional outcome (mRS 0-2).[14]

A retrospective pooled analysis from 10 academic stroke centers of patients with AIS presenting within 8 hours of onset with distal large vessel occlusion (M2 MCA segment) found higher proportions of favorable clinical outcomes with endovascular therapy in comparison to medical therapy alone. [15]

Posterior circulation large vessel occlusions were also not included in the positive endovascular trials of 2015, however due to the poor natural history of basilar thrombosis, endovascular therapy is considered reasonable. [2] Quality evidence regarding its efficacy is lacking and a multicenter randomized controlled trial is ongoing. [16]

Size of core infarct:

In current practice CT and MR imaging are employed in acute stroke imaging, however given the widespread availability and speed of imaging acquisition, CT may be best suited for use in the rapid decision making required for successful treatment of acute stroke. Patient selection based on acute imaging protocols may also include perfusion analysis to demonstrate salvageable tissue or “penumbra” prior to deciding on endovascular treatment.

In clinical practice patients with large ischemic core may be excluded from therapy based on the presumption of poor outcome regardless of therapy.

A match case-control study of patients with anterior circulation internal carotid artery (ICA) and/or MCA proximal occlusion with large baseline core infarct (greater than 50mL on CT perfusion) showed benefit of endovascular therapy in selected patients. [17]

Size of core infarct is commonly described using the Alberta Stroke Program Early CT Score (ASPECTS). [18]

Recently a subgroup analysis of the MR CLEAN trial suggested that lower ASPECTS (5-7) should be treated. However evidence in support of endovascular therapy in patients with scores lower than 5 is needed. [19]

Minor stroke severity:

The updated AHA/ASA guidelines designate Class IIb evidence for stent-retriever thrombectomy in patients presenting with mild stroke (as defined by NIHSS $\leq$ 5) and presence of large vessel occlusion.

Patients with mild symptoms may deteriorate neurologically as collateral circulation fails. This is associated with worse outcomes and rescue endovascular therapy may offer suboptimal benefit due to delay in recanalization therapy while waiting for neurologic decline. [20]

Direct endovascular therapy for patients with low initial NIHSS and underlying large vessel occlusion may be of utility given the observed incidence of neurologic deterioration and observed poorer outcomes with medical therapy despite rescue endovascular therapy. [21]

Optimal endovascular technique:

The evolution of mechanical thrombectomy from intra-arterial thrombolysis to mechanical thrombectomy has ultimately led to stent-retriever technology being used as the endovascular technique of choice, bolstered by its use in the positive trials. Recently reports of a first past direct aspiration technique (ADAPT) using wide bore catheter with manual or pump aspiration has yielded promising recanalization rates and short procedural times. [22, 23]

Combination therapy using the deployment of a stent-retriever along with local aspiration via large bore catheter, advanced to the proximal end of the thrombus, is a technique used to achieve successful recanalization while minimizing embolization of thrombus fragments to new vascular territory. A comparison study of stent-retriever plus aspiration technique versus ADAPT, showed significantly better 90 day clinical outcomes with direct aspiration alone. [24]

An observational comparison study of direct aspiration versus stent-retriever thrombectomy, in acute stroke patients treated within 6 hours of onset, found higher recanalization rates with aspiration technique. [25]

The Interest of Direct Aspiration First Pass Technique (ADAPT) for Thrombectomy Revascularisation of Large Vessel Occlusion in Acute Ischaemic Stroke (ASTER) trial is on-going, the estimated completion date is early 2018. The study aims to study the ADAPT technique as superior to stent-retriever in first line strategy for mechanical thrombectomy of large vessel occlusion. [26]

The use of special guide catheters in combination with distal reperfusion strategies has been described and employment of a balloon guide catheter, with proximal flow arrest and manual aspiration performed during retrieval of the thrombus, is associated with superior recanalization and faster procedure times. [27]

Conclusion:

Mechanical thrombectomy for AIS represents a new era of effective therapy for patients at risk for catastrophic disability. There are multiple areas of uncertainty regarding exclusion of patients based on the clinical and imaging variables discussed. It is worth noting that strict adherence to guidelines may result in withholding therapy that may be potentially beneficial. A retrospective observational study of consecutive large vessel occlusion stroke patients that underwent endovascular therapy, including those with strict adherence to published guidelines (using top-tier evidence from selective criteria in the recent trials), reported that up to 49% of patients would have been excluded if these criteria were upheld in practice. The data presented did not reveal an increased risk of symptomatic ICH. After adjusting for confounders, top tier treatment was not associated with early neurologic improvement, 90 day mortality or favorable mRS. [28]

Moving forward it is important that we continue to consider the risk benefit profile of available therapies, emphasizing individualized care while considering current guidelines as we strive for improved patient outcomes in large vessel occlusion AIS,

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