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Acute ischaemic stroke interventions: large vessel occlusion and beyond

Ahmad Sweid,[1] Batoul Hammoud,[2] Sunidhi Ramesh,[3] Daniella Wong,[3] Tyler D Alexander,[3] Joshua Harrison Weinberg,[1] Maureen Deprince,[1] Jaime Dougherty,[1] Dimitri Jean-Mickael Maamari,[4] Stavropoula Tjoumakaris,[1] Hekmat Zarzour,[1] Michael R Gooch,[1] Nabeel Herial,[1] Victor Romo,[5] David M Hasan,[6] Robert H Rosenwasser,[1] Pascal Jabbour [1]

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[1]Neurosurgery, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA
[2]Endocrinology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
[3]Sydney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA
[4]School of Medicine, American University of Beirut, Beirut, Lebanon
[5]Anesthesia, Thomas Jefferson University—Center City Campus, Philadelphia, Pennsylvania, USA
[6]Neurosurgery, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA

Correspondence to
Dr Pascal Jabbour;
Pascal.jabbour@jefferson.edu

ABSTRACT

Care for acute ischaemic stroke is one of the most rapidly evolving fields due to the robust outcomes achieved by mechanical thrombectomy. Large vessel occlusion (LVO) accounts for up to 38% of acute ischaemic stroke and comes with devastating outcomes for patients, families and society in the pre-intervention era. A paradigm shift and a breakthrough brought mechanical thrombectomy back into the spotlight for acute ischaemic stroke; this was because five randomised controlled trials from several countries concluded that mechanical thrombectomy for acute stroke offered overwhelming benefits. This review article will present a comprehensive overview of LVO management, techniques and devices used, and the future of stroke therapy. In addition, we review our institution experience of mechanical thrombectomy for posterior and distal circulation occlusion.

INTRODUCTION

Care for acute ischaemic stroke is one of the most rapidly evolving fields due to the robust outcomes achieved by mechanical thrombectomy. Until the mid-1990s, little to no progress had been made in the treatment of stroke. Intravenous tissue plasminogen activator (tPA) was found to have some (but limited) benefit.[1] However, due to the narrow window of treatment (that was initially 3 hours then extended to 4.5 hours) where only 3.4%–5.2% of patients who had a stroke receive tPA,[2] the low rate of vessel recanalisation (13%–50%)[3–6] and the low rate of favourable outcomes (12.9%–30%),[7 8] extensive efforts have been placed to achieve outcomes similar or equivalent to the cardiac field. In 2013, three randomised controlled trials (RCTs) failed to show real benefit for catheter-based stroke interventions for large vessel occlusions (LVOs).[9–11] Two years later, a paradigm shift and a breakthrough brought back mechanical thrombectomy for acute ischaemic stroke into the spotlights; this was because five RCTs from several countries concluded that mechanical thrombectomy (MT) for acute stroke offered overwhelming benefits.[12–16]

LVO accounts for up to 38% of acute ischaemic stroke and came with devastating outcomes for patients, families and society in the pre-intervention era.[17 18] Efficacy of intervention in preselected patients presenting within 24 hours has been an established treatment paradigm.[19 20]

EPIDEMIOLOGY AND NATURAL HISTORY OF LVO

Stroke is the second leading cause of death worldwide, with a 16 million incidence.[21] The prevalence of stroke among the US population increases with age starting with 2.7% among people 20 years of age, 6% over 60 years and reaching 13% for people above 80 years. Each year, there are ~800 000 new or recurrent cases of stroke. With all the advancements, 17.5% still die, making it the fifth leading cause of death in the USA.[21] Patients who survive stroke may end up with long-term disability, requiring rehabilitation with an associated annual cost of more than US$40 billion in the USA alone.[21] In addition, the disability burden attributed to stroke continues to grow, with an estimated increase to 68 million disability-adjusted life years in 2020. The incidence of LVO, as defined in the introduction, compromises 24% to 38% of acute ischaemic stroke.[18 22] The proportion increases to 46% on including A2 and P2 segments.[17] The estimated 10 000 annual thrombectomies performed in recent years remains well below LVO incidence[23] and suggests a potentially significant future increase in the utilisation of endovascular stroke therapies.[24] Two-thirds of LVO occur in the anterior circulation, mainly in the Internal Carotid Artery (ICA) and Middle Cerebral Artery, and the remaining occur in the posterior circulation with equivalent distribution among the Vertebral Artery, Basilar Arterty and Posterior Cerebral Artery.[17] Tandem occlusions can occur in less than 10%.[17 25]

A meta-analysis reported a double proportion of poor outcome (modified Rankin Scale (mRS) 3–6) and mortality in patients with LVO as compared with patients without LVO in the pre-endovascular era (64 vs 24%, p<0.0001, 26.2 vs 1.3%, p<0.0001, respectively).[18] Intravenous tPA has two main limitations: it has a narrow treatment window of up to 4.5 hours since 2008 and high pharmacological resistance for more proximal occlusions (4%–8% for ICA vs 31%–44% distal recanalisation).[3 26 27]

PRE-INTERVENTION WORKFLOW

The terms 'time is brain' and 'picture to puncture' reflect the importance of early reperfusion for clinical outcomes established by several studies.[28–31] Every 30 min delay in MT decreases favourable outcomes by 11%,[32] and every 15 min acceleration at initiating tPA is associated with 4% greater odds of walking independently at discharge.[33] Tremendous effort has been made by individual institutions and the healthcare system overall to overcome barriers to reduce the time for stroke treatment.[34–36] Several modifiable factors have been improved and refined (such as stroke assessment tools, pre-hospital notification, communication between emergency personnel and stroke specialists, 'stroke telemedicine', mobile stroke units and direct transfer to comprehensive stroke centres), resulting in improved stroke care timing. Still, a small proportion of thrombectomy eligible patients, 27%, receive a MT.[23]

Emergency medical personnel triage suspected patients who had a stroke based on the clinical examination alone. An efficient and rapid assessment has a profound influence on stroke outcomes. Multiple stroke scales have been validated for clinical use in the stroke field and have shown to speed up the triage process. The National Institutes of Health Stroke Scale (NIHSS) is complicated and time intensive (as time is often limited in field assessment); because of this, multiple alternative stroke scales exist specifically for quick field triage such as the Cincinnati Prehospital Stroke Severity Scale, the Los Angeles Motor Scale and the Rapid Arterial Occlusion Evaluation. However, a recent meta-analysis reported that the scales have a low predictive value for the presence of LVO (35% to 50%).[37] Another factor that reduces the time for treatment duration is a prehospital notification. The American Heart Association (AHA)/American Stroke Association (ASA) recommends pre-hospital notification of potential patients who had a stroke to the destination medical centre.[38] A recent analysis showed that the pre-hospital notification procedure improves stroke outcome by shortening onset to needle time.[39] The introduction of mobile stroke units with imaging capabilities, teleconsults with stroke specialist to assist with triaging, and potential to initiate intravenous thrombolysis tPA en route to an advanced stroke centre have been an extra step towards more prompt care and have also been shown to improve care.[40–47] Finally, there has been a stance to directly transfer suspected patients with LVO to comprehensive stroke centres and bypass non-comprehensive centres to improve treatment time for patients.[48] In a study, the median hospital-to-hospital distance was 14.7 miles, and median transfer time was 104 min.[49]

Even hospital workflow has been adjusted for better outcomes. The change from the traditional hierarchical linear method of patient care to a single-call stroke code activation where all essential personnel are notified concurrently has been shown to reduce time to treatment in acute stroke care.[50 51] The Society of NeuroInterventional Surgery recommends stroke code activation,[52] and similarly, the AHA urges for protocols that limit treatment delays.[38]

MECHANICAL THROMBECTOMY

Over the last decade, the natural history of ischaemic stroke has been dramatically improved following the five pivotal trials that set the ground for MT as the standard of care. The first attempt was in 2013, when three RCTs (Interventional Management of Stroke III (IMS III), Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR Rescue) and A Randomized Controlled Trial on Intra-arterial vs Intravenous Thrombolysis in Acute Ischemic Stroke (SYNTHESIS)) failed to exhibit the superiority of mechanical thrombectomy compared with standard medical treatment.[9–11] The main limitation present within these three RCTs was the use of old thrombectomy devices and the lack of uniform protocol for confirming LVO on CT angiography, which introduced bias against endovascular therapy.[48] In IMS III, 20% of patients randomised to the endovascular arm did not have a LVO. As a result, the 2013 AHA/ASA guidelines for the early management of patients with acute ischaemic stroke advised that the "ability to improve patient outcomes has not yet been established" for thrombectomy devices.[53] Two years later, The Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR Clean) RCT was published, showing the superiority of mechanical thrombectomy using newer thrombectomy devices compared with medically treated patients. In 2015, four other RCTs (Solitaire With the Intention For Thrombectomy as PRIMary Endovascular Treatment Trial (SWIFT PRIME), Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE), Randomized Trial of Revascularization With Solitaire FR Device vs Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 hours of Symptom Onset (REVASCAT), and A Randomized Controlled Trial of Intra-arterial Reperfusion Therapy After Standard Dose Intravenous t-PA Within 4.5 hours of Stroke Onset Utilizing Dual Target Imaging Selection (EXTEND-IA)) that were running at the same time had to prematurely stop enrolling following MR Clean results, observing superiority of MT compared with intravenous tPA alone.[13–16] A

meta-analysis of the five trials by HERMES collaborators reported that MT for anterior circulation groups significantly reduced overall 90-day disability, with a number needed to treat of 2.6 to reduce the mRS in one patient by at least one point.[8]

More recently, the Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) and A multicentre RCT of endovascular therapy following imaging evaluation for ischaemic stroke (DEFUSE 3) trials showed functional benefit following MT in patients presenting after 6 hours from insult. Eligible patients for MT had a mismatch on perfusion imaging. The DAWN trial showed a benefit from 6 to 24 hours, and the DEFUSE 3 showed benefit from 6 to 16 hours.[19 20] DEFUSE 3 found that MT along with standard medical therapy resulted in a higher percentage of functionally independent patients than standard medical treatment alone (45% vs 17%).[20] The CT Perfusion to Predict Response to Recanalization in Ischemic Stroke Project (CRISP) trial results are consistent with DEFUSE 3 and DAWN. Perfusion scans were used to identify patients with perfusion mismatch, and results showed that a higher rate of improvement on the NIHSS of >8 points was observed in subjects with a significant mismatch (83% vs 44%).[54] Importantly, this favourable rate of improvement remained regardless of whether patients were treated within or beyond 6 hours. Based on those five RCTs the AHA/ASA published updated guidelines in 2018, recommending that endovascular thrombectomy be considered for LVOs of the posterior circulation up to 6 hours from symptom onset and that intervention is recommended/can be considered up to 16 and 24 hours, respectively, in select patients with anterior circulation LVOs based on perfusion imaging. Also, the 2018 guidelines stress the need for perfusion scan as triaging imaging for patients presenting between 6 and 24 hours from symptom onset.[38]

The posterior circulation is still a grey zone, where perfusion is limited in stratifying patients that may be good candidates for mechanical intervention. Consequently, physician experience and judgement play a paramount role.[55]

We reviewed our cohort of mechanical thrombectomy for posterior circulation. Out of 453 thrombectomy procedures, 45 were located in the posterior circulation and were mainly a basilar artery occlusion (87%). A solumbra technique, which is the simultaneous use of a stent retriever and aspiration catheter, was used in more than half of the procedures, and an optimal recanalisation rate (TICI >2b) was achieved in 69%. Revascularisation was achieved using a single pass in 44%. When compared with the anterior circulation, posterior thrombectomy procedures were associated with a significant higher rate of extravasation (9% vs 4%, p<0.01) and post-procedural symptomatic Intracerebral Hemorrhage (ICH) (13% vs 4 %, p<0.01). Mortality occurred in 38%, and only 20% achieved functional independence at 90 days. While the functional outcomes are lower in posterior circulation compared with the anterior circulation, the comparison should be made to tPA alone for acute basilar occlusion since the natural history of posterior circulation occlusion is worse compared with anterior circulation.[55] When interpreted in this context, mechanical thrombectomy for posterior circulation results in superior outcomes.

We also reviewed our case series of distal thrombectomy procedures. The M2 was involved in 89%, and ~80% of thrombectomy procedures were performed using the Solumbra technique. Peri-procedural complications including distal emboli and subarachnoid hemorrhage (SAH)/ICH occurred at a rate of 7% and 8.5%, respectively. Compared with proximal occlusions, distal emboli occurred at a significantly higher incidence in the distal circulation occlusions (7% vs 2%, p=0.01). Effective recanalisation rates occurred in 89%, with no difference compared with proximal circulation. Favourable outcomes occurred in 64.7%, and mortality in 8%.

MT TECHNIQUES

Retrievable stents

The improvements introduced to the first-generation Merci device (Concentric Medical, CA, USA) resulted in improved recanalisation rates by the second-generation devices, Solitaire (Medtronic, MN, USA) and Trevo (Stryker, MI, USA). Second-generation devices showed threefold improved recanalisation rates compared with the first-generation.[56]

More than 80% of enrolled patients in the five RCTs published in 2015 underwent thrombectomy using second-generation stent retrievers contrast to the Merci device used in earlier RCT resulted in superior outcomes in the endovascular arm.[12–16] The safe and effective results achieved by stent retrievers led to off-label use and a push in the industry for refinements in succeeding designs. Effective recanalisation rates (58%–88%),[12–14] high rates of functional independence at 3 months (53%–71% using stent retriever vs 19%–40% using tPA alone), along with the low incidence of complications were achieved in the five RCTs.[12–16] Such favourable results encouraged the development of novel retrievable stent designs. Both the Penumbra 3D revascularisation device (Penumbra, CA, USA) and the EmboTrap retrievable stent (Cerenovus/Johnson & Johnson, NJ, USA) achieved very promising effective revascularisation rates, 84% and 92.5%, respectively.[57 58] The off-label use of mechanical thrombectomy encompasses posterior and distal circulation. Effective recanalisation rates following posterior mechanical thrombectomy using stent retriever were reported in 90% and good functional outcomes at 3 months were achieved by 46.9%.[59]

Similarly, optimal results have been achieved with the use of stent retrievers for distal circulation occlusions, with successful reperfusion achieved in 85%, favourable outcomes in 60% and symptomatic ICH at 2%.[60]

Aspiration devices

Due to the limitations of early aspiration devices and the use of stent-retriever devices in Mr Clean, Extend IA, Escape and Swift Prime, most succeeding trials have used stent-retriever devices as the modality for thrombectomy. However, recent data suggest that aspiration provides an efficient and effective means of recanalisation in patients with LVOs.[61–64]

The Contact Aspiration vs Stent Retriever for Successful Revascularization study assessed outcomes in thrombectomy procedures using contact aspiration compared with stent retriever. The study concluded that outcomes were not different among both modalities; recanalisation rate (85.4%), functional outcomes (45.3%) and morbidity.[61] Promising results pushed the envelope and paved the way for aspiration first pass technique (ADAPT). Efficacy of ADAPT has been endeavoured by the recently completed Comparison of Direct Aspiration vs Stent Retriever as a First Approach (COMPASS) trial. The investigators found no difference in functional outcomes, revascularisation rates (92% aspiration, 89% retrievable stents) and morbidity.[65] Aspiration catheters may be valuable in distal occlusion because there is no need for stent deployment, and it may be more gentle on the vessels causing fewer manipulations.

Combination therapy

Recently, thrombectomy techniques have been modified where both stent retriever and direct aspiration are used concurrently (the 'Solumbra technique') in an attempt to improve recanalisation rates. In a series from six high-volume centres, Humphries *et al* reported favourable outcomes following the use of the Solumbra technique for mechanical thrombectomy. The authors reported achieving 88% TICI 2b/3 recanalisation and 44% favourable mRS outcomes at 90 days.[66]

FUTURE OF STROKE THERAPY

Technological innovations have resulted in a significant shift in patient care, two of which are worth mentioning; The volumetric impedance phase shift spectroscopy device (Cerebrotech, CA, USA) has demonstrated high sensitivity and specificity in detecting LVOs in patients who had a stroke.[48 67] It is a non-invasive device that is placed on the patient's head that detects changes in bioimpedance in the brain caused by several pathologies, including ischaemia.[48 67] Another non-invasive device is the SONAS device (BURL Concepts, CA, USA) that uses transcranial ultrasound and microbubble intravenous contrast to identify potential LVOs.

Perhaps more notably, catheter advancements are occurring at a rapid pace aiming to improve manoeuvrability, efficacy and safety of the devices. The Lazarus Effect Cover (Medtronic, MN, USA) is designed to provide a protective sheath around retrievable stents to protect against distal embolisation. Once the stent engages with the clot, it is re-sheathed to prevent clot fragmentation and dislodgment.[68] A small case series of 20 patients reported high rate of effective recanalisation and no evidence of distal emboli.[69] Another innovative concept is the R4Q aspiration catheter (MIVI Neuroscience, MN, USA). The distal one-quarter of the catheter functions as an extension of the guide catheter, allowing the full guide catheter to be used to deliver suction.[70] The future of stroke will be stem cell therapy to stimulate prompt neurological recovery.

CONCLUSION

We are in an era where the second leading cause of death in the world that carries a high burden has become a treatable disease. Huge efforts on all levels have been placed and are still laid to improve time for stroke treatment; beginning with field triage to clot retrieval and post-procedural care and rehabilitation.

Twitter Pascal Jabbour @PascalJabbourMD

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ORCID iD

Pascal Jabbour http://orcid.org/0000-0002-8965-2413

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