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Endovascular therapy for acute ischemic stroke: The standard of care

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Abstract:

Acute ischemic stroke continues to be a major cause of permanent disability and death worldwide. Outcomes are particularly poor in patients presenting with large vessel occlusive disease with resultant ischemia and tissue injury in large and eloquent territories. Intravenous thrombolysis has been the mainstay of medical therapy, however treatment is limited to a subset of patients and many patients continue to have poor outcomes. Three trials in 2013 investigating the benefit of intra-arterial therapy failed to demonstrate benefit over medical therapy alone. More recently, five trials in 2015 were completed demonstrating superior outcomes with intra-arterial therapy with improved results attributed to higher and faster rates of recanalization in a select patient population. These trials have introduced a new standard of care in the management of acute ischemic stroke patients.

Key words:

Acute ischemic stroke, large vessel occlusion, mechanical thrombectomy, stent retriever, therapy

Introduction

Abrupt blockages in the cerebral vasculature quickly lead to depletion of energy and nutrients to the metabolically demanding central nervous tissue with ensuing tissue dysfunction ('ischemia') and eventual cell death ('infarct'). Neurological dysfunction precedes permanent brain injury with a small temporal window of opportunity to introduce therapies to either preserve cellular function (neuroprotection) or restore blood flow (reperfusion therapy). While many investigational approaches have been proposed, no therapies to date have been successful in achieving neuroprotection. Reperfusion therapy has been proven to benefit select patients. In this article, we focus on the recent data supporting the use of intra-arterial reperfusion therapy in achieving improved outcomes after acute ischemic stroke.

Endovascular Therapy for Acute Ischemic Stroke: The Standard of Care

Since the completion of the neurological disorders and stroke IV tpa trial in 1995,^[1] no therapy for acute ischemic trial has been proven to have Class IA level evidence. In the past few months, five randomized control trials have been completed demonstrating superior clinical outcomes in patients undergoing mechanical thrombectomy

compared to medical therapy alone.^[2] These studies have cumulatively provided American Heart Association (AHA) Class IA evidence supporting the use of endovascular therapy as standard of care in patients presenting with large vessel occlusion.^[3-7] These results are in stark contrast to several prior studies.^[8-10] This discrepancy in results can be attributed to five important factors (the five P's, Table 1): (1) patient selection, (2) presence of occlusion, (3) process of care, (4) procedural time, and (5) perfusion restoration. Future studies are necessary to understand the role of endovascular therapy for areas of uncertainty including (1) patients presenting at late time windows, (2) posterior circulation occlusions, (3) patients with distal occlusions, (4) patients with mild symptoms, and (5) patients with moderate-large stroke burden on presentation.

Patient Selection: Small Core, Severe Clinical Deficit

Patients undergoing recanalization in the setting of a large vessel occlusion can be considered as three groups: likely to benefit, uncertain to benefit, and unlikely to benefit. Maximal benefit is expected in patients with a significant clinical deficit (large tissue at risk or penumbra) in the setting of minimally completed infarct (small core).^[11] At the other extreme, restoring flow to already infarcted tissue is considered futile. In

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the Interventional Stroke Management (IMS) III trial, 40% of patients had poor Alberta Stroke Program Early Computed Tomography (ASPECT) scores on presentation (ASPECT 0-7). Accordingly, patients with poor ASPECT scores had a 2-fold less likelihood to benefit with IV or IA therapy.^[12] In the MR RESCUE trial, patients were selected for intra-arterial (IA) therapy based on penumbral imaging, and while baseline imaging demonstrated a large territory risk, the median infarct burden at baseline was already large (36 mL).^[8] While the median National Institutes of Health Stroke Scale (NIHSS) was 15–18 in the recently completed trials and comparable to the median NIHSS of 17 in IMS III, the core infarct size was smaller. The median core in the treatment arm of EXTEND-IA was 12 mL.^[4] In the ESCAPE trial, only 3.6% of patient had an ASPECT <6.^[6] The smaller region of permanently injured tissue and larger area of salvageable parenchyma was a key factor in patient selection [Table 2].

Presence of Occlusion

A major limitation of prior endovascular trials was the lack of uniform documentation of vessel status before randomization. In IMS III, nearly half of the enrolled patients had no documentation of large vessel occlusion before enrollment likely leading to the enrollment of patients without target lesion for interventional therapy. Of 47% patients with baseline computed tomography angiography (CTA)/magnetic resonance angiography, subgroup analysis did suggest a trend ($P = 0.011$) toward favorable outcome in the endovascular therapy by mRS shift analysis. Furthermore, many patients had M2 occlusion, but interestingly in patients with proximal occlusion (ICA terminus or tandem ICA/M1), good outcomes were observed in 26% of endovascular group versus 4% of the IV tPA group ($P = 0.047$).^[13]

Accordingly, the second generation of interventional trials all required documentation of a large vessel occlusion before enrollment. MR CLEAN and REVASCAT particularly both enriched for r-tPA failures by enrolling patients with persistent occlusions and severe clinical deficit at >2 h and 30 min after IV tPA administration, respectively.^[5] Proximal occlusions, in particular, were associated with the highest likelihood benefit. In MR CLEAN, patients with an ICA occlusion had more relative benefit with endovascular therapy than patients without ICA occlusion (odds ratio [OR] 2.43 vs. 1.61). In ESCAPE, the presence of cervical carotid occlusion (40 out of 315 patients) was associated with particularly high likelihood of benefit (OR 9.6 in the presence of cervical occlusion versus 2.2 in the absence of cervical occlusion).^[6] The SWIFT PRIME trial specifically excluded cervical occlusions, but the likelihood of benefit was higher with proximal (M1 or ICA occlusions) compared to distal occlusions (M2) with OR 2.96 and 3.11 versus OR 1.75.^[2]

Process of Care: Door to Groin Puncture Time

A strong link between time from symptom onset to treatment and outcome has been long appreciated in both coronary and cerebral revascularization therapies. In the IMS III trial, mean time to reperfusion was 325 min in the endovascular therapy group with a time-treatment interaction such that every 30 min delay led to worse outcomes (risk ratio 0.85). In patients treated

Table 1: The 5 P's of achieving optimal outcomes

	Strategies
Patient selection	Aim for small baseline core - higher CT aspects, favorable perfusion scan
Presence of occlusion	Baseline CTA/MRA with documented proximal occlusion
Process of care	Early hospital and interventional team activation, parallel processing, minimizing unnecessary steps (i.e., arterial line placement, Foley catheter placement, intubation)
Procedural time	Experienced operators with standardized equipment and methodology to reach target vessel
Perfusion restored	Use of stent retriever to achieve fast and high-quality recanalization (TICI 2b or better)

CT: Computed tomography, CTA: Computed tomography angiography, MRA: Magnetic resonance angiography, TICI: Thrombolysis in cerebral infarction

Table 2: Features of patient selection in IA clinical trials

	Speed/workflow	Perfusion imaging	Collateral imaging	CTA
Escape	X		X	
Swift prime	X	X		
MR clean				X
Revascat				X
Extend IA		X		

MR: Magnetic resonance, IA: Intra-arterial, CTA: Computed tomography angiography

within 300 min, 41.1% had good outcomes whereas only 26.5% of patients had good outcomes if they were treated beyond 360 min.^[14]

Before arrival to the angiosuite, multiple factors can significantly contribute to delays at every level of patient care. Once symptoms are detected and recognized as concerning for an ischemic stroke, first medical contact is made. Patients are subsequently transferred to the closest IV tpa capable center. Prehospital notification allows advanced preparedness at the referring facility where ideally the patient is directly transported from the ambulance to the CT scanner. Point of care testing and direct administration of IV tpa while the patient is on the scanner table can greatly facilitate rapid delivery of drug. Once a large vessel occlusion is suspected or confirmed, the neurocath team is activated at facilities with endovascular capability, or the patient is transferred to a higher level of care. Additional interventions such as placement of an arterial line, foley catheter, or intubation are rarely necessary and only further contribute to treatment delays. Procedural trays are prepared in advance.

Emphasis on workflow and parallel process have had great impact on improving treatment times in percutaneous coronary interventions (PCIs). Significant workflow delays were noted in IMS III with mean IV tpa start to groin puncture time of 81 ± 27 min and the mean groin to IA start time was 41 ± 21 min with >2 h delay between CT head and groin puncture.^[15] No clear time benchmarks were established in the first-generation endovascular trials although such an established metric has been beneficial in improving door to balloon times in PCI and improving door to IV tpa times for acute stroke. In the ESCAPE and SWIFT PRIME trials, significant

emphasis was placed on speed of initiating treatment and workflow. In the ESCAPE trial, the goal time from emergency department (ED) arrival to groin puncture was 60 min.^[6] Similarly, the SWIFT PRIME established a goal time from ED arrival to groin puncture of 70 min.^[2] Iterative feedback was provided at study sites when delays were observed, and best practices were shared among centers. While MR CLEAN and REVASCAT purposefully introduced delays between IV tpa administration and groin puncture to enrich for IV tpa failures, the overall median last seen well to groin access time was fast in all trials: ESCAPE-200 min, EXTEND IA-210 min, SWIFT PRIME-224 min, MR CLEAN-260 min, and REVASCAT-269 min.

Procedural Time: Groin Puncture to Reperfusion Time

Once groin access is achieved, attention is focused on fast and high-quality recanalization. Key procedural steps include access to the placement of base catheter, base catheter to clot access, and clot access to final recanalization. In the IMS III trial, total groin access to final reperfusion time was 120.5 min.^[15] In contrast, in the EXTEND-IA and ESCAPE trials, the groin access to final perfusion time was 43 and 30 min, respectively.^[4,6] This improvement in treatment time has been a major advance in endovascular technique and is largely attributable to the high rates of first pass effect with stent-retriever devices [Table 3].

Perfusion Restoration: High Quality Recanalization

Akin to coronary revascularization, good outcomes in acute ischemic stroke are predicated on near or complete recanalization. In the IMS III trial, 39.2% of patients in the treatment arm achieved TIC12b/3 quality recanalization.^[16] Most of the patients were treated with first-generation technology including IA alteplase, MERCI clot retrieval device, and Penumbra aspiration. In contrast to coronary vessels, cerebral vessels tend to be more fragile, thin-walled, tortuous, and highly-arborized. These anatomical challenges in addition to the large and heterogeneous clot burden lead to more refractory lesions. Higher rates of recanalization have been noted in

Table 3: Study differences between IMSIII, EXTEND-IA and ESCAPE

	IMSIII	EXTEND-IA	ESCAPE
Study period	2006-2012	2012-2014	2013-2014
Size (patients)	656	70	316
NIHSS	18	17	17
IV tPA (%)	100	100	72.7
CT to reperfusion (min)	>200	136	84
Core size	15% had aspect <5	Median 20 cc core	3.6% had aspect <6
Stentriever (%)	2	100	86
TICI 2b/3 (%)	39.2	86	72.4
Independent (%)	41 versus 39	71 versus 40	53 versus 29
Death (%)	20 versus 22.4	9 versus 20	10 versus 19

IA: Intra-arterial, TIC1: Thrombolysis in cerebral infarction, CT: Computed tomography, IMS: Interventional Management of Stroke, NIHSS: National Institutes of Health Stroke Scale, tPA: Tissue plasminogen activator, IV: Intravenous

multiple studies of stent retriever thrombectomy devices. The second-generation trials have predominantly or exclusively employed the use of stent-retriever devices with TIC1 2b/3 rates of 59%–88%.^[3-7]

Areas of Improvement

Despite the demonstrated benefit of thrombectomy in the second-generation endovascular trials, there is a significant scope for improvement. Good outcomes in the treatment arm ranged from 30% to 71% and mortality still ranged from 9% to 21%. Clearly, faster triage time across the system, from first medical contact to definitive reperfusion, represents an important area of future inquiry. Improving times will not only improve outcomes but also broaden the number of patients likely to benefit for IA therapy. Several strategies can facilitate faster treatment times. In the prehospital setting, emergency medical services (EMS) can be trained to triage suspected large vessel occlusive disease with an abbreviated stroke scale. There is increasing interest in mobile stroke units that can be dispatched in the case of suspected acute ischemic stroke.^[17] Such units are equipped with specialized stroke personnel (stroke-trained nurses, physician extenders, or stroke physicians), telemedicine capability, and portable CT scanners. Small preliminary studies in this technology have demonstrated faster treatment times for IV tpa, but the cost and large-scale feasibility are uncertain.^[18]

Once patients are suspected to have an acute ischemic stroke with large vessel occlusion, patients should ideally be delivered to an endovascular capable center although in current practice, patients are typically brought initially to an IV tpa capable facility. While this method of triage may lead to faster delivery of IV tpa, definitive revascularization may be delayed as the patients refractory to intravenous therapy will require transfer to an endovascular capable center. Indeed, interfacility transfer times continue to be a significant source. New tools and transfer algorithms are required to direct patients to the most appropriate destination in the fastest amount of time.

Once patients arrive to an endovascular capable center, neuroimaging is utilized to determine the presence of salvageable brain tissue. ESCAPE, MR CLEAN, and REVASCAT predominantly assayed stroke burden on CTA imaging, whereas the EXTEND-IA and SWIFT PRIME relied more heavily on CT perfusion imaging. All trials were successful in identifying patients likely to benefit from IA therapy although there were differences in the absolute benefit. For example, the number needed to treat with thrombectomy ranged from 3 to 7.^[19] The EXTEND-IA trial had the highest treatment effect with a number needed to treat of 3. Enrollment was based on a strict imaging-based paradigm requiring CT perfusion with more than 7700 patients screened to identify the seventy patients that were eligible for the study.^[4] While such a rigid selection criteria enriched for the optimal patient population, this strategy most likely excluded additional patients that may have benefit from IA therapy. In addition, there is a trade-off between the time required to obtain advanced imaging and the impact of the obtained information in influencing final treatment decision. Importantly, safety profile was comparable across all five trials suggesting that selection by CTA alone did not increase the risk of hemorrhage or fatality.

In addition to shifting diagnostic testing to the prehospital setting, additional attention will need to be placed on optimal patient destination. While efforts have been made to minimize time in the ED before angiography arrival, increasing efforts are necessary to triage appropriate patients directly to the neurocath laboratory. This may be especially indicated in the case of transfer patients who have documented large vessel occlusion. Emergency services may also have to be reorganized to develop a dedicated stroke emergency room, in which patients are directly brought to a triage area adjacent to the angiography suite. Such a strategy has been successfully adopted in other conditions such as dedicated headache emergency rooms with resultant rapid triaging, diagnostic testing, and treatment.

Areas of Uncertainty

Patients presenting at late time windows

The recently completed trials focused exclusively on proximal anterior circulation occlusions in patients with significant clinical deficits in predominantly early time windows receiving IV tPA (when possible) with almost exclusive usage of stent retriever technology. Accordingly, the new AHA guidelines have interpreted the recent trials as providing Class IA evidence for mechanical thrombectomy for this subset of patient and specifically in the <6 h time window. Many questions remain and the optimal management of other populations of patients warrants further investigation. While the maximal benefit of IA therapy is predicated on fast treatment, there is a subset of patients in which the core infarct remains small, even at late time windows. We and others have previously reported on the safety, feasibility of benefit of IA therapy in patients presenting with wake-up symptoms or presenting at late time windows.^[20] To test this hypothesis, the DAWN and POSITIVE trials are ongoing studies randomizing patients with anterior circulation large vessel occlusions in the 6–24 h time window.

The role of advanced imaging

The optimal imaging modality for patient selection for IA therapy is unclear. While MRI-DWI sequences provide the most precise measure of core infarct, the logistics of rapid clearance, and access to MRI imaging presents workflow challenges at most centers. The majority of the patients were selected based on CT findings. In the SWIFT PRIME study, only 17% of patients underwent MRI imaging before randomization. CTA and CTP imaging may provide additional information over CT ASPECTS alone, but the exact advantage over CT head remains unclear. Importantly, the additional information gain needs to offset the time lost with these advanced tests. Future studies are necessary to determine the ideal neuroimaging strategy in patient selection.

Site of occlusion: M2 occlusions, basilar occlusions

The maximal treatment effect over medical therapy is in patients with proximal occlusions. Few patients with M2 occlusions were studied, and so the benefit in this population remains unclear. In one study of untreated M2 occlusions,^[21] there was a 45.8% rate of dependency and mortality suggesting that better treatments are necessary. An additional gap in the current understanding of managing large vessel occlusive disease is the preferred algorithm for managing basilar artery disease. The natural history of persistent vertebrobasilar blockages is felt to be uniformly poor if untreated.^[22] Recanalization can

be achieved with intravenous therapy, and the additional benefit of IA therapy has not been systemically studied in a randomized controlled trial. The recently completed THRACE trial did randomize patients with medical therapy versus IA therapy including basilar artery occlusions. Further details of this trial will further inform the treatment of this subpopulation.

Continued benefit in patients with mild symptoms or moderate-large stroke burden on presentation

Additional populations excluded from the recently completed trials included patients with mild or fluctuating symptoms in the setting of a large vessel occlusion. When eligible, this population may continue to benefit from intravenous thrombolysis, but when recanalization fails to occur or patients are not eligible for IV tPA, there may be a role for IA therapy.^[23] Conversely, patients with moderate-larger stroke burden may not achieve functional independence, despite successful revascularization. However, high-quality recanalization and reperfusion may minimize further infarct growth and abrogate the likelihood of additional stroke-related complications such as malignant cerebral edema requiring decompression, tracheostomy placement, and gastrostomy placement. In addition, the use of adjunctive neuroprotection may serve as a bridging strategy in minimizing infarct growth in patients before achieving definitive reperfusion therapy.

Conclusions

The recently completed endovascular trials have heralded a new era of acute stroke care, providing the basis for a new standard of care in managing large vessel occlusive disease. Systems of care will need to be reorganized to rapidly triage and transport patients to endovascular capable stroke centers. Future studies will be necessary to better understand the optimal treatment for patients not studied in the recently completed trials such as patients presenting at late time windows or with posterior circulation occlusions.

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Conflicts of interest

There are no conflicts of interest.

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