Mechanical Thrombectomy: Review

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Abstract

Large vessel occlusion stroke contributes to disability and mortality out of proportion to its incidence. Over time it was noted that intravenous thrombolysis alone was not sufficient for this stroke type. Slowly, endovascular approach and mechanical clot retrieval have come out to be the biggest advances in the field of neurology as well as modern medicine. Although the careful selection of patients is needed as standardized by landmark trials. At the same time, thrombectomy is now being studied in patients excluded by previous trials and is seemingly coming out be effective in the vast majority of patients with large vessel occlusions. Further, techniques and devices are getting refined day by day to achieve the maximum possible benefit.

Keywords: Ischemic stroke, mechanical thrombolysis, thrombectomy, thrombolytic therapy

Introduction

Although intravenous thrombolysis (IVT) revolutionized the treatment and became the standard of care in ischemic stroke, there are several drawbacks. First, there is a relatively small time window within which treatment has to be initiated. Second, stroke due to large vessel occlusion (LVO) portends a poor prognosis, and recanalization rates even with IVT are poorer in these patients.[1,2] In one natural history study from Italy, 75% of patients with stroke due to ICA occlusion were either dead or dependent at a mean follow-up of 1.2 years.[3] A systematic review including two different multicenter studies from the US and Europe reported LVO to account for 38.7% of all ischemic strokes, still accounting for 61.6% of post-stroke dependence and 95.6% of mortality.[2] A large study including five high volume centers from India reported arterial occlusion or >50% stenosis in 42.7% of patients.[4] A study using transcranial doppler showed recanalization rates after intravenous thrombolysis in the terminal internal carotid artery and proximal middle cerebral artery to be 6% and 30% respectively.[5] Similarly, G J del Zoppo *et al*.[6] had found angiographic recanalization rates in ICA, M1 MCA, M2 MCA, and M3 MCA occlusions after intravenous duteplase to be 8.7%, 35.3%, 53.8%, and 65.9%, respectively.

It was recognized for a long time that IVT alone was not sufficient and more effective therapy is needed for ischemic stroke types which are more devastating than lacunar strokes.

PROACT-II, published in 1999, was one of the earliest randomized trials favoring the endovascular treatment approach, where 180 patients with stroke due to MCA occlusion were randomized to receive intra-arterial recombinant prourokinase (r-pro-UK) plus IV heparin or IV heparin alone within 6 hours of onset. Favorable outcome i.e., Modified Rankin scale of ≤2 at 90 days was achieved in 40% patients in the intervention arm and 25% patients in the control arm ($p = 0.04$).[7] However, the second trial with r-pro-UK did not complete and thence it did not receive FDA approval.[8] Intra-arterial thrombolysis with various fibrinolytic agents compared to IVT showed favorable results but it was never tested in larger randomized trials.[9]

Eventually, mechanical devices took over the fibrinolytic drugs because of concerns of intracranial hemorrhage. MERCI and later PENUMBRA system were approved by FDA for clot removal in ischemic stroke nearly 15 years ago, but recanalization rates were poor.

Intracranial stent placement was thought to provide high recanalization rates but at the same time concerns regarding the use of antiplatelet agents, hemorrhage, and occurrence of in-stent stenosis were also there.[10] In 2008, Kelly *et al*.[11] reported successful recanalization of MCA occlusion by partially deployed Enterprise stent leading to temporary endovascular bypass and then retrieval of the stent along with clot. Successful use of stent retrievers for large vessel occlusion stroke from India also dates back to 2010 by Huded *et al*.[12] Although, subsequent randomized trials comparing endovascular treatment to IVT alone (IMS-3, SYNTHESIS, and MR RESCUE) were negative and had one or the other of the following drawbacks- case selection without vessel imaging, poor workflows, longer stroke onset to reperfusion

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times, the predominant use of first-generation devices (MERCI or Penumbra) or poor recanalization rates.[13-15] Though these trials were discouraging, they paved the way forward for upcoming positive trials with second-generation devices. It was understood that patients with severe strokes due to large vessel occlusions who do not have large established infarcts can be benefited to great extent by an immediate and better degree of recanalization.[16]

Evidence for Thrombectomy

The current practice of thrombectomy in ischemic stroke is largely based on randomized trials published in and after 2015. All of the trials emphasized intervention by experienced interventionists, faster workflow, and better successful recanalization rates. Inclusion criteria of individual early window trials are summarized in Table 1. Overall, early window trials included adult patients with independent baseline functional state presenting in the early window (mostly <6 hours) after last seen normal and clinically measurable deficits (most were moderate to severe strokes), favorable infarct cores, and large vessel occlusion as confirmed on CT (or MR) angiography. Extended window trials additionally required either clinical-radiological or core-perfusion mismatch to identify patients with salvageable brain tissue. Detailed exclusion criteria of all trials are provided in the supplementary material. Largely, patients with any evidence of intracranial hemorrhage, large infarct cores (defined as either ASPECTS <6 or involvement of >⅓ territory of a middle cerebral artery), severe hypertension even after medications, severe hypo/hyperglycemia, coagulopathy (defined variably in different trials), pregnancy, limited life expectancy, intracranial tumors (other than small meningioma), suspected septic emboli were excluded. Notably, some of the trials also excluded patients with cervical dissection or proximal cervical occlusions where acute cervical stent might be required. Patients in whom thrombectomy could be initiated within 6 or 5 hours of onset, were included irrespective of infarct volume in MR CLEAN or THRACE trials, respectively.[17,18] In general, criteria were more inclusive compared to those for IVT. Relevant baseline and procedure characteristics are mentioned in Table 2.

Important outcomes are summarized in Figure 1. After the publication of the first and the largest trial MR CLEAN showing the benefit of thrombectomy, other trials (ESCAPE, REVASCAT, SWIFT PRIME, EXTEND IA, EASI) were stopped prematurely given the ethical concerns.[18-23] All of the trials including patients from vast geographic distribution independently showed significant benefit of mechanical thrombectomy in selected patients. Furthermore, an individual patient-level meta-analysis involving five major early window thrombectomy trials by HERMES collaboration confirmed the benefit of thrombectomy for wide strata of patients.[24] It was shown that patients can be benefited irrespective of age, sex, baseline NIHSS, time from onset (within 7 hours of time window), IVT eligibility, or presence of tandem occlusion. Although, the benefit did not reach statistical significance in patients with young age (<50 years), ASPECTS 0-5, NIHSS ≤10, and M2 occlusions, it tended to favor thrombectomy. The number needed to treat to make one more patient achieve functional independence at 3 months is 10 for thrombolysis in the early time window (<3 hours), while it is 2.6 for thrombectomy as per HERMES.[25] Absolute risk reduction was higher in late window trials (DAWN, DEFUSE 3) compared to most of the early window trials (the late window paradox) and it is likely because of the selection of slow progressors in late window trials while the fast progressors were not excluded in early window trials.

Thrombectomy for Posterior Circulation Strokes

Heterogeneity in symptoms and their onset often leads to relatively later detection of posterior circulation strokes.[26] In all positive landmark thrombectomy trials, except THRACE, posterior circulation strokes were excluded. Although routinely practised in many centers, thrombectomy for vertebro-basilar-PCA occlusions is currently not backed by evidence as in anterior circulation strokes.

The BEST trial included 131 patients (target was 344) within 8 hours of basilar artery occlusion and randomized them to endovascular arm and medical management alone. The primary outcome at 90 days (mRS score ≤3) was achieved by 42% of patients in the endovascular arm and 32% of patients in the control arm (adjusted odds ratio 1.74, 95% confidence interval 0.8-3.7). Symptomatic hemorrhage was higher in the endovascular arm (8% vs 0) and there was no significant difference in mortality at 90 days. Although in the per-protocol analysis, favorable outcome was higher in the endovascular arm (44% vs 25%, adjusted odds ratio 2.9, 95% confidence interval 1.2-7.03).[27] The BASICS trial had randomized 300 patients within 6 hours of basilar artery occlusion to endovascular therapy or medical management alone. The primary outcome at 90 days (mRS score ≤3) was achieved by 44.2% of patients in the endovascular arm and 37.7% in the medical management arm (common odds ratio- 1.18, 95% confidence interval 0.91-1.5).[28] There was no significant difference in mortality at 90 days. These trials are criticized for their slow recruitment, a significant proportion of patients having the unknown time of onset (almost 1/3rd patients in BASICS), the inclusion of patients with significantly higher baseline stroke severity, very low rates of intravenous thrombolysis (in BEST), and poor adherence to treatment allocation. These factors could have led to results that are negative with wide confidence intervals. Basilar Artery Occlusion Chinese Endovascular Trial is further assessing the usefulness of thrombectomy in patients with basilar artery occlusion up to 24 hours after onset.

While the benefit of thrombectomy is not excluded by randomized trials, many observational studies have suggested benefit. A systematic review and meta-analysis including observational studies (with a total of 1172 posterior circulation

Table 1: Inclusion criteria of randomized trials

	MR CLEAN	ESCAPE	REVASCAT	SWIFT PRIME	EXTEND IA	THRACE	PISTE	EASI	DAWN	DEFUSE 3
Age	≥18	≥18	≥18 to ≤85	18-80	≥18	18-80	≥18	≥18	≥18	18-90
Symptom duration	<6 hours	<12 hours, CT to MT <60 min	<8 hours, CT/MR to MT <90 min	<4.5 hours IVT, <6 hours MT	<4.5 hours IVT, <6 hours MT	<4 hours IVT, <5 hours MT	<4.5 hours IVT, <5.5 hours MT	<5 hours	6-24 hours	6-16 hours
NIHSS	≥2	>5	≥6	≥8-30	-	10-25	≥6	≥8	≥10	≥6
Imaging	CTA/MRA/ DSA	CTA (Single/ multiphase), CTP	CTA/CTP (>4.5 hrs)/ MRA/DSA	CTA/MRA, Perfusion, RAPID	CTA, CTP/MRA, MRP, RAPID	CTA/MRA	CTA/ MRA/DSA	Vessel imaging not mandated	CTA/MRA, RAPID	CTA/MRA, Perfusion, RAPID
Occlusion site; extent of infarcts	Distal ICA, M1/M2 MCA, A1/ A2 ACA	Carotid T/L, M1, ≥2 M2 MCAs (except ant. temporal artery); ASPECTS 6-10	Distal ICA/T, M1 MCA, both M2 divisions, +/- proximal carotid occlusion/stenosis; Age <81: ASPECTS CT >7, MR >6 Age ≥81: ASPECTS CT/MR >9	Intracranial ICA, M1 MCA; ASPECTS 6-10	ICA, M1/M2 MCA with mismatch on perfusion: mismatch ratio >1.2+ absolute mismatch volume >10 ml + core <70 ml	Intracranial ICA, M1 MCA, Superior third of basilar	Intracranial MCA, M1 MCA, M2 MCA; Infarcts <1/3 MCA territory	M1/M2 MCA, supraclinoid ICA, vertebral, basilar, clinical-imaging mismatch	Intracranial ICA, M1 MCA; Clinical imaging mismatch- 0-<21 cc core infarct and NIHSS ≥10 (age ≥80 yrs), 0-<31 cc core infarct and NIHSS ≥10 (age<80 yrs), 31 cc-<51 cc core infarct and NIHSS ≥20 (age <80 yrs)	ICA (cervical/ intrracranial), M1 MCA; Mismatch profile- core <70 ml, mismatch volume >15 ml and mismatch ratio >1.8
Baseline functional status	-	Pre-stroke independency	Pre-stroke mRS ≤1	Pre-stroke mRS ≤1	Pre-stroke mRS ≤1	-	Pre-stroke mRS 0-2	-	Pre-stroke mRS ≤1	Pre-stroke mRS 0-2

large vessel occlusion and 7726 anterior circulation large vessel occlusion strokes) comparing thrombectomy in posterior versus anterior circulation concluded that thrombectomy can be equally efficient in achieving successful recanalization and favorable outcome in posterior circulation strokes.[29] Another meta-analysis including 474 patients with posterior circulation occlusion and 3505 patients with anterior circulation occlusion showed that functional independency at 90 days was achieved by 34.8% of patients with posterior circulation occlusions (albeit lower than anterior circulation). Symptomatic hemorrhage was significantly lower in patients with posterior circulation occlusions undergoing thrombectomy (2.23% vs 5.53%).[30] A large prospective nonrandomized cohort study including 829 patients within 24 hours of the onset of basilar artery occlusion showed that functional outcomes at 3 months were significantly improved (mRS score ≤3, 32% vs 9.3%, $P < 0.001$), and mortality at 3 months was lower (46.2% vs 71.4%, $P < 0.01$) even when symptomatic ICH was higher (7.1% vs 0.5%, $P < 0.001$) in patients undergoing thrombectomy compared to patients receiving medical management alone. These findings did not differ after propensity score matching.[31] One retrospective study including 81 patients with acute basilar artery occlusion showed that factors like lower baseline NIHSS, distal basilar occlusion, better posterior circulation collateral status were significantly associated with better functional outcomes at 3 months. Interestingly, the time from onset to recanalization (even >12 hours) did not show statistical significance in predicting good outcome. Authors concluded that time from onset should not be an absolute criterion for thrombectomy in patients with acute basilar artery occlusion.[32] An institutional retrospective study including 89 patients with stroke due to vertebro-basilar occlusion showed a favorable outcome (mRS ≤2) at 90 days in 40% of patients and all-cause mortality of 36%. Patients with NIHSS >10, treated within 24 hours of onset, having infarcts not involving bilateral thalami, or more than half of pons/midbrain were more likely to get benefited from endovascular treatment.[33] In one retrospective study from Korea including 82 patients with basilar occlusion who underwent thrombectomy, embolism without vertebral steno-occlusion, embolism with tandem vertebral steno-occlusion and in-situ atherothrombosis accounted for 41%, 34%, and 24% of patients, respectively. Embolism without large artery atherosclerosis was associated with the distal location of the basilar occlusion, shorter procedure times, better successful recanalization rates, and better functional outcomes at 3 months.[34] A prospective study comparing aspiration with stent retriever in basilar artery occlusion showed that a direct aspiration first pass (ADAPT) was associated with higher complete recanalization rates, shorter procedure time, and better clinical outcomes.[35] The TOPMOST study compared mechanical thrombectomy with standard medical management in 186 matched patients with primary posterior cerebral artery occlusion and found that it was safe, feasible, and had significant treatment effects particularly in patients with high baseline NIHSS.[36]

Table 2: Baseline and procedure characteristics of randomized trials

	MR CLEAN	ESCAPE	REVASCAT	SWIFT PRIME	EXTEND IA	THRACE	PISTE	EASI	DAWN	DEFUSE 3
Total patients (%male)	500 (58.4%)	315 (47.1%)	206 (52.9%)	196 (51%)	70 (48.6%)	412 (53.4%)	65 (44.6%)	77 (49.4%)	206 (45.1%)	182 (50.5%)
Medical management	267 (58.8%)	150 (47.3%)	103 (52.4%)	98 (47%)	35 (48.6%)	208 (50%)	32 (50%)	20 (54.1%)	99 (51.5%)	90 (49.9%)
Intervention	233 (57.9%)	165 (47.9%)	103 (53.4%)	98 (55%)	35 (48.6%)	204 (57%)	33 (39%)	18 (45%)	107 (39.2%)	92 (50%)
Age (years)										
Medical management	65.7*	70*	67.2†	66.3†	70.2†	68*	64†	71*	70.7†	71*
Intervention	65.8*	71*	65.7†	65†	68.6†	66*	67†	74*	69.4†	70*
NIHSS at baseline (median)										
Medical management	18	17	17	17	13	17	14	20	17	16
Intervention	17	16	17	17	17	18	18	18	17	16
ASPECTS/Infarct core (median/ mean)						ASPECT ≥5				
Medical management	9	9	8	9	19.6	83%	9	9	8.9 ml	8/10.1 ml
Intervention	9	9	7	9	18.9	89%	9	8	7.6 ml	8/9.4 ml
Occlusion (% of intervention arm)										
Intracranial ICA±M1	25.7%	27.6%	25.5%	18%	31%	12%	14%	15%	20.5%	34.8%
M1	66.1%	68.1%	64.7%	67%	57%	86%	76%	42.5%	77.6%	65.2%
M2	7.7%	3.7%	9.8%	14%	11%	-	10%	13%	1.9%	-
A1 or A2	0.4%	-	-	-	-	-	-	-	-	-
Basilar	-	-	-	-	-	1%	-	12.5%	-	-
IVT										
Medical management	90.6%	78.7%	68%	95.9%	100%	100%	100%	62.2%	13.1%	8.9%
Intervention	87.1%	72.7%	77.7%	100%	100%	100%	100%	57.5%	4.7%	10.9%
Onset to groin access (minutes- median)	260	Onset to CT 134, CT to groin access 51	269	224	210	250	Onset to randomization 150, randomization to groin access 58	245	Onset to randomization 12.2 hours, randomization to groin access 16 min	11.5 hours
Intervention arm (Device/ technique used)										
Retrievable stents	81.5%	86.1%	93%	88.8%	80%	83%	68%	96.7%	97.4%	80.4%
Others‡	2.5%	-	1.9%	1%	-	16%‖,13%¶	32%‖,19%¶	3.3%	2.8%	5.4%, 27.2%‖
Acute cervical stent	12.9%	-	8.7%	1%	8.6%	-	-	13%	-	13%
No intervention	15.9%	8.4%	4.8%	11.2%	17.1%	29%	3.1%	25%	1.9%	2.1%
General anesthesia in the intervention arm	37.8%	9.1%	6.7%	37%	33%	49%	31%	6.7%	10.2%	28%

*median; †mean; ‡MERCI, wire disruption, thromboaspiration, intraarterial fibrinolytic, intracranial stenting; ‖ Aspiration devices; ¶ more than one device/fibrinolytic used

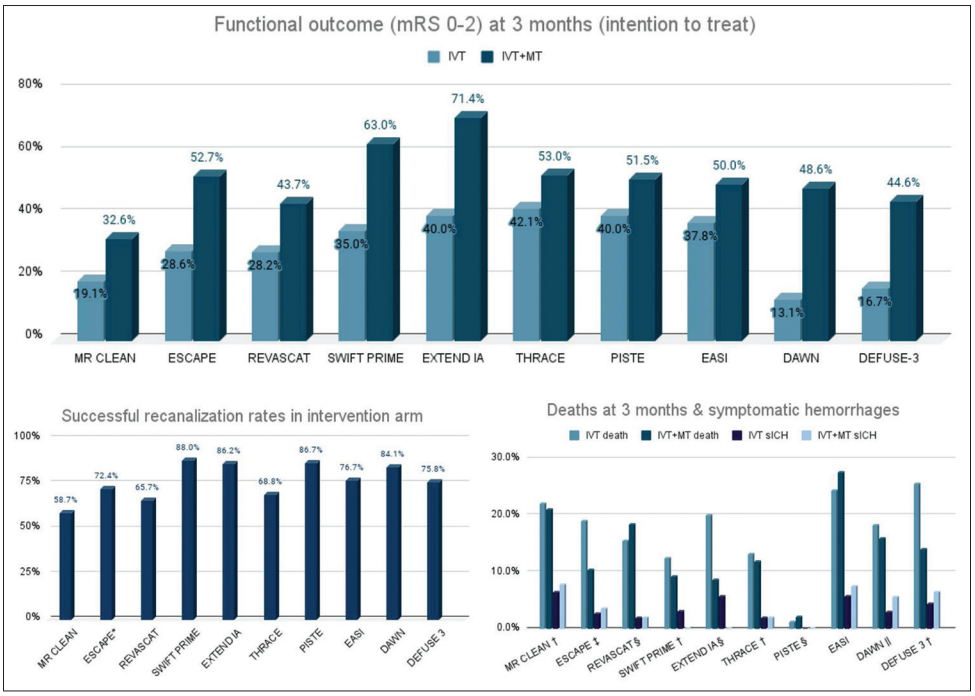

Figure 1: Important outcomes of randomized trials; Successful recanalization defined as modified TICI 2b or 3 (ESCAPE*- TICI2b or 3), Symptomatic hemorrhage definition used- † ECASS 2, ‡ ECASS, § SITS MOST, || ECASS 3 (not specified in EASI)

Other Special Populations

Large core

Irrespective of the time window they present in, patients with large established infarcts were excluded in most of the trials evaluating benefits of thrombectomy as well as IVT in ischemic stroke. Indeed, recanalization in these patients is not expected to lead to as favorable outcomes as in highly selected patients. Simultaneously, the risk of reperfusion injury and hemorrhage leading to further deteriorations might be more in these patients. Though, it is imperative to identify patients (e.g. young, fast progressors) who might get some benefit from highly effective therapies available currently. In an analysis from the STRATIS registry, including 57 patients with ASPECTS of 0-5, functional independence at 3 months was achieved by 28.8% of patients. Symptomatic hemorrhage (7%), as well as mortality (30.8%), was higher compared to patients with ASPECTS 6-10. Though no patients aged >75 years achieved functional independence, 44.8% of patients with age ≤65 years were functionally independent at 3 months.[37] Meyer *et al*.[38] included 228 patients from the German stroke registry, with stroke due to large vessel occlusion and CT ASPECTS of 0-5. They compared patients after propensity score matching, who had undergone thrombectomy to patients receiving the best medical management alone. A favorable outcome at 90 days (mRS 0-3) was achieved in 27.4% in the thrombectomy group and 25% of patients in the medical management group. Symptomatic ICH and mortality were significantly higher in the thrombectomy group. However, in patients in whom mTICI 3 recanalization was achieved with ≤2 passes, symptomatic hemorrhage as well as mortality were lesser and there was a trend towards the favorable outcome (mRS 0-3 in 42.3%, $P = 0.052$). The SELECT study included 361 patients with ischemic stroke due to large vessel occlusion to assess concordance/discordance of CT and CT perfusion and their effect on decision making regarding EVT as well as clinical outcome. In patients with discordant profiles on CT and CTP (e.g. one modality showing the favorable core, while other showing unfavorable) also, functional independence was achieved by 38% of patients.[39] Upcoming randomized trials are evaluating the effect of thrombectomy in populations with large infarct cores. (SELECT 2, TESLA, TENSION, LASTE)

Low NIHSS

In a study by Mazya *et al*.,[40] nearly 25% of patients with low NIHSS (0-5) had large vessel occlusion and non-hemorrhagic early neurologic deterioration (defined as worsening of NIHSS >3) occurred in 30% of patients with ICA occlusions; among patients with early deteriorations, 77% were dead or dependent at 3 months. Similarly, Mokin *et al*.[41] included 204 patients with NIHSS <8 and large vessel occlusions, out of these 38% were dead or dependent at discharge. In a study by Saleem *et al*.[42] one-fifth of patients with large vessel occlusion and NIHSS <6 on admission had early neurologic deterioration with a median time of 3.6 hours after the arrival. Elevated blood pressure on admission, positive head-up test, patients presenting early in the time window, and large perfusion deficit are factors hypothesized to portend a poor prognosis and to take into account while decision making for EVT.[43] A recent multicentric cohort study including 729 patients with minor stroke and LVO (basilar, ICA, M1/M2 MCA) showed early deterioration in 12.1% and was strongly associated with poorer outcomes; proximal occlusion and longer thrombus

were independently associated with early deterioration.[44] In a multicenter matched analysis, immediate thrombectomy was associated with favorable outcomes compared to rescue thrombectomy after deterioration.[45] Meta-analysis of observational studies has shown equivocal conclusions and randomized trials are needed to answer the question.[46] ENDOLOW and MOSTE are ongoing randomized trials aiming to assess the efficacy of thrombectomy in mild strokes.

Distal/medium vessel occlusions

Most of the patients included in landmark trials had occlusions of the M1 segment of the MCA. The M1 segment of MCA is considered to extend from origin to its division. The M2 segment extends from division to the origin of cortical branches. However, the definition, as well as anatomy in each patient, varies significantly. In some patients, M2 division can be as big as M1 and can be supplying a significant part of the hemisphere. Similarly, other medium vessel (lumen diameters between 0.75 to 2 mm- M3, M4, A1-A5, P1-P5, PICA, AICA, and SCA) occlusions can lead to significant morbidity or mortality.[47] This can be due to the strategic location of infarcts as well e.g., Wallenberg syndrome. Distal vessel occlusions can occur spontaneously or can complicate the mechanical thrombectomy for large vessel occlusions. Although recanalization rates with IVT are better in distal vessel occlusions, a significant proportion of patients might not get benefited or cannot be offered IVT at all due to small time windows. A study including 258 patients with medium vessel occlusions (M2/3, A2/3, P2/3) from two stroke registries showed that 32.8% of patients could not achieve functional independence despite the best medical management.[48] Currently, randomized evidence for benefit of thrombectomy in medium vessel occlusions is limited to M2 MCA occlusions. In a meta-analysis of data from HERMES collaboration, 130 patients with M2 occlusions were included. Intravenous thrombolysis was administered in 85.1% of patients in the thrombectomy group and 89.1% of patients in the medical management group. Functional independence was achieved by 58.2% of patients in the thrombectomy group and 39.7% in the medical management group. Notably, no patients in the thrombectomy group had symptomatic ICH, while 7.9% in the medical management group had symptomatic ICH.[49] Evidence for thrombectomies in other vessel occlusions is limited but intriguing. The DISCOUNT trial is randomizing patients with distal vessel occlusions (M2/3, A1/2/3, and P1/2/3) to mechanical thrombectomy and medical management arms.

Pediatric age group

Although all landmark trials excluded patients less than 18 years of age, mechanical thrombectomy in this age group also appears safe when the cause is either cardioembolic or dissection rather than underlying pathology of cerebral vessels as reported by Bhatti *et al*.[50]

Pregnancy

Although, arterial strokes are less frequent in this subset of patients, large vessel occlusion can have devastating outcomes. Pregnant or lactating patients were excluded in many of the landmark trials in view of concerns of radiation exposure to fetus. A study by Tse *et al*.[51] assessing radiation exposure to the fetus during mechanical thrombectomy showed that the estimated dose received by fetus following CT brain and mechanical thrombectomy in three pregnant patients was 0.024 ± 0.018 μGy (which was less than diagnostic imaging in trauma cases); patients had excellent neurological outcomes and babies were well at follow up. A large, national in-patient sample from the US during the period of 2012-2018 yielded 180 pregnant/postpartum patients who had undergone thrombectomy; it was shown that 50% of these patients had good functional outcomes at discharge. Although, it was lower compared to non-pregnant patients. At the same time, rates of intracranial hemorrhage were lower and rates of DVT/thromboembolic or pregnancy-related complications were higher in patients undergoing thrombectomy compared to medical management alone. The authors concluded that thrombectomy is a safe and viable option in stroke during pregnancy/postpartum.[52]

Tandem occlusions

Occlusion of both extracranial carotid and intracranial large vessel carries a poor prognosis. These patients were excluded in many of the landmark trials. A significant number of patients in other trials were having tandem occlusions and were treated by acute proximal cervical stenting. Although thrombectomy and intracranial recanalization have a proven role, a standardized approach is lacking. Which lesion to treat first and whether to do acute cervical stenting or not, are the questions that remain to be answered. Recently, a pooled analysis of two stroke registries (TITAN and ETIS) including 603 patients with tandem occlusions has shown that patients undergoing stenting had higher odds of successful recanalization and favorable outcome while symptomatic ICH was similar compared to patients receiving angioplasty alone.[53] This benefit was more pronounced in patients with low baseline NIHSS and atherosclerotic occlusion as opposed to dissection. This is likely because of the high bleeding risk in patients with large strokes and better natural history of dissection compared to atherosclerosis, respectively. Another meta-analysis did not find any significant difference between angioplasty alone or stenting group as well as no significant difference with regard to the order of the treatment.[54] EASI-TOC and TITAN are upcoming randomized trials addressing this question.

Beyond the "window"

Some patients with large vessel occlusion and good collaterals can have a very protracted course of infarct progression over several days if the arteries are not recanalized. A post-hoc analysis of the DEFUSE-3 trial had found that patients in the medical management arm had similar infarct volumes but persistent penumbral tissue beyond 24 hours while the majority of patients in the endovascular arm did not have penumbra as their vessels were recanalized. Patients in the endovascular arm not having a penumbral profile had significantly higher odds of functional independence.[55] Further trials are needed to

identify patients who might be benefited from thrombectomy beyond 24 hours

Procedural Variables

Successful recanalization

Given the high-quality data emphasizing the faster and better recanalizations to be associated with better outcomes, better techniques to achieve this are strived for. The "first-pass effect", defined as complete recanalization with a single thrombectomy pass, has been shown to be an independent predictor of good clinical outcome.[56] The definition of 'successful' recanalization is also being reconsidered. Most of the landmark thrombectomy trials used an mTICI score of 2b or greater (>50% reperfusion of affected arterial territory) to be 'successful' recanalization.[57] However, it has been shown that clinical outcomes between mTICI 2b and 3 vary significantly.[58] Hence, the expanded TICI grading scale incorporating 7 points is proposed by the HERMES group where a score of 2b67 or higher is considered successful reperfusion (0- no reperfusion; 1- thrombus reduction, no filling of distal arteries; 2a- reperfusion of <50%; 2b50- reperfusion of 50 to 66%; 2b67- reperfusion of 67 to 89%; 2c- reperfusion of 90 to 99% and 3- complete reperfusion).[59]

Devices/techniques

Stent-retrievers were the predominantly or exclusively used devices in all the landmark randomized trials mentioned above. Primary devices, as well as adjunctive materials and techniques, are evolving to achieve first-pass complete recanalization in the shortest possible time. A direct aspiration, first pass technique (ADAPT) was compared with stent-retrievers in the observational study including 243 patients; it was found that ADAPT led to better successful recanalization rates (82.3% vs 68. 9%), though the use of adjunctive devices was more frequent in ADAPT group and

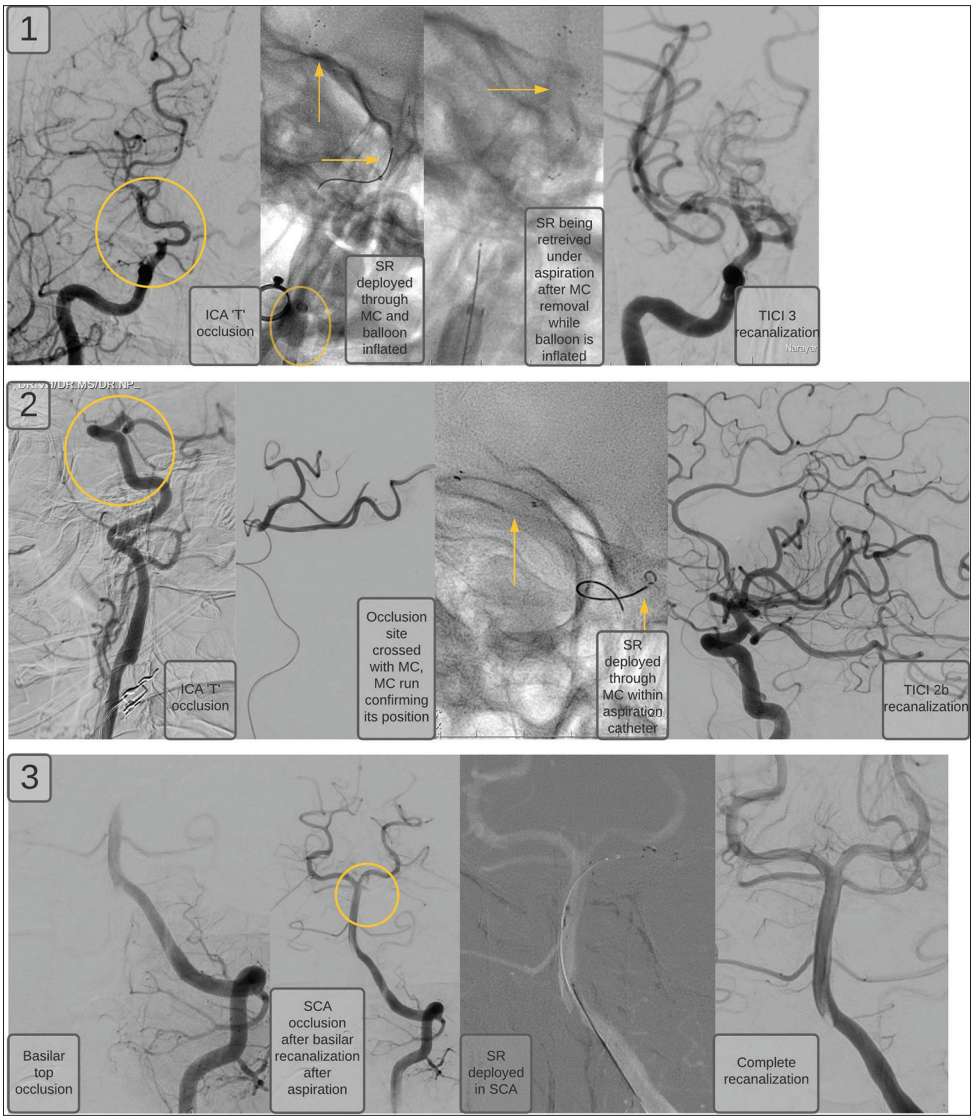

Figure 2: (1)- Stent retriever with a balloon guide catheter, (2) stent retriever with an aspiration catheter, (3) recanalization of basilar occlusion with ADAPT followed by stent retriever thrombectomy for superior cerebellar artery occlusion. SR- stent-retriever, MC- microcatheter

functional outcomes did not differ.[60] However, randomized control trial (THERAPY) comparing aspiration thrombectomy with medical management alone was negative.[61] The ASTER randomized trial failed to show superiority of aspiration to stent-retriever thrombectomy.[62] While the COMPASS randomized trial finally proved the non-inferiority of aspiration as the first pass.[63] A recent meta-analysis including 15 studies comparing balloon guide catheters to non-balloon guide catheters showed better procedural success (higher rates of first-pass effect and successful recanalization, lower distal emboli) as well as better clinical outcomes (lower symptomatic hemorrhage, higher rates of functional independence at 3 months and lower mortality).[64] There are various combination techniques described with some modifications while the principle remains the same- effective engagement of clot with the device, proximal flow arrest, and flow reversal while retrieving the clot to prevent emboli. All of these (SOLUMBRA, CAPTIVE, ARTS, SAVE, ASAP, PROTECT, PROTECT PLUS, BADDASS) report higher successful recanalization rates [Figure 2].[65-72]

Radial approach

The anatomy of the aortic arch might be unsuitable sometimes to access the vessel of interest through the femoral approach. In these circumstances, alternative approaches like a radial or direct carotid might need to be used. A systematic review and meta-analysis identified 51 patients in whom these approaches were used and found that technical success could be achieved in 84% of patients; there were no complications through radial approach and 7.4% of patients in whom direct carotid access was used had hematoma.[73] The radial approach can be the preferred primary approach as well in selected patients.[74,75]

Anesthesia

Initial observational studies, as well as meta-analysis from individual patient-level data by HERMES collaborators, had concluded that general anesthesia (GA) for thrombectomy was associated with worse outcomes compared to non-GA groups and the use of GA should be avoided.[76] However, the subsequent three randomized trials (SIESTA, AnStroke, GOLIATH) did not show any difference in primary outcomes between general anesthesia or conscious sedation.[77-79] The likely reason for the difference is the lack of standardized anesthesia protocols in previous studies. A recent meta-analysis involving four randomized trials even concluded that general anesthesia leads to better recanalization rates and better functional outcomes at three months, as far as sudden drops in blood pressure are avoided by standard anesthesia protocols.[80] Recently, local anesthesia, as opposed to GA or conscious sedation, has evolved to seem promising for better outcomes.

Direct thrombectomy

As shown in HERMES meta-analysis, outcomes in patients undergoing thrombectomy were favorable irrespective of whether they were given IVT or not. This had formulated a question of whether IVT can be skipped ineligible patients as well, as it might lead to more hemorrhagic complication rates and might have financial implications specifically in low and middle-income countries. Initial observational studies addressing this question have led to conflicting conclusions. While recent randomized trials and meta-analyses have concluded that direct thrombectomy can be a reasonable approach.[81] This holds true especially in patients with large clots, higher bleeding risk (large infarcts, basal ganglia infarcts, current antithrombotic use), or in patients requiring acute stenting and can be the preferred approach in patients presenting directly to thrombectomy ready centers.

Conclusion

Mechanical thrombectomy has proven to be one of the strongest treatments modern medicine can offer for any disease condition. Such a strong treatment needs as its companions, a robust pre-hospital and post-discharge systems of care as well to provide the best possible benefit to patients.

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Conflicts of interest

There are no conflicts of interest.

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Table 1: (Supplementary material)- Exclusion criteria of randomized trials

	MR CLEAN	ESCAPE	REVASCAT	SWIFT PRIME	EXTEND IA	THRACE	PISTE	EASI	DAWN	DEFUSE 3
Imaging	Hemorrhage	Hemorrhage; ASPECTS 0-5, no/ minimal collaterals in >50% MCA territory	Hemorrhage; Age <81: ASPECTS CT <7, MR <6 Age ≥81: ASPECTS CT/MR <9	Hemorrhage; infarcts in >⅓ MCA territory, ASPECTS <6, carotid dissection/ proximal occlusion, CTP infarct >50 ml	Hemorrhage; infarcts in >⅓ MCA territory, carotid dissection	Cervical ICA occlusion/severe stenosis	Hemorrhage; Infarcts in >⅓ MCA territory, extracranial ICA occlusion	Hemorrhage; established infarcts	Hemorrhage, >⅓ MCA territory involved, carotid dissection/proximal high-grade stenosis/ occlusion (requiring acute stenting), vasculitis,	Hemorrhage, ASPECTS <6, flow-limiting carotid dissection,
BP	≥185/110 mmHg	-	≥185/110 mmHg (even after medications)	-	≥185/110 mmHg (even after medications)	-	-	-	≥185/110 mmHg (even after medications)	≥185/110 mmHg (even after medications)
Blood glucose	<50/>400 mg/dl	-	<50/>400 mg/dl	-	Clinically significant hypoglycemia	-	-	-	<50/>400 mg/dl	<50/>400 mg/dl
Hematologic	MT-platelet <40000/μL, APTT >50s, INR >3 IAT-platelet <90000/μL, APTT >50s, INR >1.7, current use of NOACs	-	Platelet <30000/ μL, hemorrhagic diathesis, INR >3	Any contraindications for IVT	Hemorrhagic diathesis, INR >1.7, use of heparin in previous 48 hours and abnormal APTT, GpIIb-IIIa in <72 hours	Any contraindications for IVT	-	-	NOACs, heparin within 24 hours allowed (with normal aPTT), platelets <50000/μL, Hb <7mmol/L, Hemorrhagic diathesis, INR >3, aPTT ratio >3,	Platelets <50000/ μL, Hemorrhagic diathesis, INR >3, NOACs allowed if GFR >30 ml/min
Previous stroke	Infarct in same territory <6 wks, previous ICH	-	-	-	<3 months, recent ICH/SAH	-	-	-	-	-
Others	Major surgery or GI/GU bleed <2 weeks, arterial puncture noncompressible <7d, IAT-head injury <4 wks	Pregnancy, contrast allergy, intracranial dissection, chronic intracranial occlusion	Coma, life expectancy <1 yr, contrast allergy, creatinine >3 mg/ dl, pregnancy/ lactation, vasculitis, endovascular intervention/major surgery <48 hr, b/l stroke, intracranial tumors	Any contraindications to IVT, Life expectancy <90 days, pregnancy, rapidly improving symptoms, allergy to contrast/ nickel-titanium, creatinine >2 mg/ dl, aortic dissection, illicit drug use/ alcohol abuse,	Major surgery <2 wks, GI/GU bleed <3 weeks, rapidly improving symptoms, allergy to contrast/ nickel-titanium, life expectancy <1 yr, pregnancy, AVM, aneurysm, cerebral neoplasm	Any contraindications for IVT, any cause prohibiting femoral catheterization	History s/o SAH, vascular access contraindications, life expectancy <3 months, allergy to contrast	Comorbid disease suggesting poor outcome at 3 months	Head injury <90 days, dementia, seizure at onset (accurate NIHSS NA), Sodium <130, Potassium <3/>6, creatinine >3 mg/dl (except pt on dialysis), pregnancy, lactation, infective endocarditis, aortic dissection, b/l/ multiple territory stroke, cerebral neoplasm, life expectancy <6 months	Pregnancy, allergy to contrast, life expectancy <6 months, seizure at onset (accurate NIHSS NA), Infective endocarditis, tPA use beyond guidelines, cerebral neoplasm, AVM, aortic dissection, multiple territory stroke