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REVIEW

Recent Trends in Clot Retrieval Devices: A Review

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ABSTRACT

Stroke is the second leading cause of death worldwide and in Europe. Even with gold standard medical management of acute ischemic stroke, which is intravenous (IV) thrombolysis by administration of recombinant tissue plasminogen activator (rt-PA), the mortality rate remains the same. Intra-arterial (IA) thrombolysis therapy also did not achieve significant results and was not approved by the US Food and Drug Administration (FDA) because of limited sample size. This encouraged scientists and engineers to develop endovascular clot retrieval devices for the mechanical recanalization of the occluded arteries in stroke patients. Although the initial designs of clot retrieval devices failed, efforts to improve these devices continue. Recently clot retrieval devices were approved by the FDA as first-line treatment along with IV rt-PA. This article gives an in-depth review of different clot retrieval devices which includes MERCI (the first), the Penumbra Aspiration System, EmboTrap®II, stent retrievers, and the way forward with the new FDA clearance of the devices as first-line treatment for acute ischemic stroke along with IV rt-PA. The review also includes a comparison of clot retrieval devices to gold standard treatment.

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INTRODUCTION

Cerebrovascular disease is one of the leading causes of morbidity and mortality in the world. Stroke alone is the fifth leading cause of death in USA killing nearly 133,000 people a year [1]. It is the second leading cause of death worldwide [2]. In 2014, one out of every 20 deaths was caused by stroke [3]. On the basis of the

National Health and Nutrition Examination Survey (NHANES) conducted from 2011 to 2014, approximately 7.2 million Americans over 20 years old have had a stroke. The estimated stroke prevalence was 2.7% during that time period [4]. Approximately 795,000 people experience a new or recurrent stroke each year with ischemic type constituting 87% of all the cases of strokes [4]. The estimated total cost of both cardiovascular disease and stroke in the USA was $316.1 billion from 2012 to 2013 accounting for 14% of total health expenditure during that time period [4].

The current gold standard medical management of acute ischemic stroke is intravenous (IV) thrombolysis by administration of recombinant tissue plasminogen activator (rt-PA) [5]. When administered within 4.5 h of the onset of ischemic stroke symptoms, it may increase the chances of favorable neurological or functional outcome without significant disability at 3–6 months of the ischemic stroke. However, it does not decrease the mortality rate and it is unclear if it achieves the aim of complete recanalization of occluded arteries especially the large ones [5, 6]. Although IV rt-PA therapy is beneficial, the narrow therapeutic window, potential serious complication of symptomatic intracranial hemorrhage [6], and low recanalization rate of occluded arteries have driven clinicians and scientists to look for other effective and novel therapeutics for ischemic stroke.

In the quest to achieve complete arterial recanalization and broaden the therapeutic window, an intra-arterial (IA) thrombolysis method was assessed using different thrombolytic agents like rt-PA, urokinase (UK), and recombinant pro-urokinase (r-pro-UK). Theoretically IA thrombolysis has the advantage of achieving higher recanalization rate with less fibrinolytic drug use [7]. Treatment with r-pro-UK showed favorable clinical outcomes in patients with middle cerebral artery (MCA) occlusion in one of the leading clinical trials, Intra-arterial Prourokinase for Acute Ischemic Stroke (PROACT II) [8]. The median time to therapy was 5.3 h and recanalization was achieved in 66% of the patients while modified Rankin Scale (mRS) score of 2 or less was observed in 40% of the patients treated with r-pro-UK [8]. Early symptomatic intracranial hemorrhage (within 24 h) occurred in 10% of the patients which was higher than in previous clinical trials with IV rt-PA. The authors attributed it to the greater baseline stroke severity and time to treatment in the PROACT II trial [8]. Despite the favorable findings of PROACT II, the US Food and Drug Administration (FDA) did not approve IA r-pro-UK therapy because of the small sample size, marginal significant results achieved ($P = 0.043$), and early symptomatic intracranial hemorrhage. The FDA panel warranted a confirmatory trial to achieve robust results which was never performed [9, 10]. This, however, incited the enthusiasm for endovascular mechanical recanalization of occluded arteries in stroke patients and started the era of endovascular clot retrieval devices. Despite initial failures, scientists and engineers continued to improve the design of clot retrieval devices [11]. More than a decade after the first device approval in limited cases that the FDA has most recently cleared two clot retrieval devices to be used as first-line treatment along with IV rt-PA for ischemic stroke to reduce paralysis, speech difficulties, and other stroke-related disabilities.

This article does not contain any studies with human or animal subjects.

COMPARISON OF DIFFERENT CLOT RETRIEVAL DEVICES

Over the years we have seen remarkable advancements in the development of various medical devices and their transcatheter delivery systems. This is especially so in the area of cardiovascular diseases where steering the catheter may become technically challenging and demands continuous improvement of the system to achieve results with minimal procedure-related complications. With emerging transcatheter multimodal drug, patch, and stent delivery systems for various functional and structural cardiovascular diseases like myocardial infarction, intracardiac septal defects, and peripheral vascular diseases, we have learned that apart from the technical complexities,

regulatory hurdles also need to be tackled [12, 13]. This was also reflected to the area of acute ischemic stroke when disapproval of endovascular IA thrombolytic stroke therapy by the FDA paved the way for the development and improvement of innovative clot retrieval devices.

MERCI: the First

Initially designed for foreign body removal, the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retriever by Concentric Medical was the first mechanical thrombectomy device that got FDA clearance in 2004 [14]. With its corkscrew-shaped distal tip, it was designed to remove the thrombus en bloc. The MERCI trial investigated the safety and efficacy of the device to remove clots from large intracranial vessels within 8 h of the onset of stroke symptoms. Out of 151 patients recruited for the trial, 141 underwent the procedure of clot retrieval using the device. One of the inclusion criteria was the occlusion of treatable vessels which were defined as the intracranial vertebral artery, basilar artery, intracranial carotid artery (ICA), ICA terminal bifurcation, or the middle cerebral artery (MCA) first division (M1) and secondary division of the MCA (M2). It was a nonrandomized, single-arm trial. A recanalization rate of 18% from the PROACT II control (IV heparin) group was set as the benchmark. The results were promising as the recanalization was achieved in 68 out of 141 patients (48%) which was significantly higher than the benchmark set for this trial. The favorable outcome at 90 days as determined by the mRS score of 2 or less was observed in 27.7% of the patients. The overall mortality in the MERCI trial was 44%, which was higher than any other prospective trial of acute stroke treatment at that time. The team conducting the trial attributed it to the severity of the disease in enrolled patients including high median baseline National Institutes of Health Stroke Scale (NIHSS) of 19 [15]. The FDA was initially sceptical to clear the device because of the high mortality rate, but as a result of the paucity of literature reporting mortality for large vessel occlusion, the device was cleared for use in acute ischemic stroke [9]. With improvement in its design, the later trial (multi-MERCI) with a second-generation device showed better results. The device was deployed in 164 patients and the recanalization rate was 68% [16]. The mRS score of 2 or less at 90 days was observed in 36% of the patients while the overall mortality at 90 days was 34% [16].

Penumbra Aspiration System

The Penumbra Aspiration System was introduced in 2008 and works on the principle of disruption and aspiration of the clot. It uses a relatively large bore catheter as compared to the MERCI system. The bore separator wire included in the system prevents the clogging of the aspiration tip, which is a potential issue with small bore catheters used within the intracranial arteries [14, 17]. A total of 125 patients were enrolled in the clinical trial using the Penumbra Aspiration System for clot retrieval. Successful recanalization was achieved in 81.6% of the patients while mRS score of 2 or less at 90 days was observed in 25% of the patients. The overall mortality rate was 32.8% at 90 days [18]. Unlike the MERCI retriever system, once deployed, additional passes or re-access is not required with the Penumbra Aspiration System. Progressive improvement in the system was made and an improved catheter system with a larger inner diameter was introduced in later years [14].

Trials Comparing Early Generation Devices with IV rt-PA and Their Pitfalls

The Interventional Management of Stroke (IMS) III, SYNTHESIS Expansion, and The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trials were the three prospective, multicenter randomized controlled trials that did not show benefit from endovascular mechanical thrombectomy when compared to the gold standard IV rt-PA. Concerns were raised by the neurointerventionalists on various aspects of the study designs of these failed endovascular stroke trials. In general, two main reasons were attributed to the failure of

these trials: (1) Large artery obstruction was not routinely identified using imaging modalities like computed tomography angiography (CTA) or magnetic resonance angiography (MRA), except for in MR RESCUE; (2) The new generation clot retrieval devices like the stent retrievers were not widely used in these trials [19].

IMS III was an international, phase 3 trial that recruited patients from 58 centers. Good outcome was achieved in 40.8% of the patients in the endovascular therapy group while it was achieved in 38.7% of the patients in the IV rt-PA group. The trial was aborted early because of futility. Imaging was not done routinely in the IMS III trial that surely affected the patient selection and final results. Only 47% of the patients underwent CTA, and approximately 20% of the patients in the intervention group either did not have large artery obstruction or the location of thrombus was inaccessible [20]. The SYNTHESIS trial, another multicenter randomized trial, was the same in the sense that an imaging modality like CTA or MRA was not a prerequisite for the confirmation of arterial occlusion; hence all the patients enrolled did not undergo the imaging. Large artery obstruction was not present in approximately 10% of the patients in the intervention group. Apart from that IV rt-PA was compared with isolated endovascular treatment and that too was mostly IA rt-PA, while new generation devices were used in very small numbers of patients [19]. MR RESCUE was a small, multicenter, phase 2b randomized trial. Although the MR RESCUE trial did utilize imaging modalities like CTA and MRA, longer time to enrollment (5.2–5.8 h), use of early generation devices as in the other trials, and small sample size leading to low statistical power for analysis were the main contributing factors in the failure of this trial [19, 20].

A detailed discussion of the reasons for the lack of efficiency of the clot retrieval devices in these trials and weaknesses of each trial design is beyond the scope of this review article. However, the main limitations of these trials were (1) lack of using pretreatment imaging modalities to evaluate the salvageable brain as reperfusion into irreversibly damaged ischemic region is not beneficial and also to identify the location of occlusion, (2) treatment with early generation clot retrieval devices, (3) recruitment of small numbers of patients per center, (4) comparison of IV rt-PA to the endovascular treatment alone (SYNTHESIS), (5) time lag between hospital presentation and treatment.

The results of these trials were published in 2013; despite the visible limitations and weaknesses, the failure of these three trials in establishing the clinical impact of clot retrieval devices was a blow to the years of efforts of achieving better outcomes in patients with acute ischemic stroke. However, criticism of these trials laid the foundation for newer trials with robust study designs using new generation clot retrieval devices.

Stent Retrievers

A self-expanding stent retriever is deployed in the occluded vessel within the thrombus; the device entraps the thrombus within its struts and is then withdrawn back into the delivery catheter. The Solitaire flow restoration device was the first one to get FDA clearance under this category [17]. Solitaire Flow Restoration with the Intention for Thrombectomy (SWIFT) study was designed to compare the efficacy and safety of Solitaire with the standard, predicate mechanical thrombectomy device, the MERCI Retrieval System [21]. Successful recanalization was observed in 34 out of 56 patients (61%) who received Solitaire Flow Restoration therapy whereas in 13 out of 54 patients (24%) who received MERCI Retrieval System therapy. The neurological outcome at 90 days was also better with the Solitaire than MERCI system. mRS score of 2 or less was achieved in 58% of the patients in the Solitaire group as compared to 33% of the patients in the MERCI group. Various clinical trials including TREVO 2 have shown better recanalization results with the stent retriever systems as compared to MERCI Retriever and Penumbra Aspiration Systems and hence stent retrievers gained rapid and widespread adoption [14, 22, 23]. SWIFT and TREVO 2 clinical trials were significant in the way that the two versions of stent retrieval systems were compared against the MERCI

retrieval system as opposed to the previous clinical trials where MERCI Retriever and Penumbra Aspiration Systems were compared to the historical IV heparin arm of the PROACT II study [24]. Table 1 shows the comparison of the results of initial clinical trials deploying different types of clot retrieval devices in cases of acute ischemic stroke.

FDA Approval of TREVO Stent Retrieval Device as First-Line Treatment for Acute Ischemic Stroke

Most recently the FDA has approved two TREVO clot retrieval devices from Stryker Neurovascular in Fremont, California to be used as first-line treatment option in cases of acute ischemic stroke. They can be deployed within 6 h of the onset of symptoms and only after the administration of IV rt-PA that should be given within the first 3 h of the onset of symptoms. The decision was based on the results of a clinical trial which showed better 90-day functional outcome in the group of patients managed with both rt-PA and TREVO as compared to the ones who did not receive TREVO [25]. This is the biggest milestone in the journey of clot retrieval devices achieved until now as previously these devices were only indicated for patients who could not receive rt-PA or for those patients who did not respond to rt-PA therapy. This would definitely help in further reducing the disabilities like paralysis and impaired speech associated with acute ischemic stroke.

EmboTrap®II

The EmboTrap®II revascularization device is an advanced stent retriever platform for the treatment of acute ischemic stroke. The device is deigned to trap the clot with minimal compression, rapidly deliver the Thrombolysis in

Table 1 Comparison of the results of initial clinical trials deploying different types of clot retrieval devices

Trial	MERCI/multi-MERCI (2002–2007)	Penumbra (2007–2009)	SWIFT (2012)	TREVO (2012)
Patients	151	125	58	86
	164	157		
Mean NIHSS	20.1	17.6	17.4	18.3
	19	16.6		
Symptom onset to treatment (h)	4.3	4.3	4.8	4.6
	4.3	4.1		
Procedure complication (%)	13	12.8	15.7	15
	9.8	5.8		
Mortality at 90 days (%)	43.5	33	17	33
	34	20		
mRS 0–2 at 90 days (%)	27.7	25	36	40
	36	41		
Recanalization rate (%)	48	82	61	86.4
	68	87		

MERCI Mechanical Embolus Removal in Cerebral Ischemia, *SWIFT* Solitaire Flow Restoration with the Intention for Thrombectomy, *NIHSS* National Institutes of Health Stroke Scale, *mRS* modified Rankin Scale

Cerebral Infarction scale of 2b-3 (TICI 2b-3) reperfusion, and retain the clot during retrieval, protecting against embolization [22]. Optimal positioning to the occlusion is facilitated by radiopaque markers. The device is available in 5×33 mm and 5×21 mm sizes, both compatible with 0.021-in. microcatheters. In 2017, Neuravi, a company based in Galway Ireland, announced completion of enrollment in an international clinical trial assessing the effectiveness and safety of this device. Data from the ARISE II (Analysis of Revascularization in Ischemic Stroke with EmboTrap) study is submitted as part of an application to the FDA for market clearance of the device in the USA. This study enrolled 228 patients in 19 sites across Europe and USA.

COMPARISON OF CLOT RETRIEVAL DEVICES TO THE GOLD STANDARD TREATMENT

The National Institute of Neurological Disorders and Stroke (NINDS) Recombinant Tissue Plasminogen Activator (NINDS rt-PA) Stroke Study results published in 1995 demonstrated the effectiveness of the IV rt-PA in ischemic stroke when administered within 3 h of the onset of symptoms [26]. Since then, IV rt-PA has been the gold standard in the management of acute ischemic stroke. Hacke et al. analyzed the clinical trials with IV rt-PA administered within 6 h of the onset of symptoms and their results also suggested administering of IV rt-PA within 3 h to achieve greater benefits which are reduction in mortality and favorable neurological outcome. In fact better results were achieved when IV rt-PA was administered within 90 min of the onset of symptoms [27]. Emberson et al. published results from their meta-analysis of nine randomized controlled trials of IV rt-PA that showed the effectiveness of the treatment when given within 4.5 h of the onset of symptom regardless of the severity of the disease [6]. Although the current guideline suggests administering of IV rt-PA within 4.5 h of the symptom onset, the difficulties in early diagnosis and access to specialized centers in low socioeconomic regions bar the majority of the patients from getting benefit from the therapy. Furthermore, IV rt-PA is less effective in cases of large vessel occlusion [5, 14]. Thus achieving higher rates of recanalization with a broadened therapeutic window has been considered the "holy grail" in the management of acute ischemic stroke.

Current data suggests that with IV rt-PA alone, there is less than 20% chance of opening large artery occlusions [7]. However, this could be improved when combined with endovascular clot retrieval devices. Rodrigues et al. recently published results of their meta-analysis of 10 randomized controlled trials ($n = 2925$) and strongly recommended adjunctive endovascular mechanical thrombectomy within 6–8 h of the large vessel ischemic stroke [28]. In 7 out of 10 most recently published or presented randomized controlled trials, the majority of patients were treated with stent retrievers and the recanalization rate was greater than 58%. Furthermore, combined treatment with IV rt-PA and clot retrieval device was associated with better functional outcome at 90 days of stroke as compared to medical management alone [28].

The results from the five randomized clinical trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA published in 2015 clearly established the efficacy of the endovascular mechanical thrombectomy in cases of acute ischemic stroke. It was evident from these trials that the use of newer generation clot retrieval devices, robust pretreatment imaging selection criteria, and better work flow resulted in favorable functional outcome in patients with acute ischemic stroke due to proximal occlusion of large vessels in anterior circulation [29]. Table 2 gives an overview of these five clinical trials. Goyal et al. conducted a meta-analysis of these five clinical trials and analyzed the individual data for 1287 patients. Out of these 1287 patients, 634 patients were allocated to the endovascular thrombectomy while 653 patients were assigned to the control group. The meta-analysis revealed significantly reduced disability at 90 days in the endovascular thrombectomy group compared with the control group. Furthermore, better functional outcome using the newer generation clot

Table 2 Overview of the five positive randomized clinical trials that showed the efficacy of clot retrieval devices

Trial	MR CLEAN	ESCAPE	REVASCAT	SWIFT PRIME	EXTEND IA
Target lesion	Proximal anterior circulation	Proximal anterior circulation with good collaterals	Intracranial ICA or proximal MCA	Intracranial ICA or proximal MCA	Proximal anterior circulation
Interventional arm	IA therapy	IA therapy	Endovascular thrombectomy with Solitaire FR stent retriever	Endovascular thrombectomy with Solitaire FR stent retriever	Endovascular thrombectomy with Solitaire FR stent retriever
Control arm	Best medical management (±IV rt-PA)	Best medical management (±IV rt-PA)	Best medical management (±IV rt-PA)	IV rt-PA	IV rt-PA
Number of patients (intervention/control)	233/267	165/150	103/103	98/98	35/35
Mean/median age (years) (intervention/control)	65.8/65.7	71/70	65.7/67.2	66.3/65.0	68.6/70.2
Median time from stroke onset to groin puncture (min)	260	241	269	224	210
Intervention with stent retrieval device (%)	81.5	86.1	100	100	100
Improvement in mRS 0–2 at 90 days (%) (intervention/control)	32/19.1	53.0/29.3	43.7/28.2	60.2/35.5	71.4/40
TICI grade 2b/3 recanalization (%)	58.7	72.4	65.7	88	86.2

ICA intracranial artery, *MCA* middle cerebral artery, *IA* intra-arterial, *IV* intravenous, *rt-PA* recombinant tissue plasminogen activator, *mRS* modified Rankin Scale

retrieval devices, mainly the stent retrievers, was seen across a wide range of age, initial stroke severity, and also in the patients ineligible for the gold standard IV rt-PA treatment. Hence, this meta-analysis supports the notion of not restricting the endovascular mechanical thrombectomy treatment on the basis of age, severity of the disease, and ineligibility for IV rt-PA treatment [29].

The results of these five clinical trials have definitely revolutionized the management of acute ischemic stroke. As it is said that "time is brain", the only hindrance in generalizing these results is the availability of the state of the art centers across different countries and it surely will be a daunting task. Choi et al. conducted a retrospective study from 2009 to 2010 to find out the regional availability of mechanical embolectomy

for acute ischemic stroke in California and found that only 3% of hospitals performed more than 10 cases of endovascular therapy per year for acute ischemic stroke. Among the patients who received endovascular mechanical embolectomy, 93% resided within 20 miles from a hospital capable of performing endovascular mechanical embolectomy capable as compared to 7% who lived outside the 20-mile radius [30].

The FDA's recent approval of the TREVO stent retrieval device to be used along with IV rt-PA as a first-line therapy for acute ischemic stroke is definitely a step forward and reflects more than a decade-long effort of improvement in device design and efficacy. Now effort needs to be done to make it standard of care by reshaping the emergency stroke care globally so that the majority of patients get benefit from these innovative endovascular clot retrieval devices.

SHOULD INTERVENTIONAL CARDIOLOGISTS BE PERMITTED TO PERFORM THE PROCEDURE GIVEN LACK OF NEUROINTERVENTIONALISTS?

Interventional cardiology is a rapidly evolving clinical field with constant need for interventional cardiologists to up-skill to be able to use novel devices and techniques for cardiovascular diseases for better patient outcomes. This is particularly evident through advances in structural heart disease interventions such as transcatheter aortic, mitral, and now tricuspid valve interventions. In parallel, interventional cardiologists are using novel medical devices for the treatment and monitoring of heart failure, atrial fibrillation, left atrial appendage closure, hypertension, etc.

There is now evidence to treat acute stroke with embolectomy and thrombus aspiration. This is ideally performed by highly trained neurointerventionists through minimally invasive intracranial techniques. To provide a round the clock 24-h clinical service for any interventional procedure requires a significant number of trained interventionalists. At present there are only a few hundred trained interventional neurologists in comparison to thousands of interventional cardiologists in most countries. The number of interventional procedures performed in cardiology is much higher than neurology, and training of a large number of interventional neurologists for a small number of elective cases cannot be justified. In addition, the acute coronary syndrome programmes for primary PCI are well established with significant infrastructures in place for speedy patient transportation (road and air ambulance) and activation of cardiac catheterization laboratories. Most cardiac catheterization laboratories are equipped with essential hardware and software required for intracranial procedures. Studies have shown the safety and efficacy of the endovascular mechanical thrombectomy procedures performed by interventional cardiologists [31, 32]. Finally interventional cardiologists are very familiar with antiplatelet and anticoagulation therapies for patients with acute coronary syndrome (ACS) and stroke risk.

In our opinion, the training of interventional cardiologists for acute stroke intervention is appropriate and will utilize the existing emergent endovascular care infrastructure with significant costs savings to the already economically burdened heath care system.

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