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BMH Medical Journal 2016;3(3):67-71 **Review Article**

Endovascular Treatment For Acute Anterior Circulation Ischemic Stroke - New Evidence And Current Status

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Abstract

Endovascular mechanical treatment can remove large proximal clots rapidly and result in higher rates of reperfusion than IV rt-PA alone. Three initial trials of endovascular therapies in 2013 did not show a benefit for thrombectomy over IV rt-PA. But in 2015, 5 trials from around the world, namely MR CLEAN, EXTEND-IA, ESCAPE, SWIFT-PRIME, and REVASCAT, advanced the scope of endovascular therapy for acute ischemic stroke. We review these trials and discuss how they have shaped the current status of endovascular therapy in acute ischaemic stroke.

Keywords: Anterior Circulation Ischemic Stroke, Endovascular Treatment

Introduction

Intravenous recombinant tissue plasminogen activator (IV rt-PA) administered within 4-5 hours after onset of ischemic stroke improves outcomes. It has now been clearly established by several studies across the world that 35 to 45% of patients who received rt-PA become functionally independent (defined as a modified Rankin Scale score of 0-2).

However, in patients who develop stroke due to proximal intracranial arterial occlusions (ICA< proximal MCA, ACA) IV rt-PA is not very effective, 60 to 80% of such patients die within 90 days after stroke onset or do not achieve functional independence despite rt-PA therapy.

Endovascular mechanical treatment can remove large proximal clots rapidly and result in higher rates of reperfusion than IV rt-PA alone. Three initial trials of endovascular therapies in 2013 did not show a benefit for thrombectomy over IV rt-PA.[1,2,3] But these trials had many limitations, most importantly, they used early generation devices with modest reperfusion efficacy.

In 2015, a remarkable turnaround happened, with five landmark trials from around the world advancing the scope endovascular therapy for acute ischemic stroke to such an extent that it now has a class I, level A evidence based recommendation in the AHA/ASA guideline updated in June 2015. [4]

The trials that have led to this paradigm shift in acute stroke therapy are MR CLEAN, EXTEND-IA,

ESCAPE, SWIFT-PRIME, and REVASCAT.[5-7,9,10] They do have certain key underlying similarities: anterior circulation strokes were selected, therapeutic window of 6 hours from onset to puncture, confirmation of proximal artery occlusion on vascular imaging required, and newer stent based clot retrieval devices were used. One or more of these factors could explain why these trials have succeeded in giving better clinical outcomes, far beyond earlier mechanical thrombectomy trials - to such an extent that many of these had to be terminated early on ethical grounds, as the benefit in the endovascular arm was so high that continuation of the trial was deemed unnecessary.

We review these trials and discuss how they have shaped the current status of endovascular therapy in acute ischaemic stroke.

Brief Description Of The Trials

MR CLEAN [5] (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands)

Chronologically the first among these trials, 'MR CLEAN' was published in New England Journal of Medicine (NEJM) on January 1, 2015. 500 patients of acute anterior circulation stroke with radiologically confirmed proximal arterial occlusion were recruited from 16 centers in the Netherlands. Of these, 267 were randomised to usual care (IV thrombolysis); and 233 received intra-arterial treatment in addition.

Demonstration of occlusion of the distal intracranial carotid artery, middle cerebral artery (M1 or M2), or anterior cerebral artery (A1 or A2), established with computed tomographic (CT) angiography (CTA), magnetic resonance angiography (MRA), or digital-subtraction angiography (DSA) was required. To quote the study protocol, "Intra-arterial treatment consisted of arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both. The method of intra-arterial treatment was left to the discretion of the local interventionist". Initiation of intra-arterial treatment had to be possible within 6 hours after stroke onset. Retrievable stents were used in the vast majority of intra-arterial group: 190 patients (81.5%). Other devices were used in 5 patients. Additional intra-arterial thrombolytic agents were given to 24 patients (10.3%) and intra-arterial thrombolytic agents were used as monotherapy only in 1 patient. The primary outcome, disability assessed by modified Rankin scale (mRS) at 90 days was shifted in favour of intervention in all categories except death. There was no significant between-group difference in the occurrence of serious adverse events. The authors concluded that the endovascular treatment effectively lead to a clinically significant increase in functional independence in daily life by 90 days, without a corresponding increase in mortality.

EXTEND - IA [6] (Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial)

This trial was published in March 2015, again in NEJM. Conducted in various centres across Australia/New Zealand, the trial was stopped early because of efficacy after 70 patients had undergone randomization. The patients were randomly assigned to 0.9 mg of alteplase per kilogram of body weight, less than 4.5 hours after the onset of ischemic stroke, alone or with endovascular thrombectomy using the Solitaire stent retriever. All the patients had occlusion of the internal carotid (ICA) or middle cerebral artery (MCA) and evidence of salvageable brain tissue and ischemic core of less than 70 ml on computed tomographic (CT) perfusion imaging. Endovascular therapy had to be initiated (groin puncture) within 6 hours after stroke onset and completed within 8 hours after onset. The addition of CT perfusion imaging to select patients with salvageable brain tissue was an additional requirement in EXTEND-IA over MR CLEAN. Only ICA and MCA occlusions were selected in this trial.

Endovascular therapy resulted in increased reperfusion at 24 hours with a probability of reperfusion

of close to 90% without symptomatic intracerebral haemorrhage, as compared with the alteplase-only group (89% vs. 34%, P<0.001). Patients in the endovascular therapy group were also more likely to be independent at day 90 (71% vs. 40%). Symptomatic intracerebral haemorrhage occurred in two patients in the alteplase-only group (both with fatal results) and in none of the patients in the endovascular-therapy group. CT perfusion-imaging selection to exclude patients with large ischemic cores and without evidence of clinically significant salvageable ischemic brain was cited by the authors as an important factor leading to the positive outcome.

ESCAPE [7] (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times)

Also published in NEJM, March 2015, the same issue as EXTEND-IA, this trial recruited patients from multiple centres in Canada, USA, UK and South Korea. As in the previous two trials, patients with a proximal vessel occlusion in the anterior circulation were randomly assigned participants to receive standard care or standard care plus endovascular treatment. Notable differences in this trial were: patients were included up to 12 hours from symptom onset. Patients with a large infarct core (defined as Alberta Stroke Program Early Computed Tomography Score - ASPECTS [8] - 5 or less on CT) or poor collateral circulation (defined as the filling of less than 50% of the middle-cerebral artery circulation on CTA) were both excluded. Thus, in the ESCAPE trial, assessment of collateral circulation was an additional imaging parameter that was used for selecting patients for intra-arterial treatment. The trial was stopped early because of efficacy after enrolling 316 patients.

SWIFT-PRIME [9] (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment)

This trial was published in NEJM June 11, 2015 issue. The main centre was UCLA Stroke Centre, Los Angeles. The intervention arm underwent stent retriever thrombectomy within 6 hours of onset. Imaging-confirmed occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both was required. "Penumbral imaging" to exclude patients with "large ischemic-core lesions" was an additional requirement, but was not strictly enforced. This trial was also stopped early in view of efficacy after enrolling 196 patients.

REVASACT [10] (Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset)

This trial was also published in the 2015 June 11 issue of NEJM. The principal centre was in Barcelona, Spain. In addition to extending the intervention window to 8 hours, the study also used the ASPECTS - less than 7 on CT or a score of less than 6 on diffusion-weighted MRI - for excluding patient with large ischemic-core lesions. After the enrollment of 160 patients, the inclusion criteria were modified to include patients up to the age of 85 years. Endovascular treatment was done with the Solitaire stent retriever. Total of 206 patients were enrolled, and the study was stopped out of ethical consideration as already published trials had provided sufficient evidence to favour endovascular treatment in these patients. Rates of functional independence at 90 days were increased by 15.5 percentage points in the thrombectomy group.

Discussion

Although they have many similarities, the five trials have subtle but important differences which are worth noting. They are summarized in **Table 1** below:

Table 1

Parameter	MR CLEAN	EXTEND IA	ESCAPE	SWIFT PRIME	REVASACT
Onset to groin puncture (specified)	6 hours	6 hours	12 hours	6 hours	8 hours
Onset to groin puncture, (maximum reported, minutes)	313	251	315	275	340
Additional imaging parameter	None	CT Perfusion	ASPECTS >5 and Moderate - Good collaterals on CTA	"Penumbral analysis"	No consistent parameter
Thrombectomy Technique	Thrombolytic agent, mechanical thrombectomy, or both. Retrievable stents used in majority	SOLITAIRE	Retrievable stents	SOLITAIRE	SOLITAIRE
Arterial territory	Distal ICA, M1, M2, A1, A2	ICA, M1 or M2	ICA, M1 or M2	ICA, M1 or both	ICA, M1 or M2

Three trials out of these five, EXTEND-IA, ESCAPE and SWIFT-PRIME were stopped early due to overwhelming evidence of benefit in the intervention arm. The common factor in these three trials is that additional imaging parameters were used to select patients with salvageable brain tissue. Although they were all CT based, the exact method used differed. However, the fact that these three trials outperformed the other two in the final outcome highlights the relevance and importance of using advanced CT techniques - including perfusion, collateral assessment and "penumbral analysis" - in selecting patients for intervention. The ideal method is difficult to derive from available evidence and as far as is shown in these trials, all of these methods seemed to give good results.

The specified time window for intervention varied from 6 - 12 hours, but the actual reported time - from onset to groin puncture - seemed to vary less, to a maximum of 340 minutes (5 hours 40 minutes) in REVASACT. Thus, the extensibility of therapeutic window beyond 6 hours, even with advanced imaging based selection seems rather unlikely. At present the available evidence indicates that endovascular therapy should be initiated within 6 hours of symptom onset. When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with internal carotid or proximal MCA occlusions.

It is important to recognize that all the studies recruited ICA and proximal MCA occlusions, except for 3 patients with ACA occlusions in MR CLEAN. Whether these results are generalizable to posterior circulation is an open question. Posterior circulation strokes especially basilar artery occlusions may have devastating outcomes, so the question is a highly relevant one. Perhaps future trials will shed more light on this.

To conclude, these five trials have firmly established endovascular treatment - specifically stent retriever thrombectomy - in combination with IV thrombolysis as the treatment of choice in acute proximal occlusions of anterior cerebral circulation, with proof of salvageable brain tissue on

imaging. The challenge in all stroke treatment centres is now to increase adoption of the skill and technologies required for implementing this highly time bound therapy in an increasing number of centres so that many more unfortunate stroke victims get the best treatment possible.

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