

Mechanical thrombectomy for acute ischaemic stroke

R Harrichandparsad, MB ChB, MMed (Neurosurg), FCNeurosurg (SA)

Department of Neurosurgery, College of Health Sciences, University of KwaZulu-Natal and Inkosi Albert Luthuli Central Hospital, Durban, South Africa

Corresponding author: R Harrichandparsad (harrichandparsad@ukzn.ac.za)

Rapid, safe and effective arterial recanalisation to restore blood flow and improve functional outcome is the primary goal of hyperacute management of acute ischaemic stroke. This is possible either through thrombolysis or direct mechanical removal of clot from the blocked artery. Current evidence from randomised controlled trials shows that, for correctly selected patients, functional independence can be achieved in 32 - 71% of those who undergo clot removal. It is estimated that 10 - 15% of all ischaemic stroke patients have large-vessel occlusion and qualify for mechanical thrombectomy. It is important to have systems in place to identify and treat these patients.

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History of intervention for acute ischaemic stroke

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) demonstrated that treatment with intravenous recombinant tissue plasminogen activator (IV r-tPA) within 3 hours of onset of ischaemic stroke improved clinical outcome at 3 months.^[1] However, there was less benefit to patients with proximal or large-vessel occlusion, possibly because the clot burden and nature of the lesion meant that thrombolysis was less effective than in smaller-vessel occlusions. In 1998, ECASS (European Cooperative Acute Stroke Study) extended the benefit of IV r-tPA to 4.5 hours.^[2] In 1999, the PROACT II (Prolyse in Acute Cerebral Thromboembolism II) trial demonstrated the efficacy of intra-arterial pro-urokinase for proven middle cerebral artery occlusion.^[3] These early endovascular approaches ultimately led to the development of mechanical thrombectomy.

The first mechanical intra-arterial clot-retrieval endovascular device, the MERCI Retriever (UCLA, USA), used in the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) trial in 2005, showed a recanalisation rate of 46% by the MERCI device alone and 60.8% when combined with IV r-tPA.^[4] However, intracranial haemorrhage occurred in 7.8% of patients. In the Multi MERCI trial a later-generation MERCI device was used, which demonstrated a 69.5% recanalisation rate with favourable clinical outcomes in 34%; however, the trial did not include a control therapy group.^[5] Optimism about mechanical thrombectomy diminished when 3 early randomised controlled trials (RCTs) published in 2013 (IMS III (Interventional Management of Stroke III), MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy) and SYNTHESIS

(Local Versus Systemic Thrombolysis for Acute Ischemic Stroke)) failed to show improved efficacy of endovascular clot retrieval compared with IV r-tPA alone.^[6] Limitations of these early trials were as follows: patient selection (proven large-vessel occlusion was not a requirement for inclusion), use of older technology (mainly first-generation clot retrieval devices) and a long delay from stroke onset to intervention. However, a *post hoc* subgroup analysis still showed benefit in patients with proven large-vessel occlusion who underwent endovascular clot retrieval within 90 minutes of IV r-tPA.^[7]

Current evidence for mechanical thrombectomy

A paradigm shift occurred in 2015 with the publication, in rapid succession, of 5 landmark RCTs that tested new-generation stent retriever devices. These trials showed consistent superiority of endovascular clot retrieval over standard medical therapy in reducing disability at 90 days, as measured by the modified Rankin scale (mRS) (Table 1) in patients with acute ischaemic stroke (AIS) due to large-vessel occlusion in the anterior circulation.^[8]

The first study was MR CLEAN (Multicenter Randomised Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), with all subsequent studies discontinued early owing to efficacy, loss of equipoise or both. Functional independence (mRS 0 - 2) was achieved in up to 60% of patients. There was an absolute benefit of 13.5 - 31% for patients who had undergone mechanical thrombectomy compared with those who received best medical treatment alone. Some key features of these trials are summarised in Table 2. In contrast to the earlier RCTs, selection was confined to patients with proven large-vessel occlusion diagnosed

Table 1. Modified Rankin scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to bodily needs without assistance
5	Severe disability; bedridden, incontinent and requires constant nursing care and attention
6	Dead

Table 2. Summary of randomised controlled acute stroke trials

	MR CLEAN	ESCAPE	EXTEND-IA	SWIFT PRIME	REVASCAT
Time to EVT, hours	<6	<12	<6	<6	<8
ASPECTS	9	9	Perfusion imaging	9	7 - 8
IV r-tPA used, %	87	73	100	100	68
Time to groin, min	260	241	210	224	269
Use of stent retriever, %	81	86	100	100	100
mRS 0 - 2 at 90 days, %	32.6	53	71.4	60	-
Absolute improvement, %	13.5	23.7	31.4	24.7	15.5
TICI 2b/3 reperfusion, %	58	72	86	88	65
EVT	Intra-arterial	Intra-arterial	Solitaire	Solitaire	Solitaire
NIHSS, median	17	16	17	17	17
Symptomatic ICH, %	7.7/6.4	3.6/2.7	0/5.7	0/3.1	1.9/1.9

MR CLEAN = Multicenter Randomised Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; ESCAPE = Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial; SWIFT PRIME = Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment; REVASCAT = Thrombectomy within 8 hours of symptom onset in ischemic stroke; EVT = endovascular therapy; ASPECTS = Alberta Stroke Program Early CT Score; IV r-tPA = intravenous recombinant tissue plasminogen activator; mRS = modified Rankin scale; TICI = thrombolysis in cerebral infarction; NIHSS = National Institute of Health Stroke Score; ICH = intracerebral haemorrhage.

on computed tomography (CT) angiography, randomisation of patients within 6 hours of stroke onset and mandatory use of newer-generation stent retrievers in the later trials.

HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke) trials pooled data from the abovementioned 5 trials in a meta-analysis to investigate outcomes in subgroups that were too small to investigate in the individual trials.^[9] A total of 1 287 patients ($n=634$ endovascular therapy patients and $n=653$ controls) were included. There was significantly reduced disability at 90 days in the endovascular group, with good (independent) functional outcome (mRS 0 - 2) in 46% compared with 26.5% in the medical control group. Subgroup analysis further showed that benefit was seen in patients >80 years of age, those randomised >300 minutes after onset and those not eligible for IV r-tPA. There was no difference in risk of symptomatic intracerebral haemorrhage at 90 days. The number needed to treat for patients to achieve an improvement of ≥ 1 points on mRS was 2.6. This provided robust evidence for the safety and efficacy of mechanical thrombectomy for most patients with AIS caused by occlusion of proximal anterior circulation, irrespective of patient characteristics or geographical location. Subsequent RCTs (THRACE (mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke), THERAPY (The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke), PISTE (Pragmatic Ischaemic Stroke Thrombectomy Evaluation) and EASI (Endovascular Acute Stroke Intervention)) confirmed the benefit of mechanical thrombectomy. Based on evidence from these trials, updated practice guidelines were rapidly published in the USA, Canada, Europe and the UK, recommending that mechanical thrombectomy be provided to patients with occlusion of the internal carotid artery or proximal middle cerebral artery who had received treatment with IV r-tPA within 4.5 hours of onset and who could undergo the procedure (arterial puncture) within 6 hours of symptom onset.^[7]

Patient selection

The decision for mechanical thrombectomy should be made by a physician trained in the diagnosis and treatment of stroke, in conjunction with a neurointerventionalist who has the relevant images (non-contrast CT of the brain and a CT angiogram) available for review. Prompt assessment of stroke severity using the National Institute of Health Stroke Score (NIHSS (Table 3)), baseline functional status (mRS) and consideration of comorbidities is essential. To

Table 3. National Institute of Health Stroke Score (NIHSS)*

Score	Stroke severity
0	No stroke symptoms
1 - 4	Minor stroke
5 - 15	Moderate stroke
16 - 20	Moderate to severe stroke
21 - 42	Severe stroke

*Parameters scored: level of consciousness, horizontal eye movements, visual fields, facial palsy, motor function – arms, motor function – leg, limb ataxia, sensory, language, speech, extinction/inattention.

achieve optimal clinical outcomes, patient selection criteria should parallel those of the successful mechanical thrombectomy trials:

- Documented anterior circulation large-vessel occlusion (proximal middle cerebral artery, anterior cerebral or internal carotid artery).
- Significant clinical deficit at the time of assessment (NIHSS >5).
- Lack of extensive early ischaemic change (ASPECTS (Alberta Stroke Program Early CT Score) >5) as assessed on non-contrast CT of the brain. ASPECTS is a 10-point quantitative score (Fig. 1). Each area of the middle cerebral artery territory is allocated 1 point. For each region showing ischaemic change, 1 point is deducted. A normal CT scan receives an ASPECT score of 10 points; a score of <7 is equal to involvement of one-third of the middle cerebral artery territory. A score of 0 indicates diffuse ischaemic involvement throughout the middle cerebral artery territory.
- Reasonable pre-stroke functional status and lack of serious comorbidities, indicating potential to benefit from treatment (age >80 years alone is **not** a contraindication for treatment).
- Treatment with IV r-tPA within 4.5 hours (patients ineligible for IV r-tPA owing to bleeding risk can be considered for treatment).
- The occluded vessel can be opened by mechanical thrombectomy within 6 hours.

The speed of delivery of mechanical thrombectomy is key to achieving the best possible outcomes. Therefore, the question of benefit in patients with unwitnessed stroke, wake-up stroke (a patient goes to bed well, but wakes up with symptoms of a stroke) or delayed presentation after 6 - 8 hours, requires assessment with more advanced imaging. The DAWN trial (Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention) was a prospective, multicentre RCT comparing mechanical thrombectomy

and medical treatment with medical treatment alone for AIS. The therapeutic window was extended to 24 hours. Patients had to have proven large-vessel occlusion and an NIHSS ≥ 10 . Advanced imaging (DWI or CT perfusion) was used to assess core infarct volume relative to volume of salvageable penumbra. A total of 206 patients were enrolled (enrolment discontinued before the target of 500 after interim analysis). Results showed significantly reduced post-stroke disability and improved functional independence at 90 days (48.6% v. 13.1%) in the endovascular group. There was a relative reduction in disability of 73%, with 1 in 2.8 patients saved from severe disability.^[10] The DEFUSE-3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) also showed improved functional outcomes with mechanical thrombectomy for ischaemic stroke 6 - 16 hours after onset compared with medical therapy alone for patients with anterior circulation large-vessel occlusion and a region of tissue that was ischaemic but not yet infarcted.^[11]

Practical aspects

Devices and techniques

After successful RCTs, the Solitaire FR (Medtronic, USA) stent retriever became the benchmark for mechanical thrombectomy. However, rapid and safe recanalisation and reperfusion of the occluded territory is the key factor, rather than any specific device or technique. Multiple options are available, including the use of supplementary devices, such as balloon-guide catheters, intermediate catheters and suction pumps v. manual aspiration.^[7] After femoral artery puncture, an 8 Fr guide catheter is navigated into the internal carotid artery, where an intermediate catheter (5 - 6 Fr) is directed to the circle of Willis. Through this, a microcatheter is navigated under fluoroscopic guidance distal to the clot over a microwire. The microwire is removed and a run is done through the microcatheter to confirm position past the clot, filling the distal occluded territory. The stent retriever is navigated through the microcatheter, positioned at the level of the clot and opened by unsheathing, i.e. pulling the microcatheter back while keeping the stent in place. This exposes the struts of the stent to the clot. Once the stent is integrated into the clot, the device is pulled back into the intermediate catheter, which has suction applied simultaneously. A balloon guide, forming a cuff around the guide catheter, may be used to stop the forward flow and reduce the chance of distal emboli. When using such a guide, the intermediate catheter may be omitted. Fig. 2 shows angiographic

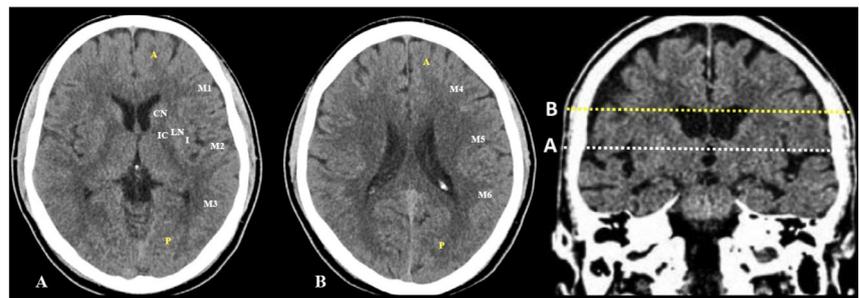


Fig. 1. ASPECTS (Alberta Stroke Program Early CT Score). A = at level of basal ganglia; B = at level of ventricles immediately above basal ganglia; CT = computed tomography; CN = caudate nucleus; IC = internal capsule; LN = lentiform nucleus; I = insular cortex; M1 = anterior middle cerebral artery (MCA) cortex; M2 = lateral MCA cortex; M3 = posterior MCA cortex; M4 = anterior MCA cortex superior to M1; M5 = lateral MCA cortex superior to M2; M6 = posterior MCA cortex superior to M3; A (yellow) = anterior; P (yellow) = posterior.

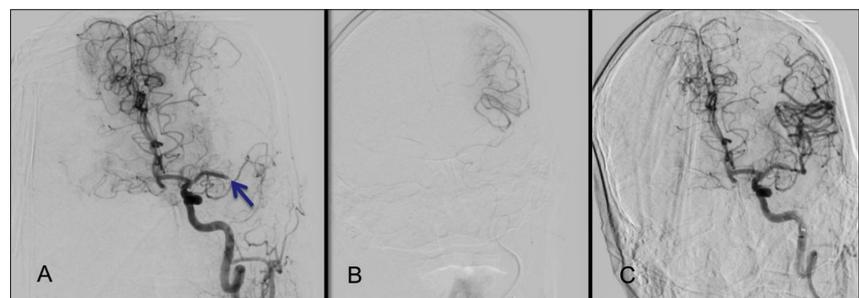


Fig. 2. Digital subtraction angiogram during mechanical thrombectomy. (A) Left internal carotid artery injection showing proximal middle cerebral artery (MCA) occlusion (arrow). (B) Contrast injection from microcatheter distal to thrombus. (C) Reperfusion of the previously occluded MCA territory after thrombectomy.

images of mechanical thrombectomy in a 59-year-old man who presented with acute right hemiparesis and dysphasia. The freshly removed clot in the stent retriever device is shown in Fig. 3. The patient's functional status improved to mRS 1 after mechanical thrombectomy.

An increasingly popular approach is to attempt to aspirate the clot directly into the intermediate catheter, which has become feasible since the advent of large-lumen soft catheters that can be safely navigated into the M1 segment of the middle cerebral artery and beyond. It is critical to choose a catheter with a lumen approaching the size of the vessel where the clot is lodged, allowing the clot to be suctioned completely. If this fails, a stent retriever may be easily deployed through the initial system.

Anaesthesia

The use of general anaesthesia (GA) v. local anaesthesia (conscious sedation) currently varies, with each strategy having potential advantages. GA associated with systolic blood pressure < 140 mmHg was also associated with poor functional outcome (mRS > 2) at 90 days. However, more recent studies suggest that GA and conscious sedation are equally safe; therefore, the

choice should be individualised, based on patient and institutional factors.^[12,13]

Complications

The complications of endovascular procedures can be device related, access related or contrast related. Device-related complications include vessel perforation, symptomatic intracranial haemorrhage, subarachnoid haemorrhage, arterial dissection, emboli to new vascular territories and vasospasm. Access-related complications include femoral artery dissection, pseudoaneurysm, retroperitoneal haematoma and infection. The overall procedural complication rate from recent RCTs is $\sim 15\%$; however, many of these complications do not adversely affect clinical outcome.

Who should perform mechanical thrombectomy?

To minimise complications, the key strategy is for mechanical thrombectomy to be performed only in high-volume centres by trained physicians competent in intracranial endovascular procedures and who undertake these regularly to maintain skills. Mechanical thrombectomy should only be performed in the context of a multidisciplinary team, operating in comprehensive stroke



Fig. 3. Freshly removed clot in stent retriever device.

centres with adequate neurointerventional procedural volumes (e.g. >200 per year), of which a reasonable proportion are mechanical thrombectomy, and where regular assessment/audit of technical and clinical results, process times and complications is undertaken.^[7] When complications do occur, the immediate availability of neurocritical care and/or neurosurgical support is mandatory and may be lifesaving.

Challenges and future questions

The practical implementation of mechanical thrombectomy in South Africa (SA) presents many challenges. For the trial results to be replicated, identification and support of comprehensive stroke units with appropriate referral pathways of selected patients from primary stroke centres are needed.^[14] A comprehensive stroke unit should include qualified neurointerventionalists who are able to offer mechanical thrombectomy 24 hours a day, 7 days a week. To get the right patient to the right place within the right time frame requires reorganisation of SA stroke services that involves substantial investment, great attention to care pathways and extensive co-operation between services, including ambulances and hospitals.

The value of mechanical thrombectomy for posterior circulation strokes, distal middle cerebral artery strokes, mild stroke symptoms

(NIHSS <5) and the role of direct thrombectomy without IV r-tPA remain to be defined. Ongoing RCTs should provide these answers in the next 3 - 5 years.

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