ISA consensus statement:
Recommendations for the Early Management of Acute Ischemic Stroke with Endovascular Treatment.

1. Endovascular Treatment of Ischemic Stroke:

Early reperfusion is crucial for the good outcome of reperfusion therapy. The recanalization efficacy of IV rtPA is not as high as that of endovascular treatment especially when there is occlusion of larger intracranial arteries such as the internal carotid artery (ICA) or proximal MCA.[1] A recanalization rate of 6% and 30% was observed with IV rtPA in the terminal ICA and M1, respectively.[2] In addition, a large proportion of patients still present > 4.5 hours after the onset of stroke symptoms and are compelled to be excluded from rtPA therapy. These limitations of rtPA therapy have prompted widespread use of endovascular therapy to treat patients having contraindications for rtPA therapy to improve recanalization rates. Especially in the Indian context, endovascular therapy is one of the viable options because of poor availability of resources and delayed presentation (outside door-to-needle window period).[3]

Endovascular revascularization includes intra-arterial fibrinolysis, mechanical clot retrieval with the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Retrieval System (Concentric Medical, Inc, Mountain View, CA, USA), clot retrieval with the second generation 'stent retreivers' like Solitaire (Medtronic), Trevo (Stryker) and Revive SE (Codman), mechanical clot aspiration with the Penumbra System (Penumbra, Inc, Alameda, CA, USA), and acute angioplasty and stenting. Different intra-arterial agents have been used for thrombolytic treatment of acute ischemic stroke. These include tissue plasminogen activator (tPA), urokinase (UK), and prourokinase (pro-UK). Mechanical thrombectomy devices are divided into two major groups based on their mechanism of action: those that use an approach distal (retrievers) or proximal to thrombi (aspiration devices).

The MERCI was the first stroke mechanical thrombectomy device approved by the FDA in 2004. The aspiration devices include the Penumbra System (Penumbra Inc.), the QuickCat (DSM Inc., PA, USA), and PRONTO (Vascular Solutions Inc., MN, USA) extraction devices.[4]

Recent times have seen completion of major trials of endovascular therapy and establish it as an accepted treatment for proximal large vessel occlusive stroke. A meta-analysis of eight trials included 1313 patients who underwent endovascular thrombectomy and 1110 patients who received standard medical care with tPA. Endovascular therapy was associated with a significant proportional treatment benefit across modified Rankin scale (mRS) scores (OR, 1.56; 95% CI, 1.14–2.13; P=0.005). Functional independence at 90 days (mRS score, 0-2) occurred among 557 of 1293 patients (44.6%; 95% CI, 36.6%-52.8%) in the endovascular therapy group versus 351 of 1094 patients (31.8%; 95% CI, 24.6%-40.0%) in the standard medical care group (risk difference, 12%; 95% CI, 3.8%-20.3%; OR, 1.71; 95% CI, 1.18-2.49; P=0.005). Compared with standard medical care, endovascular thrombectomy was associated with significantly higher rates of angiographic revascularization at 24 hours (75.8% vs. 34.1%; OR, 6.49; 95% CI, 4.79-8.79; P<0.001) but no significant difference in rates of symptomatic intracranial hemorrhage

within 90 days (70 events [5.7%] vs. 53 events [5.1%]; OR, 1.12; 95% CI, 0.77-1.63; P=0.56) or all-cause mortality at 90 days (218 deaths [15.8%] vs. 201 deaths [17.8%]; OR, 0.87; 95% CI, 0.68-1.12; P=0.27).[5]

Based on the recent stent retriever trials, a time window of 6 hours from stroke onset has been recommended for mechanical clot retrieval using stent retrievers. The DAWN trial was designed to demonstrate superior clinical outcomes at 90 days with Trevo plus medical management compared to medical management alone in appropriately selected patients treated 6 – 24 hours after last seen well. Imaging criteria included <1/3rd MCA territory involved as evidenced by CT or MRI, occlusion of intracranial ICA or MCA-M1 as evidenced by CTA or MRA and clinical - imaging mismatch on RAPID MR-DWI or CTP-rCBF. For clinical imaging mismatch, patients older than 80 years had to have NIHSS of 10 or above and core infarct volume less than 21 ml. Patients 80 years or younger had to have a core infarct volume less than 31 ml and NIHSS 10 or above or infarct volume 31 – 50 cc and NIHSS 20 or above. Interim analysis showed that the proportion of patients achieving good function outcome (MRS 0 – 2 at 90 days) was 48.6% in the thrombectomy group compared to 13.1% in the control group (treatment benefit 35.5%, 95% CI, 23.9 – 47.0). The proportion of patients achieving good function outcome was significantly more in the thrombectomy group in both the 6 – 12 hours and 12 – 24 hours groups. The final analysis of the trial data is to be published soon.[6]

Recently, studies have compared the ADAPT (A Direct Aspiration first Pass Technique) with stent retrievers. Lapergue et al studied 243 consecutive patients with large intracranial artery occlusions of the anterior circulation treated within 6 hours with either ADAPT (with PENUMBRA reperfusion catheters) or the Solitaire stent. Compared with the Solitaire device, patients treated with ADAPT achieved higher final recanalization rates (82.3% versus 68.9%; adjusted relative risk, 1.18; 95% CI, 1.02-1.37; P = .022). Differences in clinical outcomes and embolization rates did not differ.[7] The results of the ASTER trial showed no difference in outcome between aspiration and stent retrievers.[8]

Evidence from RCTs is lacking for vertebrobasilar occlusions. A recent meta-analysis of 45 studies (n=2056) of reperfusion of acute basilar occlusion showed numbers needed to treat (NNT) of 3 and 2.5 to decrease death or dependency and death alone, respectively.[9] The time window for reperfusion is not yet clearly defined and needs further investigation.

In the MR CLEAN trial 146 (29%) patients had an additional extracranial ICA occlusion (tandem pathology), with treatment effect in favor of thrombectomy (OR 1.43, 95% CI 0.78-2.64).[10] In a systematic review of 32 studies including 1107 patients with intra and/or extracranial ICA occlusions, intraarterial thrombolysis was compared with any kind of mechanical treatment and/or stent placement. Acute stenting of occlusions of the extracranial ICA resulted in a higher recanalization rate (87% vs 48%, p=0.001) and favorable outcomes (68% vs 15%, p<0.001) as well as lower mortality (18% vs 41%, p=0.048) when compared to intra-arterial thrombolysis.[11] Recently published cohort studies indicate that tandem stenosis/occlusions of the ICA/MCA can be treated

with acute stenting of the extracranial internal carotid and stent retriever mechanical thrombectomy in the MCA with a reasonable risk profile.[12–14] However further evaluation of this treatment strategy is warranted.

Recommendations[15]

- All patients eligible for IV rtPA should receive IV rtPA even if endovascular treatments are being considered.
- Observing patients after IV rtPA for clinical response prior to endovascular therapy is not recommended.
- Reduced time from symptom onset to reperfusion with endovascular therapies is associated with better clinical outcomes. To ensure benefit, reperfusion to thrombolysis in cerebral infarction (TICI) grade 2b/3[16] should be achieved as early as possible and within 6 hours of stroke onset.
- Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria:
    - ➢ Prestroke mRS score 0 to 1,
    - ➢ Acute ischemic stroke receiving IV rtPA within 4.5 hours of onset according to guidelines from professional medical societies,
    - ➢ Causative occlusion of the ICA or proximal MCA (M1),
    - ➢ Age ≥18 years,
    - ➢ NIHSS score ≥6,
    - ➢ ASPECTS score ≥6, and
    - ➢ Treatment can be initiated (groin puncture) within 6 hours of symptom onset.
- When mechanical thrombectomy is pursued, stent retrievers such as Solitaire and Trevo are generally preferred to coil retrievers such as MERCI. Recent studies have demonstrated the effectiveness of the ADAPT technique with PENUMBRA reperfusion catheters in acute stroke.
- In carefully selected patients with acute ischemic stroke who have occlusion of M2 or M3 segments of MCA, anterior cerebral arteries, vertebral arteries, basilar artery or posterior cerebral arteries, endovascular therapy with stent retrievers or aspiration may be considered if it can be initiated within 6 hours of symptom onset. The optimal time window for posterior circulation stroke is not clearly defined and needs further investigation.
- In carefully selected patients with anterior circulation occlusion who have contraindications to IV rtPA, endovascular therapy with stent retrievers or aspiration completed within 6 hours of stroke onset is reasonable.
- The technical goal of the thrombectomy procedure should be a TICI 2b/3 angiographic result to maximize the probability of a good functional clinical outcome. Use of salvage techniques including intra-arterial fibrinolysis or angioplasty and stenting may be considered to achieve these angiographic results.
- If endovascular therapy is contemplated, a noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation but should not delay IV rtPA (if indicated in eligible patients).

- Noninvasive intracranial vascular imaging should then be obtained as quickly as possible.
- When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischemic stroke who have causative occlusion of the ICA or proximal MCA (M1). Pending final analysis of the DAWN trial, selected patients presenting 6 – 24 hours from onset may be offered

  endovascular treatment, however, this is still considered investigational.
- While benefits are uncertain, endovascular therapy may be considered in selected patients < 18 years of age, prestroke MRS > 1, ASPECTS < 6 or NIHSS < 6 and causative occlusion of the internal carotid artery or the proximal MCA (M1).
- Angioplasty and stenting of proximal cervical stenosis, complete occlusion or tandem occlusion at the time of thrombectomy may be considered. Further studies are needed.
- Conscious sedation may be preferable over general anesthesia during endovascular therapy for acute ischemic stroke. This should be individualized on a patient to patient basis. Further trial data are needed.

2. Combined Intravenous and Intra-arterial Fibrinolysis

The combined IV and IA fibrinolysis approach can address the concern that delays to IA therapy may negate the potential benefits of more efficacious recanalization. This allows immediate initiation of IV fibrinolysis in an emergency setup, followed by transportation of the patient to the angiographic suite for further titrated IA fibrinolytic therapy, if necessary. This approach has been evaluated in a series of pilot trials showing mixed findings.[17–19] As demonstrated in a post-hoc pooled analysis of the Interventional Management of Stroke I and II pilot trials, reducing the time to reperfusion with endovascular therapies (like IV fibrinolysis) is likely to be pivotal in achieving the best clinical outcomes. Table 16 summarizes the findings of studies with the combined approach.[20]

10.3 Operator guidelines

Endovascular thrombectomy is the standard of care after publication of the 5 multicenter randomized trials. All the trials allowed only experienced neuro-interventionalists to perform the procedures. Thus operator experience is a major determinant for outcomes. It is thus necessary to establish the minimum standards regarding who should perform the procedures.[21–23] The Society of Neuro-Vascular Intervention has also established criteria for training of neuro-interventionists.[24]

Recommendations

- Residency program in Neurology (DM /DNB Neurology or equivalent), Neurosurgery (MCh/DNB Neurosurgery or equivalent) or Neuroradiology (DM/DNB Neuroradiology or equivalent)
- At least **two years** of neuro-intervention training after the Residency programme, which should include:
    - Understanding of neurovascular anatomy and Physiology

- Stroke assessment and management, including Intensive care management of Acute stroke
- At least 150 diagnostic cerebral angiograms independently performed under supervision over 2 years
- At least 50 therapeautic neuro-interventional procedures assisted or performed under guidance over 2 years, including at least 10 endovascular stroke interventions.

- The center for neuro-intervention training should be doing at least 75- 100 neuro-intervention cases yearly.
- National accrediting body recognized fellowships are recommended but not mandatory.
- Short term 'fellowships' or 'Observerships' not satisfying the above criteria are not considered adequate for training of Stroke Interventionists

10.4 Hospital requirements

In order to perform endovascular stroke interventions in time and with safety and efficacy comparable to the endovascular trials, a multi-displinary team approach is needed.[21]

Recommendations

Thus centers performing endovascular stroke interventions should have 24/7 availability of the following:

- Experienced neuro-interventionist, stroke physician or neurologist & neurosurgeon.
- Stroke ICU or Medical ICU with trained staff for stroke patient care.
- Adequately equipped catheterization suite with well trained staff, anaesthetist and on-shelf availability of all hardware required for emergency stroke interventions.
- Neuroimaging modalities (CT/CTA, MR/MRA, Trans-cranial Doppler [TCD]), including 24/7 access to CT and MRI.

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