Endovascular therapy for acute stroke: Quo vadis?

Venkatesh S. Madhugiri, Paritosh Pandey[1]

Departments of Neurosurgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, [1]National Institute of Mental Health and Neuro Sciences, Bangalore, Karnataka, India

ABSTRACT

Endovascular therapy (EVT) has gained vogue in the management of patients with acute stroke. Newer stent-retriever devices have led to better recanalization rates. In many centers, EVT is slowly being used as an add on to or in some instances, even as an alternative to intravenous tissue plasminogen activator (IV tPA). The publication of the results of the SYNTHESIS expansion, Interventional Management of Stroke III and Mechanical Retrieval Recanalization of Stroke Clots Using Embolectomy trials in 2013 has questioned the enthusiastic use of EVT in acute stroke. They demonstrate that EVT (using a variety of devices) is no superior to IV tPA in the management of acute stroke. In the light of these controversial findings, we review the current status of EVT in the management of acute stroke.

Key words: Acute stroke, clot retrieval, endovascular therapy, intravenous alteplase, stent-retrievers

INTRODUCTION

Stroke is the fourth leading cause of death in India. In the year 2007, the prevalence of stroke was estimated to be 99-222 per 100,000 persons.[1,2] Effective prevention and treatment strategies are required to deal with the increasing burden of cerebrovascular disease. The National Institute of Neurological Disorders and Stroke trial in 1995 demonstrated that intravenous (IV) thrombolytic treatment if started within 180 min after the onset of symptoms, was beneficial in the treatment of stroke.[3] A pooled analysis of data from tissue plasminogen activator (tPA)/alteplase trials showed that early treatment led to better outcomes up to 4.5 h after symptom onset.[4] This finding was also confirmed by the European Cooperative Acute Stroke III study.[5] Currently, IV tPA (alteplase) at the dose of 0.9 mg/kg body weight administered within 3-4.5 h of stroke onset is the standard of care against which all other modalities of management are compared. Limitations of IV tPA include dependence on available serum plasminogen in the body, the resistance of an old or large thrombus to fibrinolysis and the risks of systemic and cerebral hemorrhage.[6]

Access this article online	
Quick Response Code:	Website: www.ijns.in
	DOI: 10.4103/2277-9167.118110

In most centers that offer IV thrombolysis for stroke, only 5-15% of patients with acute ischemic stroke are usually eligible for treatment with alteplase. The reasons for this include patients arriving in hospital after the approved time-window, alteplase not being approved for patients older than 80 years and for individuals with unknown onset of symptoms (e.g., wake up stroke), a group that represents 8-28% of the stroke population.[6] The efficacy of IV tPA is limited in certain situations. tPA achieves partial-to-complete recanalization in only 20-40% of patients and in even fewer people (10-15%) with major artery occlusion – e.g., of the proximal middle cerebral artery (MCA), distal internal carotid artery (ICA) (T-occlusions), or basilar artery.[7] Attempts to improve outcomes in such patients led to trials of intra-arterial (IA) thrombolysis with tPA administered at or within the thrombus. The Prolyse in Acute Cerebral Thromboembolism II and MCA embolism local fibrinolytic intervention trials demonstrated the efficacy and safety of IA tPA in the treatment of acute stroke.[8,9] However, to date there has been no randomized trial directly comparing IV tPA with IA tPA.

Progress in endovascular therapy (EVT) led to the development of numerous devices for stroke treatment. The available endovascular options for acute stroke include IA pharmacologic thrombolysis, manipulation of the clot with a guidewire or microcatheter, mechanical and aspiration thrombectomy and most recently, stent retriever technology. The main disadvantage of EVT is the delay in the initiation of treatment because of

Address for correspondence: Dr. Paritosh Pandey,
Department of Neurosurgery, National Institute of Mental Health and Neuro Sciences, Hosur Road, Bangalore - 560 029, Karnataka, India.
E-mail: paritosh2000@gmail.com

the logistics involved in these techniques. Technical limitations include difficulty in navigating the catheter to the thrombus, damage to the arterial wall from the devices, fragmentation and distal embolization of the clot and complications of systemic and cerebral hemorrhage. In the absence of data from randomized controlled trials (RCTs), it was uncertain whether EVT, with or without the previous use of IV tPA, is more effective than IV tPA alone. As a current approach to improve outcomes in patients with acute ischemic stroke, many stroke centers start IV tPA (either full-dose or part-dose) during the transfer for IA thrombectomy or stenting – an approach known as bridging therapy.[10]

In early 2013, the results of three RCTs have been published in the New England Journal of Medicine that generates Class Ia evidence that demonstrates the absence of any therapeutic superiority of EVT over IV tPA. This, therefore, compels one to evaluate more thoroughly and rigorously the role of EVT in acute stroke.

IV THROMBOLYSIS VERSUS EVT – THE SYNTHESIS EXPANSION TRIAL

Ciccone *et al.* have reported the results of the SYNTHESIS expansion trial, a randomized multi-center open clinical trial with a blinded end point assessment.[11] Three hundred sixty-two patients with acute ischemic stroke were randomized in a ratio of 1:1 within 4.5 h of symptom onset to either EVT (IA thrombolysis with tPA, mechanical clot disruption or retrieval or a combination of these approaches) or IV tPA. The primary outcome was survival free of disability at 3 months (defined as a modified Rankin score [mRS] of < 2). At 3 months, 30.4% of the patients in the EVT group and 34.8% in the IV tPA group (34.8%) were alive without disability (odds ratio [OR] adjusted for age, sex, stroke severity and atrial fibrillation was 0.71; 95% CI: 0.44-1.14, $P = 0.16$). Intracranial hemorrhage occurred in 6% of the patients in each group and there were no significant differences between groups in the rates of other serious adverse events or the case fatality rate. Surprisingly, rates of recanalization were not reported for either group.

There are several points in this study that are worth examining carefully. The time window for treatment with IV tPA was 4.5 h as per standard recommendations. However, patients were considered eligible for treatment with EVT up to 6 h after stroke onset. Correspondingly, the time from stroke onset to treatment was 2.45 h in the IV tPA arm and 3.45 h in the EVT arm. It is well known that the outcome after treatment for acute stroke is time dependent.[12] Thus, extending the eligibility by 1.5 h for the EVT arm and the time to treatment by 1 h may have significantly affected the results of the study, although patients in the two treatment arms were otherwise well-matched with low levels of heterogeneity.

The sample size in this study was powered to detect a difference of 15% between the two arms with a power of 80%. This was arrived at on the basis of a previous pilot study where 48% of patients in the IA tPA arm had a good outcome at 90 days as against 27.6% in the IV tPA arm.[13] However, these findings are not necessarily in concordance with those of other studies. The mean National Institutes of Health Stroke Scale (NIHSS) score was 13 for both groups (indicating only moderately severe strokes). Despite an NIHSS score of 13, only 34.8% in the IV tPA arm and 30.4% in the endovascular arm had disability free survival at 3 months. However, the best results with tPA show that 50.8-52.4% of patients had disability free survival at 90 days.[5,14] Moreover, the best outcome reported after EVT (in the Solitaire with the Intention for Thrombectomy [SWIFT] trial) is 58%, which means that the potential difference in clinical outcome between IV tPA and EVT may be as small as 6-8%. This raises the possibility that the SYNTHESIS expansion trial was underpowered and the sample size inadequate.

The heterogeneity of therapies employed for patients in the endovascular arm is a significant confounding factor. Class I evidence exists that the use of stent retrievers is associated with significantly better outcomes than when first generation devices are used.[15,16] This implies that any future studies should compare a single device, preferably stent-retrievers with either IV/IA tPA. There were significant protocol violations in this trial. Although the authors analyze and state that elimination of these results does not alter the final results, the elimination of these cases from an already possibly underpowered study could mean that the results are of doubtful validity.

IV tPA VERSUS IV tPA FOLLOWED BY EVT – THE INTERVENTIONAL MANAGEMENT OF STROKE (IMS III) TRIAL

IV tPA thrombolysis is the only internationally approved treatment for acute stroke if administered within 3-4.5 h. However, rates of partial or complete recanalization in a large vessel occlusions with IV tPA alone have been shown to be as low as 6% for terminal ICA occlusions and the site of occlusion (ICA, MCA or the basilar artery) determines the response to IV thrombolysis.[17,18]

This led to the concept of bridging therapy where all patients receive IV tPA within 3-4.5 h of stroke onset, followed by EVT if required (based on thrombus size and location). Previous studies have shown that combining IV tPA with EVT did not lead to better outcomes vis a vis EVT alone.[17] However, no Class I evidence was available comparing the outcomes of IV tPA with IV tPA followed by EVT.

Broderick *et al*. have reported the results of the IMS III trial, which began recruitment in 2006 and was prematurely terminated in 2012.[6] Patients were randomized to receive either IV tPA alone within 3 h after symptom onset or to receive additional EVT, in a 1:2 ratio. The primary outcome measure was a mRS of 2 or less at 90 days. The study was stopped early after an interim analysis revealed futility after 656 participants had undergone randomization (434 patients to EVT and 222 to IV tPA alone). The proportion of participants with a mRS of 2 or less at 90 days did not differ significantly according to treatment (40.8% with EVT and 38.7% with IV tPA.

The two patient groups in this study were well-matched with low heterogeneity. The mean NIHSS score in the endovascular arm was 17 and in the IV tPA group was 16. The initial planned sample size was 900 patients, drawn from centers across the USA, Canada, Australia and Europe. A variety of endovascular devices were employed – (i.e., thrombectomy with the Merci retriever [Concentric Medical], Penumbra System [Penumbra] or Solitaire FR revascularization device [Covidien] or endovascular delivery of tPA by means of the Micro-Sonic SV infusion system [EKOS] or a standard microcatheter). The time window for beginning EVT (after IV tPA) was 5 h after the onset of stroke. Subgroup analyses of patients with NIHSS scores between 8 and 19 and those > 20 failed to show any significant differences between the two treatment groups. This is a well-designed and implemented study. However, there are two minor concerns when accepting the results of the IMS III trial, both of which have been elucidated vis a vis the SYNTHESIS expansion trial.

The first concern pertains to the variety of endovascular devices used in the EVT arm. As discussed, this heterogeneity could skew results since stent retrievers have significantly better rates of recanalization and clinical outcomes.[15,16] The second concern is that for a large international RCT such as this, only 656 patients were recruited over 6 years – this is an average of nine patients a month from across three continents. Given the stroke burden, the authors appear to have super-selectively chosen patients, even among those who met their inclusion criteria. This selection bias may not mirror actual practice situations. However, despite these concerns, the IMS III trial raises serious doubts about the role of EVT as an add-on to IV tPA.

THE USE OF IMAGING TO SELECT PATIENTS FOR EVT – THE MECHANICAL RETRIEVAL RECANALIZATION OF STROKE CLOTS USING EMBOLECTOMY TRIAL

One of the criticisms leveled at previously published stroke studies has been the inadequate use of imaging to select patients for EVT. Many studies have relied on a single non-contrast enhanced computed tomography (CT) image series to randomize patients. Lansberg *et al*. had shown that patients who had target mismatch (indicating a viable penumbra) on MR images and had early recanalization after treatment had better clinical outcomes (the DEFUSE 2 study).[19] The main issue with this study was that the window for patients to receive EVT was as long as 12 h after stroke onset. The adjusted OR for favorable clinical response associated with reperfusion was 8·8 (95% CI: 2·7-29·0) in the target mismatch group and 0·2 (0·0-1·6) in the no target mismatch group (P = 0·003 for the difference between ORs). Reperfusion was associated with increased good functional outcome at 90 days (OR 4·0, 95% CI: 1·3-12·2) in the target mismatch group, but not in the no target mismatch group (1·9, 0·2-18·7). Thus, it appeared that selecting patients on the basis of target mismatch as evaluated on magnetic resonance imaging (MRI) could lead to better outcomes.[19]

Kidwell *et al*. have reported the results of the MR RESCUE trial that concluded in 2012.[20] This was a phase 2b, randomized, controlled, open-label (blinded outcome), multicenter trial conducted at 22 study sites in North America. Patients between the ages of 18 and 85 years, with NIHSS scores of 6-29 who had a large-vessel, anterior circulation ischemic stroke were randomly assigned within 8 h after stroke onset to undergo either mechanical embolectomy (using the Merci Retriever or Penumbra System) or standard medical care. Patients who were treated with IV tPA without successful recanalization were eligible if MR angiography or CT angiography after the treatment showed a persistent target occlusion. In patients with a favorable penumbral pattern, embolectomy was not found to be superior to standard care (mean score, 3.9 vs. 3.4; P = 0.23). Even in patients with a non-penumbral pattern, embolectomy was not superior (mean score, 4.0 vs. 4.4; P = 0.32).

Although the MR RESCUE trial is a well-designed trial, several factors may have led to the equivocal results. The first is the extended time window from stroke onset to embolectomy (8 h). Only first generation devices were used in the endovascular arm, probably leading to poorer results. Patients in the endovascular arm thus had lower rates of recanalization than would be expected with stent retrievers, probably affecting the final results. Some of the patients in the standard medical care group did receive IV tPA. Another concern is the fact that both CT and MR angiograms were used to evaluate target mismatch. Despite these concerns, it is possible that presence of a penumbra may not predict outcomes after EVT for stroke.

RECANALIZATION vs. CLINICAL OUTCOMES

EVT has evolved from the first generation devices such as the Merci retriever (Concentric Medical) to the current stent-retrievers (the Trevo Pro Stentriever, Stryker Inc. and the Solitaire device, ev3 Inc.). Progress in device technology has been associated with better rates of recanalization and better clinical outcomes. The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial (2005), which was the first trial of an endovascular device for acute stroke showed a recanalization rate of 48% and a good outcome (mRS ≤ 2) in 27.7% of patients.[21] In 2009, the results of the RECANALISE study that compared IV tPA with IV tPA + EVT were published. Recanalization rates were 52% in the IV tPA group versus 87% in the IV tPA + EVT group. Good clinical outcomes were seen in 44% and 57% respectively.[22] These and several other single arm studies that were subsequently reported served to establish EVT as not merely a supplement, but a possible alternative to IV tPA in the management of acute stroke.

The SWIFT trial compared the Merci device with the Solitaire stent-retriever. The results, published in 2012 showed a recanalization rate of 69% and good clinical outcome in 58% with the Solitaire device as against a recanalization rate of 30% and good clinical outcome in 33% with the Merci device.[15] The TREVO2 trial (2012) compared the Trevo Pro stentriever with the Merci device. Recanalization rates were 86% and 60% in the Trevo and Merci arms respectively. These studies clearly establish the superiority of stent retrievers over earlier devices. They underline the shortcoming common to all stroke studies-the use of different devices on patients selected for EVT.

However, the results of the IMS III and MR RESCUE trials published in 2013 are quite contrary to the previous studies. In the IMS III trial, recanalization rates were 65% for ICA occlusion, 81% for an M1 occlusion, 70% for a single M2 occlusion and 77% for multiple M2 occlusions in the IV tPA + EVT group. In the IV tPA-alone arm, recanalization rates were 38% for ICA occlusion, 44% for M1 occlusion M1, 44% for a single M2 occlusion and 23% for multiple M2 occlusions. The proportion of patients with better clinical outcomes within each arm increased with better recanalization scores. However, although recanalization rates were significantly better in the IV tPA + EVT arm, there was no difference in clinical outcome between the two groups. Similarly, in the MR RESCUE study, the calculated overall recanalization rates are 86.7% in the standard medical therapy arm and 71% in the EVT arm (ignoring the presence of penumbra). A good 90-day clinical outcome was achieved more often in patients with substantial reperfusion and in patients with 7-day revascularization Thrombolysis in Cerebral Infarction scores 2a-3.

Thus, it is evident from these studies that within each treatment group, rates of recanalization and reperfusion do correlate with 90 day clinical outcomes. Thus, recanalization rates may be an effective surrogate marker of ultimate clinical outcome since in all these trials, higher recanalization rates correlated with better mRS at 90 days. However, it is equally evident that there is no significant difference in clinical outcomes between EVT and IV tPA groups. Much research has been focused on developing new device technology. However, it would probably be worthwhile to also focus on reducing the time to treatment in acute stroke patients. It would also be necessary to develop neuroprotection strategies so as to improve clinical outcomes. Future studies would need to focus on homogenous groups - comparisons between IV tPA and stent-retrievers as homogenous groups with matched time windows.

SUMMARY

Based on current evidence, IV tPA administered within 3-4.5 h of symptom onset is the standard of care for acute stroke. Attempts to perform EVT may lead to undue delays in treatment initiation and should not be made until IV tPA has been administered. IV tPA leads to poor rates of recanalization in patients with long clots or major vessel involvement. Since the degree of recanalization does appear to correlate with outcome, such patients may be candidates for embolectomy after IV tPA. This decision needs to be individualized. The choice of the device seems to veer clearly in favor of stent retrievers. The decision to select a patient for EVT is an individual one, since the role of target mismatch on MRI appears unclear in selecting patients and predicting outcome. Until such

robust data becomes available, the jury is out on the role of EVT for acute stroke.

REFERENCES

1. Dalal PM, Malik S, Bhattacharjee M, Trivedi ND, Vairale J, Bhat P, *et al*. Population-based stroke survey in Mumbai, India: Incidence and 28-day case fatality. Neuroepidemiology 2008;31:254-61.
2. Dalal PM, Bhattacharjee M. Stroke epidemic in India: Hypertension-stroke control programme is urgently needed. J Assoc Physicians India 2007;55:689-91.
3. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-7.
4. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, *et al*. Association of outcome with early stroke treatment: Pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768-74.
5. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-29.
6. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, *et al*. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;368:893-90.
7. Mokin M, Kass-Hout T, Kass-Hout O, Dumont TM, Kan P, Snyder KV, *et al*. Intravenous thrombolysis and endovascular therapy for acute ischemic stroke with internal carotid artery occlusion: A systematic review of clinical outcomes. Stroke 2012;43:2362-8.
8. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, *et al*. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: A randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA 1999;282:2003-11.
9. Ogawa A, Mori E, Minematsu K, Taki W, Takahashi A, Nemoto S, *et al*. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: The middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. Stroke 2007;38:2633-9.
10. Kass-Hout T, Kass-Hout O, Mokin M, Thesier DM, Yashar P, Orion D, *et al*. Is bridging with intravenous thrombolysis of any benefit in endovascular therapy for acute ischemic stroke? World Neurosurg 2013; S1878-8750(13)00196-4. doi: 10.1016/j.wneu.2013.01.097. [Epub ahead of print].
11. Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, *et al*. Endovascular treatment for acute ischemic stroke. N Engl J Med 2013;368:904-13.
12. Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA, *et al*. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology 2009;73:1066-72.
13. Ciccone A, Valvassori L, Ponzio M, Ballabio E, Gasparotti R, Sessa M, *et al*. Intra-arterial or intravenous thrombolysis for acute ischemic stroke? The SYNTHESIS pilot trial. J Neurointerv Surg 2010;2:74-9.
14. Yeo LL, Paliwal P, Teoh HL, Seet RC, Chan BP, Liang S, *et al*. Timing of recanalization after intravenous thrombolysis and functional outcomes after acute ischemic stroke. JAMA Neurol 2013;70:353-8.
15. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, *et al*. Solitaire flow restoration device versus the Merci retriever in patients with acute ischaemic stroke (SWIFT): A randomised, parallel-group, non-inferiority trial. Lancet 2012;380:1241-9.
16. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, *et al*. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): A randomised trial. Lancet 2012;380:1231-40.
17. Albuquerque FC. Bridging treatment and stroke. World Neurosurg 2013;S1878-8750(13)00396-3. doi: 10.1016/j.wneu.2013.02.086. [Epub ahead of print].
18. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, *et al*. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke 2007;38:948-54.
19. Lansberg MG, Straka M, Kemp S, Mlynash M, Wechsler LR, Jovin TG, *et al*. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): A prospective cohort study. Lancet Neurol 2012;11:860-7.
20. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, *et al*. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med 2013;368:914-23.
21. Smith WS, Sung G, Starkman S, Saver JL, Kidwell CS, Gobin YP, *et al*. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: Results of the MERCI trial. Stroke 2005;36:1432-8.
22. Mazighi M, Serfaty JM, Labreuche J, Laissy JP, Meseguer E, Lavallée PC, *et al*. Comparison of intravenous alteplase with a combined intravenous-endovascular approach in patients with stroke and confirmed arterial occlusion (RECANALISE study): A prospective cohort study. Lancet Neurol 2009;8:802-9.

How to cite this article: Madhugiri VS, Pandey P. Endovascular therapy for acute stroke: Quo vadis?. Indian J Neurosurg 2013;2:119-23.

Source of Support: Nil, **Conflict of Interest:** None declared.