Endovascular therapy in acute ischemic stroke: The way forward after results from the IMS 3, SYNTHESIS and MR Rescue trials

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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

Not all ischemic strokes benefit from intravenous (IV) thrombolysis.[1] Thrombus lysis rates within the first few hours of IV tissue plasminogen activator (tPA) administration in patients with proximal occlusions (internal carotid artery or M1 segment middle cerebral artery) are so low and ischemic territory so large that a search for alternative methods of achieving recanalization is inevitable.[2] For the last many years, endovascular therapy has offered that alternative. Early recanalization remains the most critical process for impacting clinical outcome by restoring blood flow to salvageable brain tissue.[3,4] The magnitude of benefit is directly related to the speed that recanalization is achieved.[4,5] Higher recanalization rates reported in several major intra-arterial (IA) studies in the past resulted in regulatory approval for the use of these mechanical devices and techniques in the management of patients with acute ischemic strokes.[6-10]

Newer mechanical devices like stentrievers not just fragment and retrieve thrombus but create a temporary bypass for anterograde blood flow to ischemic brain while achieving the former goals.[1,11] Recent trials, SWIFT (solitaire with the intention for thrombectomy and Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischemic stroke (TREVO 2) have shown recanalization rates in proximal occlusions higher than 80% with the use of these devices.[9,10] These results created a shift in clinical practice in the last couple of years with more and more stroke centers attempting endovascular procedures for proximal occlusions. This shift in clinical practice was however, not accompanied by evidence suggesting better clinical outcomes with endovascular treatment. Randomized trials of endovascular therapy versus standard of care had not yet been performed in our field.

"There is no such thing as a failed experiment, only experiments with unexpected outcomes." - Richard Buckminster Fuller.

Recently published randomized controlled trials [Interventional Management of Stroke 3 (IMS 3), SYNTHESIS and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR Rescue)] have shown that endovascular therapy is no better than the current standard of care (including IV tPA) in the management of patients with acute ischemic stroke.[12-14] The IMS 3 trial randomized patients presenting within 3 hours of stroke symptom onset with a National Institute of Health Stroke Scale Score (NIHSS) of 10 or more (8 or more with an evident occlusion

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on baseline computed tomography (CT)-angio) to IV tPA or to IV tPA+ additional endovascular therapy. The primary outcome of this study was a modified Rankin Scale (mRS) of 2 or less (indicating functional independence) at 90 days. The study was stopped early because of futility after enrolling 656 participants. There was no difference in the primary outcome, i.e., the proportion of participants with a mRS of 2 or less at 90 days (40.8% with endovascular therapy and 38.7% with IV tPA; absolute adjusted difference, 1.5% points; 95% confidence interval (CI), −6.1 to 9.1. Even in patients with severe strokes; with an NIHSS score of 20 or higher, the difference in the proportion of patients achieving the primary outcome (6.8% points; 95% CI, −4.4 to 18.1) was not statistically significant.[12]

The SYNTHESIS trial randomized patients with acute ischemic stroke presenting within 4.5 hours of stroke symptom onset to standard of care IV tPA versus endovascular treatment alone.[13] As such, this trial was different from the IMS 3 trial and sought to answer a different research question. Primary clinical outcome in this trial was mRS of 0-1 at 90 days indicating none to minimal functional disability. A total of 181 patients were assigned to each arm of the study. At 3 months, 55 patients in the endovascular-therapy group (30.4%) and 63 in the IV tPA group (34.8%) achieved primary outcome (odds ratio adjusted for age, sex, stroke severity and atrial fibrillation status at baseline, 0.71; 95% CI, 0.44-1.14; $P=0.16$).[13]

The MR-Rescue trial randomized patients presenting within 8 hours of stroke symptom onset to standard of care versus endovascular treatment (with or without IV tPA).[14] By mandating perfusion imaging in all patients and stratifying randomization by the presence or absence of a favorable penumbral pattern (substantial salvageable tissue and a small core), the trial, in addition, was also testing the use of this imaging paradigm in selecting patients for endovascular therapy. The trial did not show any significant difference in mean scores on the mRS between the standard of care and endovascular treatment (3.9 vs. 3.9, $P=0.99$). Endovascular treatment was not superior to standard care in patients with either a favorable penumbral pattern (mean score, 3.9 vs. 3.4; $P=0.23$) or a non-penumbral pattern (mean score, 4.0 vs. 4.4; $P=0.32$).[14]

Results of these trials can be summarized by stating that endovascular treatment is no better than standard of care within 8 hours of stroke symptom onset. When these results were first published a few months ago, it was quite a surprise.

"*No experiment is ever a complete failure. It can always be used as a bad example*" - Paul Dickson.

A common factor across all three randomized controlled trials was that they did not use newer devices like stentrievers that could potentially achieve higher recanalization rates.[12-14] When compared with recanalization rates reported in the SWIFT and TREVO-2 studies, recanalization rates in IMS 3, SYNTHESIS and MR Rescue are lower.[10-14] In addition, metrics like procedural times that indicate how fast the patients achieved recanalization after stroke symptom onset and initial clinical and imaging assessment were slow. Mean time from stroke symptom onset to groin puncture in the IMS 3 trial was 205 min while it was 381 min in the MR Rescue trial.[15] Median groin puncture to recanalization time in IMS 3 was more than 80 min; many centers are now capable of consistently achieving groin puncture to recanalization times less than 60 min (Personal communication Dr. Goyal). Evidence is now increasingly irrefutable that chances of achieving good clinical outcome improves with faster recanalization.[3,8] In the IMS 1 and 2 trials, a 30-min delay in initiating treatment was associated with a 10% decrease in the probability of achieving good clinical outcome.[16,17] Are the results from IMS 3, SYNTHESIS and MR Rescue trials therefore, outdated since newer mechanical devices were used minimally and current focus on fast recanalization never achieved in the endovascular arm?

Interestingly, a comparison of the results of IMS 3, SYNTHESIS and MR Rescue trials with SWIFT and TREVO-2 paints a vivid picture of the challenges we face when answering the above question.[15] The latter two trials are recent and reflective of current endovascular practice. Even though, recanalization rates with stentrievers were significantly higher in the SWIFT and TREVO-2 studies when compared with rates in the endovascular arms of the IMS 3 and MR Rescue trials, the rates of good clinical outcome (mRS 0-2) at 90 days were similar.[12-15] In the SWIFT study, the rate of good clinical outcome (mRS 0-2 at 90 days) was 37% with the stentrievers; in TREVO-2, the rate was 40% with stentrievers while in the endovascular arm of IMS 3, the rate was 33% (41% for those with evident proximal occlusion on CT-angio).[15] Of note, time from stroke symptom onset to groin puncture in the stentriever arms of both SWIFT and TREVO-2 were prolonged when compared with similar times in IMS 3. (SWIFT and TREVO-2 included patients presenting within 8 h of stroke symptom onset unlike IMS 3).[15] The rate of good clinical outcome in the endovascular arm of MR Rescue was around 20%.[17] Mean time from stroke symptom onset to groin puncture in this study was 381 min.[14,15] An

analysis of two metrics (recanalization rate and time from stroke symptom onset to groin puncture) in these studies shows us that the rate of good clinical outcome increases with increasing recanalization rate and shorter time from stroke symptom onset to initiation of endovascular treatment. Nonetheless, a point worth noting is that the rate of good clinical outcome in the IV tPA arm of IMS 3 in patients who had evident proximal occlusion on CT-angio is 38%![15]

"*One who thinks he knows does not know; one who knows he does not know, knows.*" - Ishavasya Upanishad

What do these recent trials tell us? What are the implications of these results for our clinical practice? These trials show us that IV tPA, with all its limitations, is still the best therapy available for patients presenting with acute ischemic stroke. These trials also tell us that initiating treatment (IV tPA and/or endovascular) as early as possible increases the probability that the patient will achieve good clinical outcome. These trials do not tell us that newer mechanical devices like stentrievers could be better than IV tPA; on the contrary, clinical outcomes are similar to that achieved with IV tPA. Nonetheless, these trials do indicate to us possibilities for the future. If we can treat patients very early with endovascular treatment, we could possibly achieve higher rates of good clinical outcome than those reported in these trials.[18] We do however need to realize that we truly do not know; the only way we can know is by including such patients in randomized controlled trials.[19]

"*The experimenter who does not know what he is looking for will not understand what he finds.*" - Claude Bernard

So is a simple randomized controlled trial including "all" patients with acute ischemic stroke and proximal occlusions and focused on achieving fast recanalization times the answer to our questions?

Variables such as age, extent of infarcted brain and leptomeningeal collaterals on presentation, blood glucose and blood pressure are significant determinants of patient prognosis even before treatment initiation.[20,21] Some patients have a very low probability of achieving good clinical outcome even if recanalization is achieved quickly and safely.[22] Many studies have shown that patients with a large infarct core or very poor leptomeningeal collaterals at baseline do poorly even if treated.[4,22,23] The likelihood that there would be differential response to endovascular treatment versus standard of care in such patients is low. Including such patients with an inherently poor prognosis in a randomized controlled trial will therefore reduce statistical power. Heterogeneity in prognosis at baseline in patients with acute ischemic stroke also means that careful consideration needs to be given to the choice of the primary outcome in a randomized controlled trial of endovascular therapy versus standard of care. Since variables at baseline (known and some unknown) are an important determinant of the final outcome, the primary outcome measure needs to reflect this heterogeneity in stroke prognosis due to such determinants. By using the appropriate age and imaging criteria, we may rule out some patients with a low probability of a good outcome even with treatment, but we may not have ruled out all such patients. The MR Rescue trial stratified by penumbral imaging is a classic example of the failure of imaging selection tools to exclude patients with inherently poor prognosis at baseline.[4] Even though, median absolute infarct growth in patients with a penumbral pattern on imaging was relatively small (27.1 ml in the endovascular arm and 6.1 ml in the control arm) with median final infarct volumes of 58.1 ml and 37.3 ml respectively, final clinical outcome was poor (median mRS at 90 days in the endovascular arm was 4 and in the control arm was 3).[14] If baseline prognostic determinants in patients with acute ischemic stroke and proximal occlusion results in a majority of patients not achieving good functional status (mRS 0-2 at 90 days < 40%), but quick and safe endovascular treatment results in less patients dead or bed-ridden, then the use of an outcome measure that captures a shift in the outcome across the whole spectrum of possible functional outcomes would seem more appropriate than the mRS dichotomized at mRS 0-2 versus 3-6. Sliding dichotomy and variants of proportional odds modeling are some statistical techniques that could potentially help in such an analysis.

Carotid T occlusions have very low recanalization rates with IV tPA.[2] Many studies have shown that clinical outcome in such patients with IV tPA is also abysmally low.[2,24] A subgroup analysis of the IMS 3 study shows a significant difference in proportion of patients with carotid T occlusions who achieve good clinical outcome when receiving additional endovascular treatment versus IV tPA alone (personal communication with Dr. Demchuk). It therefore makes sense to balance both arms of a randomized controlled trial with carotid T occlusions and other significant baseline prognostic determinants. Stratified randomization or minimization algorithms before randomization can achieve this balance within randomized controlled trials.

In summary, future randomized controlled trial should include strategies to account for heterogeneity in stroke prognosis and outcome.

"*The gods love what is mysterious and dislike what is evident.*" - Brhadaranyaka Upanishad

When randomized controlled trials such as IMS 3, SYNTHESIS and MR Rescue enrolled their first patients, the prevailing belief in the stroke and endovascular community was that endovascular treatment was better than standard of care. These randomized controlled trials were designed to prove those beliefs. Results from these trials have shown that the prevailing beliefs some years ago were incorrect. We are in a similar situation now. The prevailing belief even after IMS 3, SYNTHESIS and MR Rescue is that endovascular treatment with newer mechanical devices and faster recanalization could potentially be better than the current standard of care. Nonetheless, these trials have helped us recognize the fallibility of our knowledge. What is evident to us may not be what is true. If endovascular treatment is truly superior to the current standard of care, then it is a matter of time before we start getting more and more positive randomized controlled trials. Until then, let us do what the Gita says so eloquently: "Action is better than inaction. Selfish action imprisons the world. Act selflessly, without any thought of personal profit." Let us act now; immerse ourselves in designing and participating in clinical trials so that patients benefit from what is truly best for them.

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