

Intra-arterial Therapy for Acute Stroke: Trials and Tribulations

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STROKE IS A DEVASTATING DISEASE, AFFECTING over 750,000 individuals in the United States each year. For patients with acute ischemic stroke, intra-venous tissue plasminogen activator (tPA) is a breakthrough treatment which improves outcomes when given within 4.5 hours from symptom onset.¹⁻⁶ However, some patients are ineligible for intra-venous tPA (IVT) and some fail to respond. In those instances, direct intra-arterial therapy (IAT) offers patients a treatment option. In this article, we will examine the past, present and future of IAT for acute ischemic stroke.

HISTORICAL BACKGROUND – THROMBOLYSIS AND THROMBECTOMY

Soon after the publication of the NINDS trial in 1995, the earliest randomized trials of IAT for stroke were published.⁷⁻⁸ The first such study, PROACT, used an intra-arterial infusion of pro-urokinase (pro-UK) for patients who were within six hours of symptom onset with acute MCA occlusion. The authors showed recanalization in 58% of patients receiving pro-UK as compared with only 14% of those receiving placebo.⁷ However, the improvements in outcome were not as dramatic, with 31% of pro-UK patients having a modified Rankin score (mRs) of zero or one at 90 days compared with 21% in the placebo arm. Nevertheless, this study proved the safety and potential efficacy of this treatment paradigm and a larger, follow-up study, PROACT-II showed similar improvements in recanalization (66% pro-UK vs 18% placebo) and in clinical outcome (40% pro-UK patients had mRs zero to two at 90 days versus 25% of placebo). The most significant complications seen were symptomatic intracranial hemorrhage, which was seen in 10% of the pro-UK group in PROACT-II (as compared with 6% in the NINDS IV tPA study). Regardless, the improvements in outcome spurred a new era in acute stroke therapy.

The major limitations to intra-arterial thrombolytic infusion were

related to the variability of clinical response. Recanalization could not be consistently achieved in a high percentage of patients, and even those patients who recanalized did not always improve. The thought of mechanically removing the embolus rather than relying on pharmacological thrombolysis has spurred the invention of the next generation of IAT devices (Figure 1). The first FDA approved device for this indication was the Merci retriever (Concentric Medical, Aliso Viejo, CA). The MERCI and Multi MERCI trials selected patients who were ineligible for IV tPA or who failed to clinically improve following IV tPA and were treated with mechanical thrombectomy with adjunctive thrombolysis. While recanalization rates were 70%, favorable clinical outcome (mRs zero to two) still remained low at 36%, and symptomatic hemorrhage rates were 9.8%.⁹ Another new device, the Penumbra system (Penumbra Inc., Alameda, CA) showed recanalization rates of 82% with 25% of patients mRs zero to two at 90 days.¹⁰ Both of these trials showed that despite increases in recanalization rates, the overall clinical outcomes have not improved substantially over IA tPA infusion. Patient selection, including the inclusion of patients with more proximal occlusion, as well as treatment up to eight hours from symptom onset may account for some of these differences in outcome.¹¹ However, when compared with patients in whom mechanical thrombectomy was attempted and unsuccessful, those in whom recanalization was obtained had significantly better clinical outcomes.¹²

Certainly the availability of mechanical thrombectomy as a treatment option has further expanded our armamentarium. Unlike intra-arterial thrombolysis however, there have been no randomized trials comparing mechanical thrombectomy with no therapy or placebo infusion.

CURRENT DIRECTIONS – BRIDGING AND RESCUE THERAPY

Initially, patients with acute ischemic stroke were treated either with IV tPA or IAT, based on time from onset to presentation. However, with the expansion of the IVT window to 4.5 hours,⁶ an alternative approach has gained traction – that of a combined paradigm where both intra-venous and intra-arterial techniques are combined with the goal of optimizing patient outcomes. In order to understand the rationale for this approach, we need to better define the subgroup of patients in whom IVT alone is unlikely to result in a good outcome. A re-analysis of the NINDS IV tPA trial stratified patients by admission National Institutes of Health Stroke scale (NIHSS), and showed the greatest benefit for IV tPA was for those patients with moderate strokes.⁵ Indeed,

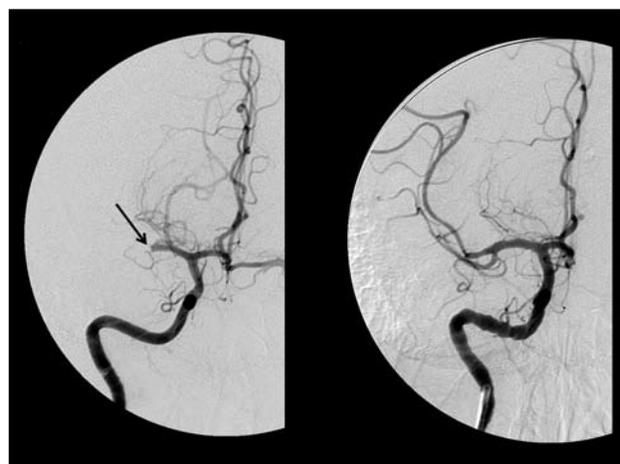


Figure 1. A frontal projection from a right internal carotid arteriogram demonstrates an abrupt occlusion of the proximal middle cerebral artery (arrows, left). This patient was ineligible for intravenous tPA due to recent abdominal surgery and was treated with intra-arterial mechanical thrombectomy. Post-treatment angiogram (right) shows complete restoration of flow. The patient had no residual deficit.

patients with an NIHSS of zero to five tended to have good outcomes regardless of therapy performed, those with NIHSS between six and 15 seemed to have the greatest benefit from IVT. Patients with more severe strokes (NIHSS 16 and above) did benefit from IVT, but the absolute benefit was not as great as with less severe strokes. Since the severity of the NIHSS is linked with the volume of infarction, it would follow that the more severe NIHSS is associated with a more proximal arterial occlusion.¹³⁻¹⁴ It has been shown from trials using continuous **transcranial Doppler (TCD)** monitoring that the more proximal the arterial occlusion, the less likely that IV tPA will result in complete recanalization.¹⁵ For example, only 6.3% of terminal **internal carotid artery (ICA)** occlusions recanalized with IV tPA as compared with 48% of more distal occlusion at the M2 branches of the MCA. A final determinant is the time to recanalization with IV tPA. Using TCD, Ribo showed that the vast majority of recanalization occurs in the first hour after the tPA bolus.¹⁶ Based on these analyses, we would presume that patients with more severe strokes who fail to improve clinically within one hour from IV tPA administration may be those most likely to benefit from IAT. Patients with minor strokes (NIHSS one to five) are unlikely to benefit from IAT but should still receive IVT if eligible.

The safety of this combined approach has been demonstrated in the **interventional management of stroke (IMS)** trials.¹⁷⁻¹⁸ The IMS-I trial showed safety, with a 6.4% symptomatic hemorrhage rate in patients treated with a lower dose of IV tPA combined with IA tPA infusion. In IMS-II, the recanalization rate was 62% and the rate of favorable clinical outcome at 90 days was 46%.¹⁸ Interestingly, this rate was not significantly superior to the IV tPA treated group from NINDS, which raises the question of whether every patient needs a combined approach. The currently enrolling IMS-III trial randomizes patients into either IVT alone, or combined IVT plus IAT using either thrombolytic infusion or mechanical thrombectomy using Merci or Penumbra devices, and aims to show a difference in efficacy among the approaches.¹⁹

FUTURE GOALS – IMPROVING PATIENT OUTCOMES

Ultimately IAT for stroke needs to show improved patient outcomes. Despite gains in recanalization rates from the early days of PROACT, there is still a substantial cohort of patients who do not have a clinical benefit from IAT. One area of improvement is in device development. It would be logical to ask why the cardiac model of angioplasty and stenting for acute stroke is not routinely performed. Indeed, case series have demonstrated technical success when using stent based recanalization.²⁰ However, unlike cardiac lesions, an underlying stenosis is not usually present in intracranial occlusion. In addition, the tortuous anatomy can make delivery of stents challenging in the intracranial circulation. Nevertheless, there are newer devices which have shown promise in preliminary trials, and it is possible that self-expanding stents may play a role in IAT for stroke.²¹⁻²⁴ Another promising paradigm is the use of a combination stent and thrombectomy device, where the stent is used to open the vessel and after thrombolysis the device can be completely removed.²⁵⁻²⁶ Future studies will need to show whether or not these technical developments can translate into improved clinical outcomes.

Improvements in patient selection and reductions in time to treatment may also improve outcomes. A strong linear relationship between time from symptom onset to recanalization and outcome has been shown for the IMS I and II trials,²⁷ with patients recanalized beyond seven hours from symptom onset not seeming to benefit from reperfusion. Stroke centers which perform IAT should have mechanisms in place to rapidly identify and treat appropriate patients. The use of advanced imaging studies such as **CT perfusion (CTP)**, or diffusion weighted MRI has been proposed as a means of better identifying patients who would benefit from IAT, but no series has shown a clear improvement in clinical outcomes when compared with using non-contrast CT alone.

SUMMARY

Intra-arterial therapy (IAT) for acute ischemic stroke has undergone great evolution during the past decade. While intra-venous therapy remains the standard

of care for eligible patients, there are those patients in whom IV tPA is contraindicated, or those who fail to improve following IV tPA. In those cases, patients with accessible arterial occlusions may benefit from IAT, especially when recanalization can occur within six hours from symptom onset. Future advancements in device development and patient selection may further improve outcomes.

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