Review

Intra-Arterial Therapy for Acute Ischemic Stroke

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Key Words

Acute ischemic stroke · Embolectomy · Intra-arterial therapy · Intravenous tissue plasminogen activator · Multimodal approaches

Abstract

Intra-arterial therapy (IAT) for acute ischemic stroke treatment is evolving. Whereas the efficacy of recanalization with traditional intra-arterial fibrinolysis is relatively poor, mechanically based recanalization with multimodal approaches, stenting and mechanical embolectomy is more effective. Until recently, this has not resulted in overwhelming clinical benefit and has not always equated with reperfusion. The reasons for this are not clearly known but may include inadequate patient selection, poor technique, low operator experience, direct injury from thrombolytics or devices, microvascular occlusions, complications of general anesthesia, or some other unknown factors. Intracerebral hemorrhage still complicates 2–11% of procedures. Large prospective and randomized clinical trials are needed to determine the safety and efficacy of IAT be it pharmacological therapy, embolectomy, stenting, or multimodal therapy. Comparative studies between the newer stent retriever devices and intravenous tissue plasminogen activators may also be needed especially for the 3- to 4.5-hour window.

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Introduction

Intravenous tissue plasminogen activator (tPA) is the only approved recanalization therapy for acute ischemic stroke (AIS) treatment but due to a narrow 3- to 4.5-hour treatment window it is used in a minority of AIS patients [1]. Furthermore, its benefit is limited, with regard to both clinical and recanalization efficacy, particularly for large vessel occlusions, the

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most common cause of severe and fatal AIS [2, 3]. Major advances in endovascular therapy in the past 10–15 years have rendered intra-arterial therapy (IAT) a viable option for a larger number of AIS patients with the potential for remarkable recovery. Large vessel occlusions are particularly amenable to endovascular therapy much like acute coronary syndromes presenting as ST elevation myocardial infarction which are better treated with percutaneous interventions rather than intravenous thrombolysis (IVT) [4]. Unlike acute coronary artery syndromes, however, which are most often caused by atherosclerotic plaque rupture, AIS causes are more varied, and as a consequence no single specific therapy will be effective for all cases especially when the numerous factors affecting neurological outcome are considered.

Indications

The indications for IAT are evolving. Since there is no approved IAT for stroke, there is a great deal of variability between practitioners in the field with regard to the indications. In general, patients with AIS meeting the <3-hour criterion should be offered intravenous tPA, and IAT should be offered to all others and to those who refuse intravenous tPA [5, 6]. It is important to note that treatment with intravenous tPA does not reduce mortality from stroke, and patients with large vessel occlusions [7, 8], large thrombus burden (i.e. thrombi longer than 8 mm) [9], and those with more severe strokes respond less well to IVT [10]. For these patients, IAT may be considered as an (unproven) alternative to IVT [11]. In one observational study of 112 patients with hyperdense middle cerebral artery (MCA) sign, half of whom received intravenous tPA and the other IAT, favorable outcome was doubled and risk of death reduced in two thirds for the patients treated with IAT [12]. While provocative, such studies merely emphasize the need for a randomized trial comparing IVT with endovascular therapy.

The traditional time window for IAT is up to 6 h for thrombolysis and 8 h for mechanical embolectomy [5]. The duration of ischemia is a leading predictor of neurological outcome but with modern penumbral imaging, selection of patients for IAT may be time independent (see below) [13–16].

Patients must also have a clinical deficit severe enough to warrant intervention since patients with mild strokes [NIHSS (National Institutes of Health Stroke Score) <4] are unlikely to have a visible arterial occlusion and are likely to have a good outcome without therapy [17]. In contrast, patients with the most severe strokes (NIHSS >20) are less likely to benefit from treatment, although penumbral imaging to identify patients with small ischemic cores and large perfusion deficits may help select who may benefit [13, 14]. The recent prospective cohort study [DEFUSE 2 (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke)] tested whether a complex MRI perfusion-based definition of target mismatch (TMM) could appropriately detect who would benefit from IAT within 12 h of stroke onset [18]. Of the 99 patients with perfusion imaging, 78 had a TMM, 42 of whom were treated beyond the 6-hour time window. With recanalization and TMM there was an odds ratio (OR) of 8.5 for good neurological outcomes in patients treated >6 h along with a 2.9 OR for those treated <6 h compared to those without TMM. Importantly, no reperfusion led to infarct growth and patients without TMM did not benefit from recanalization (OR 0.2, $p = 0.004$). Still, there is no consensus on the exact definition of penumbra, which technique best defines it and, importantly, there has not been unequivocal validation of the clinical utility of such imaging modalities. An alternative is to select patients using ASPECTS (Alberta Stroke Program Early CT Score). A score >7 is associated with good neurological outcomes following thrombolysis [19]. In addition to parenchymal imaging, vascular imaging either by CT angiography or MR angiography may be helpful in selecting patients for the IAT approach.

Clinical Aspects

It may be valuable to determine the likely etiology of the stroke prior to the initiation of IAT. A lesion likely to be due to atherosclerotic occlusion can be approached differently than one due to cardioembolism (for example, the former may be directly stented and the latter approached first with an embolectomy device) [20]. This approach of tailoring the intervention to the presumed mechanism of occlusion has not been validated and most IAT studies have not considered etiology. Other factors such as age of the patients, duration of ischemia, presence of early infarct signs, presenting blood pressure, serum glucose, underlying dementia, and the presence of collaterals are also considered [5, 15, 21, 22].

It has been common practice to perform IAT with the aid of general anesthesia, however most patients with AIS are able to breathe spontaneously. In a pooled analysis of 980 consecutive patients from 12 medical centers receiving IAT, those treated under general anesthesia had a 2.3 OR of poor outcomes and a 1.68 OR of death [23]. Importantly, those treated awake did not have any increase in the risk of wire perforation or intracerebral hemorrhage (ICH). In a subanalysis of 75 of 81 patients with anterior circulation strokes enrolled in IMS (Interventional Management of Stroke) II, the use of heavy sedation/pharmacologic paralysis was associated with an increased risk of poor clinical outcomes (OR 7.0, $p = 0.002$) and death (OR 5.0, $p = 0.02$) [24].

Intra-Arterial Thrombolysis

The intra-arterial infusion of thrombolytics directly at the site of the occlusion has been utilized for over 20 years with numerous case reports and small case series but only two significant randomized trials [25–27]. The first was PROACT II (Prolyse in Acute Cerebral Thromboembolism II), a phase 3 trial of recombinant pro-urokinase in angiographically documented MCA occlusion of <6 h duration [17]. One hundred and eighty patients (median NIHSS = 17 and median time-to-initiation of treatment = 5.3 h) were randomized to 9 mg i.a. recombinant pro-urokinase infused over 2 h or intravenous heparin. The 2-hour partial or complete recanalization [TIMI (Thrombolysis in Myocardial Infarction) 2 or 3] rate was 66% in the treatment group and 18% in controls but complete recanalization (TIMI 3) was only 19 and 2%, respectively. The proportion of patients with modified Rankin score (mRS) ≤ 2 at 90 days was 40% with treatment but 25% in controls – a 58% relative benefit and a number-needed to treat of 7 ($p = 0.043$). This benefit was greatest in patients with mild and moderate strokes (NIHSS 11–20), those younger than age 68, those who had early infarct volume <5.25 ml, and those with an ASPECTS score >7 [19, 28]. The symptomatic ICH (sICH) rate was 10% with treatment. These data were not sufficient for approval of recombinant pro-urokinase but they proved that IAT is safe and effective.

The second randomized trial was the Japanese MELT (Middle Cerebral Artery Embolism Local Fibrinolytic Intervention) trial of intra-arterial urokinase in patients with M1 or M2 MCA occlusions of <6 h duration [29]. Intra-arterial infusion of 120,000 U was given over 5 min and repeated up to a maximum of 600,000 U, 2 h had passed, or complete recanalization was achieved. The trial was stopped after enrolling 114 patients because of approval of intravenous tPA in Japan. Although the primary endpoint of mRS ≤ 2 was not significantly different, the rate of sICH was 9% and a preplanned secondary analysis showed that the rate of recovery to normal or near normal (mRS ≤ 1) was higher in the treatment group (42.1 vs. 22.8%, $p = 0.045$).

In clinical practice, tPA is the most widely used agent despite the lack of any large randomized trial data. Other agents used for IAT have included urokinase, reteplase, and

tenecteplase [30, 31]. Thrombolytics are not all equivalent: for example streptokinase was associated with excessive sICH [32]. Similarly, tPA has some neurotoxic effects resulting in higher rates of ICH [33]. The optimal dose and mode of administration of each thrombolytic is unknown; it is not surprising then that a meta-analysis of published studies on IAT found no overall benefit [34].

Increasingly the combination of both thrombolytic agents and glycoprotein IIb/IIIa antagonists has been described in small series and case reports [20, 27, 35]. Their use makes sense in cases of atherosclerotic occlusions or artery-to-artery emboli but less so in the setting of cardioembolism in which fibrin-rich clots are expected. Another potential role of the glycoprotein IIb/IIIa antagonists is following emergency stent implantation to prevent acute stent thrombosis. These agents should be used judiciously and in the lowest doses possible due to the lack of data on safety, efficacy, agent, route, and dosage; there appears to be no role for continuous infusion of these agents due to high rates of sICH [36].

Combined IVT/IAT

IVT can be initiated much more quickly than IAT in most circumstances. Therefore, an approach of IVT followed by IAT has been described and tested, i.e. the preliminary IMS I and II studies. IMS I was a phase 1 feasibility and safety trial of combined intravenous/intra-arterial tPA, and the IMS II assessed the feasibility of this approach with the aid of the MicroLys US™ infusion catheter (EKOS Inc., Bothell, Wash., USA). In the IMS II treatment arm, the OR of attaining an mRS ≤ 2 were 1.74 and 2.82 compared with tPA and placebo-treated subjects, respectively [37]. The phase 3 IMS III trial has recently been stopped due to a futility analysis on the primary outcome of mRS at 3 months after the enrollment of 656 of 900 patients. Therefore, there are no data to support a combined IVT/IAT strategy in intravenous tPA-eligible patients; however, in IMS III, patients were randomized to IAT before completion of the intravenous infusion so it remains unclear if rescue IAT should be considered in patients who failed intravenous tPA. Furthermore, there is no agreed-upon definition of ‘failure’ – the embolectomy trials that included failed intravenous tPA patients did not clearly define failure and there is no agreement on the timing of rescue IAT [38]. Using transcranial Doppler ultrasound in 179 patients treated with intravenous tPA, Ribo et al. [39] documented that the majority of recanalization occurs within the 1st hour, with few recanalizations thereafter, making it reasonable to consider IAT if patients do not recanalize or improve clinically within 1 h of receiving intravenous tPA.

Mechanical Clot Disruption and Extraction

Mechanical approaches to arterial recanalization utilizing balloons, snares, or the embolectomy devices are becoming the dominant approaches to IAT in clinical practice. Angioplasty – especially of underlying atherosclerotic or stenotic lesions – has been highly effective in several large Japanese series, which reported recanalization rates of up to 91% with lower risk of ICH compared to IAT fibrinolysis (3 vs. >10%, respectively) [40, 41]. These results may be unique to the Japanese/Asian populations studied since they have a high incidence of intracranial atherosclerosis as the cause of ischemia compared with the lower incidence of 8–10% in the USA [42]. Angioplasty is sometimes effective even without an underlying stenosis [20, 43]; more data are needed on the safety and efficacy of this approach.

Anecdotally, stenting of an underlying stenosis or occlusion is nearly universally effective in achieving recanalization [20, 44–46]. A prospective study of 20 patients with AIS (mean

NIHSS = 14 ± 3.8) treated with a self-expanding stent demonstrated a TIMI 2/3 recanalization rate of 100% with a 5% sICH rate [47]. The 30-day rate of mRS ≤ 3 was 60%, and 45% of patients had an mRS ≤ 1 . Corroborative data are still needed, especially of the long-term risk of in-stent stenosis. Stenting may be particularly effective for atherosclerotic, acute cervical internal carotid artery (ICA) origin occlusions but comes at the cost of a potentially increased risk of complications (i.e. ICH) due to the need for dual antiplatelet therapy [46, 48].

Mechanical embolectomy with the Merci™ clot retriever (Stryker Inc.) was approved by the Food and Drug Administration (FDA) in August 2005 for the removal of 'blood clots from the brain in patients experiencing an ischemic stroke' [49]. Approval was based on the single-arm MERCI (Mechanical Embolus Removal in Cerebral Ischemia) study of 151 patients with AIS of 3- to 8-hour duration, which showed feasibility and safety of mechanical embolectomy. The average age of the patients was 67.0 years, and patients had a mean NIHSS of 20.1 ± 6.6 with a mean time from symptom onset to groin puncture of 4.3 ± 1.7 h [49]. The patients in this study had significantly larger clot burden on average than those studied in PROACT II and MELT, and likely a larger clot burden than most if not all of the intravenous tPA trials: occlusions were located in the ICA (19%), ICA terminus (14%), M1 or M2 MCA branches (57%), intracranial vertebral artery (1%), and basilar artery (9%). Device-only recanalization (TIMI 2–3) was achieved in 46%, but with adjunctive thrombolysis it increased to 60.3%. The overall rates of good outcome (mRS ≤ 2) and mortality at 90 days were 27.7 and 43.5%, respectively. sICH was noted in 7.8% of patients. Importantly, successful revascularization was the strongest predictor of good neurological outcome (OR 12.82, $p = 0.0001$). Other factors such as age (OR 0.94, $p = 0.0009$) and baseline NIHSS score (OR 0.78, $p = 0.0007$) were also associated with good 90-day outcomes. The absence of recanalization, higher age, and higher NIHSS scores were independently associated with 90-day mortality.

The follow-up Multi MERCI trial was another multicenter single-arm trial of the first-generation Merci retrievers (X5/X6) and the second-generation Retriever (L5) with the added goal of exploring the safety and technical efficacy of embolectomy in patients who 'fail' IVT [38]. The device was deployed in 164 of 177 patients with a median NIHSS of 19. Twenty-nine percent had 'failed' intravenous tPA and 34.8% received intraprocedural intra-arterial thrombolytics. Device-only recanalization was noted in 55% but was 68% with adjunctive thrombolysis. The clinical results were similar to Merci with a good outcome in 36% and 34% mortality. The rate of sICH was 9.8%. Much has been made of the relatively poor clinical outcomes in these trials compared to the intravenous tPA trials. Those are inappropriate comparisons, however, since the MERCI trials had patients with more severe strokes and bigger thrombus burdens with far longer durations of ischemia. These trials were not designed or powered to show clinical efficacy, rather they were designed to show effectiveness in clot removal. It is a valid argument that these devices are not proven effective in stroke treatment, but by the same token they are effective at recanalization, which is the most effective treatment for stroke. Also, these devices may have a role in patients who cannot receive IVT or IAT.

The MERCI Registry, the largest prospective registry of mechanical embolectomy, included 1,000 patients treated 'in the real world' with no predefined exclusion criteria (MERCI Registry, Oral Presentation, ISC, 2011, Los Angeles, Calif., USA). Ninety-day follow-up data have been presented for 872 patients who had demographics, stroke severity, and intravenous tPA failure rates similar to those in the Multi MERCI trial. The Registry patients were treated on average later than in the earlier studies with 16.9% treated ≥ 8 h from stroke onset. Occlusions were located in the ICA (32%), MCA trunk (52%), MCA branch (8%), and verte-brobasilar artery (8%). Recanalization was achieved in 80.1% of patients, but only 31.6% had good outcomes and 33.4% died. Again, recanalization was the best predictor of good outcome (mRS ≤ 2) but with an age disparity: compared to patients < 60 years old, those > 79 years had

about a 50% lower probability of good outcome with recanalization and 40% mortality. Without recanalization, the probability of good outcome approached 0%. Mortality with successful recanalization in those <60 years was 15%. With complete recanalization, good neurological outcomes (70 vs. 10%) and mortality (<15 vs. 40–50%) were better in those with NIHSS <16 compared to those with NIHSS >25, respectively. The sICH rate was 7% overall but was lower with successful recanalization [5.4% with TICI (thrombolysis in cerebral infarction score) 3 vs. 9.2% with TICI 0–1]. In a multivariate analysis, predictors of good outcome were the baseline NIHSS (OR 0.88, $p < 0.0001$), age (OR 0.95, $p < 0.0001$), revascularization (TICI 2a/2b/3; OR 4.02, $p < 0.0001$), and endotracheal intubation (OR 0.41, $p < 0.0001$). Although not a randomized dataset, the MERCI Registry and the previous MERCI trials help define subsets of patients who may fare better with treatment and they reinforce the effect of recanalization on improving outcomes.

The Penumbra™ clot extraction system was the second FDA-approved device for embolectomy. Its clot extraction efficacy was validated in a study including 125 patients with an 8-hour time window [50]. The baseline NIHSS score (17.3 ± 5.2), average age (63.5 ± 13.5 years), and median time from stroke onset (4.1 h) were comparable to the other embolectomy studies. Revascularization success (TIMI 2–3) and 90-day good outcomes were achieved in 81.6 and 25% of the patients, respectively. Ninety-day mortality was 32.8%, with 11.2% sICH. There was a trend to a benefit with successful recanalization.

There are advantages and drawbacks to each of these devices, but both the Merci and Penumbra devices have been associated with subarachnoid hemorrhage and vessel perforation and poor clinical outcomes. As a result, a new class of devices that promise to be safer and more effective has been developed. The so-called ‘stentriever’ or ‘stent retrievers’ combine the benefits of stenting (immediate flow restoration) with embolectomy devices (clot extraction) without leaving a stent permanently in the vessel. Two randomized, non-inferiority trials have been published comparing the recanalization and clinical efficacy of stent retrievers versus the Merci retrievers in patients treated within 8 h of stroke onset. The SWIFT (Solitaire with the Intention for Thrombectomy) trial tested the Solitaire™ (Covidien/EV3 Inc.) device and TREVO 2 tested the Trevo™ (Stryker Neurovascular Inc.) device [51, 52]. SWIFT was stopped early after the randomization of 113 patients because an interim analysis showed that the primary efficacy outcome (TIMI 2 or 3 flow) was achieved more often with Solitaire (61 vs. 24%, OR 4.87, $p < 0.0001$) [51]. In addition, good neurological outcome (58 vs. 33%, OR 2.78, $p = 0.0001$) and 90-day mortality (17 vs. 38%, OR 0.34, $p = 0.0001$) were more favorable in the Solitaire group. The sICH rate was also remarkably lower with Solitaire (2 vs. 11%, OR 0.14, $p = 0.057$).

The TREVO 2 trial results were similar but not equivalent with 178 patients being randomized [52]. Recanalization ($\geq$ TICI 2) was higher with Trevo (86 vs. 60%, OR 4.22, $p < 0.0001$) as was good clinical outcome (40 vs. 22%, OR 2.39, $p = 0.013$). There was no difference in sICH (7 vs. 9%, OR 0.75, $p = 0.78$) or 90-day mortality (33 vs. 24%, OR 1.61, $p = 0.18$). The trials differed in some endpoint definitions and there was a very mild difference in the mean NIHSS before treatment (Solitaire 17.3 vs. Trevo 18.3) as well as the use of intravenous tPA (Solitaire 33% vs. Trevo 58%). These differences could explain some of the differences especially in sICH and good outcomes although given the small sample size in both trials many other factors including chance need to be considered. At this time, there are insufficient data to differentiate between stent retrievers although their superiority over the older Merci device seems to be real. Certainly, the speed of recanalization with the stent retrievers in general is a major advantage (e.g. time to achievement of recanalization from guide catheter placement was 36 min with Solitaire vs. 52 min with Merci, $p = 0.038$). The SWIFT trial results were sufficient for FDA approval of Solitaire followed shortly by approval of Trevo. Several other devices with variations in the design are also being tested.

Expansion of the Time Window for IAT

In the MERCI Registry, 112 patients were treated ≥ 12 h from stroke onset with identical neurological outcomes to those treated < 8 h (81.3% revascularization rate, 90-day mRS ≤ 2 of 37.8%, and mortality of 18.8%). In an earlier study of 55 consecutive IAT patients selected by perfusion imaging with a mean NIHSS of 19.7 ± 5.7 , 34 were treated on average 3.4 ± 1.6 h from stroke onset and 21 were treated on average within 18.6 ± 16.0 h. Recanalization rates were similar (82.8 vs. 85.7%, $p =$ nonsignificant) between the two groups as were the rates of good neurological outcome (41.2 vs. 42.9%, $p =$ nonsignificant). Importantly, the rates of sICH were not higher even in patients with anterior circulation strokes (8.8 vs. 9.5%, $p =$ nonsignificant). The best predictor of poor outcome and death was the presenting NIHSS not the duration of ischemia. An even larger multicenter, retrospective study confirmed these results in 237 anterior circulation stroke patients treated with IAT on average 15 ± 11.2 h after stroke onset [16]. In that study, patients were selected based on either CT- or MRI-based perfusion imaging; the mean NIHSS was 15 ± 5.5 , and recanalization was achieved in 73.8%. Ninety-day good clinical outcomes and mortality were 45 and 21.5%, respectively. Remarkably, sICH occurred in 8.9%. Although both of these series were retrospective, have limitations, and need to be confirmed, these data suggest that patients with severe stroke syndromes who have a poor prognosis without recanalization and who have salvageable brain tissue may be considered for IAT regardless of the duration of ischemia. More studies are also needed to validate the penumbral imaging techniques and definitions for selecting patients for IAT, particularly those outside the traditional treatment window [14, 53].

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