Intra-arterial Stroke Management

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Semin Intervent Radiol 2013;30:282–287

Abstract

Keywords

- ▶ ischemic stroke
- ▶ intervention
- ▶ thrombolysis
- ▶ thrombectomy
- ▶ interventional radiology

Acute ischemic stroke is a leading cause of death and the leading cause of disability in the United States. Cerebral neuronal death begins within minutes after threshold values of blood oxygen saturation are crossed. Prompt restoration of oxygenated blood flow into ischemic tissue remains the common goal of reperfusion strategies. This article provides a brief overview of acute ischemic stroke, a summary of the major intra-arterial stroke therapy trials, and comments on current training requirements for the performance of intra-arterial therapies.

Objectives: Upon completion of this article, the reader will be able to discuss the role of intra-arterial interventions in the treatment of patients with acute ischemic stroke.

Accreditation: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Tufts University School of Medicine (TUSM) and Thieme Medical Publishers, New York. TUSM is accredited by the ACCME to provide continuing medical education for physicians.

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There are an estimated 800,000 strokes per year in the United States,¹ a number that is rising as the population continues to age.² Risk factors for ischemic stroke include hypertension, diabetes, smoking, and increased blood cholesterol and fat.³ Ischemic stroke accounts for nearly 80% of all strokes, with hemorrhagic strokes accounting for the remaining 20%. The mechanism for ischemic stroke is acute mechanical obstruction to the flow of oxygenated blood into brain tissue. This obstruction is usually due to thromboembolism, a blood clot that forms in one part of the body (such as the heart), which travels through the cervical and cerebral arteries until it lodges in a sufficiently small vessel. A less common

cause of acute ischemic stroke is rupture of an atherosclerotic plaque in the carotid artery or one of its terminal branches such as the middle cerebral artery (MCA). The result is hyperacute, in situ thrombosis of the diseased vessel. Additional subtypes of ischemic stroke have also been described.

Regardless of the mechanism of ischemic stroke, the goal of treatment remains the same: safe and rapid reestablishment of oxygenated blood flow to the affected tissue. Reperfusion strategies can be broadly divided into intravenous (IV) and intra-arterial (IA) therapies. IV treatment involves thrombolysis and IA treatment may include thrombolysis, thrombectomy, or a combination of the two. An additional common approach merges these broad strategies by combining salvage IA treatment with initial IV thrombolysis.

Thrombolysis is the act of dissolving a thrombus or clot. A thrombolytic medication, such as human recombinant tissue plasminogen activator (rt-PA), is administered into the blood stream with the goal of exposing the clot to sufficient medicine to dissolve it. Thrombolysis can be achieved by administration of the medication distant from the clot (IV), in close proximity to the clot (IA), or in combination (IV followed by IA thrombolysis).

Thrombectomy is the act of physical or mechanical clot manipulation within the lumen of the target vessel to remove it or displace it, allowing blood to flow past it. Thrombectomy can only be achieved in the target vessel using an IA approach. Thrombectomy can be performed in the absence of thrombolytic medication, in combination with IA thrombolysis, or following IV thrombolysis.

Issue Theme Neurointerventions for the Interventional Radiologist; Guest Editors, Gregory M. Soares, MD, FSIR and Sun Ho Ahn, MD

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Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0033-1353481>.
ISSN 0739-9529.

Algorithmic Approach to Ischemic Stroke

The approach to management and treatment of patients suffering from acute ischemic stroke has been the topic of numerous publications and is addressed in guidelines from the American Stroke Association.⁴ This section presents the current algorithm in use at a major academic medical center and certified comprehensive stroke center. For the sake of simplicity, the discussion will be limited to anterior circulation stroke. The major distinction between treatment in the anterior and posterior circulations is the acceptable temporal window for therapy.

Triage of patients can begin in the prehospital phase. Emergency medical service providers should be educated about the signs of acute stroke. They may be encouraged to bypass hospitals without stroke services in favor of medical centers able to provide these therapies.

Stroke treatment cannot currently be initiated without obtaining a baseline neuroimaging study. The most readily available and widely studied screening evaluation is the noncontrast head computed tomography (CT). This study can be obtained and interpreted rapidly. The presence of intracranial hemorrhage can be readily excluded and the parenchyma can be evaluated for signs of acute ischemia. The European Cooperative Assessment of Stroke Study (ECASS) trial⁵ established the presence of ischemia effecting greater than one-third of the MCA distribution as a contraindication to stroke therapy. This principle has been supported by several prospective and retrospective trials, and refined by the Alberta Stroke Program Early CT Score (ASPECTS) system. This system seeks to standardize the evaluation of a non-contrast head CT by assessing 10 prespecified locations over two representative image slices. The score starts at a perfect 10, indicating no evidence of acute ischemia. A point is subtracted for each prespecified location in which there is evidence of ischemia.⁶ A score of 7 or less has been shown to predict a poor outcome in patients undergoing revascularization during stroke.⁷ Not surprisingly, a score of 7 also indicates that one-third of the MCA territory is ischemic. Advanced stroke imaging and analysis of ischemic penumbra and core infarct using CT and magnetic resonance imaging (MRI) are beyond the scope of this article. The authors have evaluated these at their institution and have concluded that their addition does not improve clinical outcomes (personal communication, M. Jayaraman); therefore, the noncontrast head CT and ASPECT score is the screening test of choice at the authors' institution.

Patients arriving at the authors' hospital within 4.5 hours of symptom onset are candidates for IV thrombolysis.^{8,9} IV therapies must be initiated within a strict time limit to avoid unacceptable rates of intracranial hemorrhage. The therapeutic window for administration of IV rt-PA was extended from 3 to 4.5 hours based on the outcome of European Cooperative Acute Stroke Study III (ECASS III).⁵ Studies have shown that only 3 to 5% of patients experiencing a stroke arrive at the hospital within 4.5 hours of symptom onset, and therefore the majority of stroke victims are not eligible for IV thrombolytics (the only Food and Drug Administration (FDA)-approved

treatment).¹⁰ IA therapies offer the possibility of extending the window of therapeutic opportunity to a larger population. Nonresponders and those excluded from IV thrombolysis may still be eligible and are evaluated for IA therapy. An important component of expeditious stroke management is communication to all team members that a patient with acute ischemic stroke has entered the system. At the authors' institution, this is accomplished via a page system notification of "Code Stroke." Unlike the 4.5-hour window of opportunity for IV thrombolytics, IA treatment must be initiated within 6 hours of symptom onset.

Patients presenting more than 6 hours from symptom onset are excluded from IA therapy. Patients with a National Institute of Health Stroke Severity (NIHSS) Score < 10 and without aphasia are also excluded from IA therapy. Initiating IA therapy beyond the timeframe carries an unacceptable benefit/risk ratio, while patients with an NIHSS score < 10 tend to have vessel occlusion distal to the second division branches of the intracranial arteries and a reasonable likelihood of clinical improvement regardless of intervention.¹¹ Though emergency department or neurology providers typically provide NIHSS scores, it is helpful for the interventionalist to have a working knowledge of scoring. NIHSS scoring certification can be obtained online.

Patients with an NIHSS score > 10 or with aphasia are candidates for IA therapy as long as the patient can be delivered to the angiography table prior to 6 hours after symptom onset. NIHSS scores above 10 are associated with more proximal clot and better improvement following intervention. After obtaining informed consent, the patient is positioned supine on the table. The groins are prepared in sterile fashion. A right transfemoral approach is the authors' preferred access. Diagnostic cervicocerebral angiography is performed in anterior and lateral projections. Brief evaluation of the ipsilateral carotid bifurcation provides useful information concerning the need for carotid revascularization and to avoid possible catheter-related complications during cerebral catheterization. For further discussion of diagnostic cerebral angiography, please refer to the article entitled "Basic Neuroangiography: Review of Technique and Perioperative Patient Care" of this issue of *Seminars in Interventional Radiology*.¹²

Basic equipment needed to perform evaluation and management of ischemic stroke includes a 6F or 7F guiding sheath or catheter, a diagnostic catheter with a simple "hockey stick" or multipurpose shape, and a neurointerventional microcatheter and micro-wire. If mechanical therapy is entertained, a revascularization device such as the Penumbra Suction Embolectomy catheter (Penumbra Inc., Alameda, CA) or the Solitaire retrievable self-expanding stent (eV3 Neurovascular, Irvine, CA) is useful. If one of these devices is not available, rt-PA can be administered via the microcatheter or one of the other guides or catheters depending on the operators' experience and judgment. In the authors' practice, IA thrombolysis is performed from as close a position to the clot as is feasible given constraints of anatomy and technical challenges to catheter placement.

IV heparin is administered immediately prior to microcatheter placement to help prevent catheter-associated thrombosis. The goal is not full therapeutic anticoagulation, but is typically accomplished with a 3,000- to 5,000-unit bolus followed by an additional 1,000-unit bolus every 60 minutes for the duration of the intervention. If the arch anatomy or carotid selection is complex, anticoagulation may be administered earlier. At least one study has shown that heparin administration does not increase the risk of intracranial hemorrhage.¹³

The ideal neuro-microcatheter position for IA thrombolysis is within or immediately beyond the clot. The clot is laced with 2-mg rt-PA using a pulse-spray injection technique while slowly pulling the catheter back into the vessel proximal to the occlusion. This is a modification of the technique used in the Prolyse in Acute Cerebral Thromboembolism (PROACT) trials.^{14,15} An additional 8 mg of rt-PA is slowly infused into the clot over 20 to 30 minutes using an infusion pump. Repeat catheter angiography is obtained when the infusion is complete; technical success is judged using a modified, "cerebral" version of the Thrombolysis in Coronary Ischemia score.¹⁶ If there is limited or no reperfusion, a second 10-mg dose of rt-PA is infused over an additional 20 to 30 minutes followed by repeat angiography. While more thrombolytic agent can be administered, the authors tend to abandon thrombolysis at a threshold dose of 20-mg rt-PA in favor of mechanical thrombectomy.

The choice of drug volume and duration of administration are somewhat arbitrary; however, data exist to support this approach. Infusion time was 1 hour for half of the thrombolytic in subjects enrolled in the PROACT study. Pharmacomechanics have been invoked in support of this decision. Thrombolytic drugs are thought to disintegrate thrombus through an enzymatic reaction that is subject to the laws of thermodynamics and cannot be sped up by increasing the concentration of the catalyst. However, a randomized trial of peripheral thrombolysis for deep venous thrombosis or arterial graft occlusion comparing alteplase and urokinase showed that alteplase led to improved clot removal in a significantly shorter time period and with a significantly smaller dose of medication.¹⁷ In the authors' opinion, waiting 1 hour to infuse half of the thrombolytic is clinically inefficient when treatment is subject to time limits.

Early experience with the Solitaire retrievable stent has been extremely favorable. This device has become the authors' primary revascularization device. The device comes in two diameters, 4 and 6 mm, and several lengths. It is intended to be used with any microcatheter of sufficient inner diameter and length. The catheter is advanced over the guidewire and beyond the clot, and placement confirmed with a small gentle hand injection of contrast. Forceful injections and multiple microcatheter injections should be avoided due to the risk of hemorrhage or contrast staining.¹⁸ The stent is delivered to the end of the microcatheter and deployed by pulling the microcatheter back while stabilizing the stent delivery wire. The stent is allowed to open fully over the course of 5 minutes. During this time, the stent expands and the clot is squeezed through the tines of the stent, trapping the clot within the

stent. Suction aspiration is applied to the guiding catheter or sheath, and the stent and microcatheter are pulled out of the body simultaneously. Clot is often visualized on inspection of the stent. A follow-up angiogram is performed to assess treatment response. If response is incomplete, the microcatheter can be repositioned and the same Solitaire device can be reused. There have been reports of the stent dissociating from the delivery wire after the device is reused two or three times, but this has not happened in the authors' practice to date.¹⁹

Evidence for Intra-arterial Therapies for Acute Ischemic Stroke

Thrombolysis

The only randomized controlled trials to investigate the role of IA thrombolysis as a standalone treatment for acute ischemic stroke are the PROACT trials parts I and II.^{14,15} These two trials investigated whether or not there was a treatment benefit for ischemic stroke patients who received IA pro-urokinase in combination with IV heparin therapy, versus patients who only received IV heparin as a treatment for stroke within 6 hours of symptom onset. Each of these two trials showed statistically significant improvements in the percentage of patients regaining neurological function and independence, or near independence, after receiving IA pro-urokinase and heparin versus heparin alone. However, this improvement was realized at the cost of increased intracranial hemorrhage, both silent and clinically symptomatic.

In PROACT I, a total of 40 patients were treated. Twenty-six patients received the experimental protocol including 6-mg IA pro-urokinase administered over 2 hours in addition to IV heparin, while the remaining 14 patients received the control protocol of heparin alone. Fifty-seven percent of the experimental patients had partial or complete recanalization versus only 14% of the controls. This translated into a clinical benefit for approximately 10% of the experimental patients at 90 days. The rate of any intracranial hemorrhage within the first 24 hours after treatment among patients receiving the experimental protocol was more than three times greater than that of the control patients. Additionally, the experimental patients had twice the rate of symptomatic intracranial hemorrhage as the controls.

In PROACT II, a total of 180 patients were treated. Two-thirds of the patients received the experimental protocol including 9 mg of IA pro-urokinase administered over 2 hours in addition to IV heparin, while 59 patients received the control protocol of heparin alone. Sixty-six percent of the experimental patients had partial or complete recanalization versus 18% of the controls. This translated into an absolute clinical benefit for 15% of the experimental patients at 90 days. The rate of any intracranial hemorrhage within the first 24 hours after treatment among patients receiving the experimental protocol was slightly more than double that of the control patients (35 vs. 13%). Intracranial hemorrhage with clinical deterioration occurred in 10% of the experimental group and only 2% of the controls.

Despite the positive results of these trials, the FDA decided not to approve IA pro-urokinase for the treatment of acute ischemic stroke. This decision was based on several concerns about the design and execution of the PROACT trials as well as the safety of the experimental treatment itself. Chiefly, there was concern about the increased rate of intracranial hemorrhage between patients receiving IA thrombolytics (35%) in the PROACT II trial and IV thrombolytics (6%) in the National Institute of Neurological Disorders and Stroke (NINDS) trial.²⁰ One explanation for this observation is that patients enrolled in the PROACT trial underwent treatment at a longer time interval from symptom onset than patients in the NINDS trial. Therefore, patients in PROACT had sustained a longer duration of ischemia and presumably more neuronal injury than patients in NINDS. Another factor contributing to the high rate of hemorrhage in PROACT was the use of IV heparin in both the experimental and control arms of the trial. Retrospective analysis confirmed that the increased rate of hemorrhage seen in these studies was related to both heparin and pro-urokinase. Several failed trials of heparin alone as a therapy for acute ischemic stroke were published contemporaneously with the PROACT studies.²¹

The concomitant use of both IV and IA thrombolysis is often referred to as “bridging” therapy. The rationale behind the design of these studies is based on the possibility that outcomes realized with IV thrombolysis might be limited in some patients and might be improved upon by the addition of IA therapy. There is also a practical reason behind this type of trial design. Although IV thrombolytics may be widely available in the community setting, IA therapies require a certain level of specialization that is often absent outside of referral centers. This has led to the development of “drip and ship” protocols, in which a patient is triaged in a community hospital where a noncontrast head CT is obtained and IV thrombolysis is initiated but then transferred to a referral center where IA therapies can be performed.

Several trials have looked at the effect of combining IV and IA thrombolytics for the treatment of acute ischemic stroke. Among these were the Emergency Management of Stroke (EMS) trial²² and the Interventional Management of Stroke (IMS) study, parts I, II, and III.^{23–25}

The EMS trial was a relatively small, double blind, randomized controlled trial that assessed clinical safety and neurological improvement between 17 experimental patients receiving both IV and IA rt-PA and 18 control patients receiving an IV placebo and IA rt-PA. This trial demonstrated no difference in clinical outcomes or symptomatic intracranial hemorrhage in either arm. There was an increase in both asymptomatic intracranial hemorrhage and better rates of recanalization in patients receiving both IV and IA rt-PA.

The IMS study included two nonrandomized Phase II safety trials assessing the effect of combined IV and IA rt-PA in comparison to the historical cohort from the NINDS trial, and a Phase III open-label randomized controlled trial that was stopped early. The initial IMS trial included the use of standard microcatheters for the administration of the IA thrombolytic, while the subsequent IMS II trial investigated the use of either a standard microcatheter or the EKOS

microcatheter (EKOS Corp, Bothell, WA). Each of these trials included 80 experimental subjects. Overall, the IMS patients experienced a nonsignificant decrease in mortality at 3 months compared with all patients in NINDS, an identical rate of intracranial hemorrhage at 36 hours compared with experimental patients in NINDS, and a similar clinical outcome at 3 months compared with the experimental patients from NINDS (as measured by the modified Rankin scale). The effect of the EKOS microcatheter was not significantly different from standard microcatheters with regard to vessel recanalization rate or any other measure. The final part of the IMS study was a Phase III randomized controlled trial in which the intention was to randomize a stroke population in a 2:1 design to either combined IV and IA therapy or IV therapy alone. The IA treatment could include thrombolysis or any of the available FDA-approved IA thrombectomy devices including MERCI (Concentric Medical, Mountain View, CA), Penumbra, or Solitaire. The study was stopped early because there was a low probability of detecting a minimum 10% difference between the experimental and control groups. Three additional IA stroke therapy trials have recently been published^{26–28}; none of these have succeeded in demonstrating a clear clinical benefit to these interventions.

In conclusion, trials assessing the clinical utility of IA thrombolysis for management of acute ischemic stroke fail to significantly improve on the outcomes of IV thrombolytic trials. However, these trials did show a clear improvement in the rate and degree of vessel recanalization, which is an important surrogate for clinical improvement in ischemic stroke.²⁹ Additionally, subgroup analysis indicates that patients with large proximal clots (M1 or terminal internal carotid artery) might preferentially benefit from IA treatment.³⁰ Additionally, retrospective analysis of the IV thrombolysis data indicates that standalone IV thrombolysis has a low likelihood of clearing a large proximal clot.²⁹

Thrombectomy

The disruption, displacement, or removal of clot from the target vessel in ischemic stroke is quickly becoming the preferred IA therapy. This is because technological advances have made mechanical vessel recanalization a relatively straightforward, highly reproducible, and angiographically successful strategy. Devices that have shown utility during mechanical revascularization include simple items such as guidewires that are used to create pilot holes in clot to increase the surface area that is exposed to t-PA, in addition to sophisticated “stent-trievers” designed to rapidly open the vessel and facilitate clot extraction. Similar to thrombolysis, there is a relative paucity of data from randomized controlled trials of these devices; in fact, to date there are no data. Despite this, there is ample evidence that outcomes are improved in patients undergoing IA thrombectomy for treatment of ischemic stroke compared with matched case controls who do not receive the therapy.^{19,31,32}

Reported trials include the multi-MERCI trial,³¹ the Penumbra trial,³² and the Solitaire trial.¹⁹ These trials have shown dramatically improved recanalization rates, extremely rapid recanalization, and relatively low rates of intracranial

hemorrhage. However, despite such improvements in surrogate parameters, there has been little or no improvement in clinical outcomes when compared with the benchmark trials of IV and IA thrombolysis. The reasons for this lack of clinical response remain elusive.

The multi-MERCI trial was a prospective single-arm trial assessing the efficacy of combined IV thrombolysis followed by IA thrombectomy for patients with a persistent large vessel clot; the MERCI retriever device was used, with or without adjunctive IA thrombolysis. One hundred and sixty-four patients were treated; successful recanalization occurred in 57% of patients using the MERCI device, which increased to 69% with the addition of IA thrombolysis and other mechanical treatments such as stenting. Favorable clinical outcomes were seen in 36% of patients, and the overall mortality rate was 34%.³¹ Retrospective analysis suggests that clinical improvement is significantly related to improved vessel recanalization and shorter times to vessel recanalization.

Suction thrombectomy is another useful treatment. In the Penumbra Pivotal Stroke trial, the Penumbra suction thrombectomy catheter was used in a prospective single-arm trial of patients nonresponsive to or ineligible for IV thrombolysis. One hundred and twenty-five patients were enrolled; there was an 82% recanalization rate in the targeted vessels. There was a 28% rate of intracranial hemorrhage, with nearly half deemed symptomatic. One quarter of the patients had a good neurological response to treatment at 90 days as measured using the modified Rankin scale.

Self-expanding retrievable stents have entered the market recently and are proving to be excellent devices for stroke revascularization. Results of the Solitaire device were reported in 2011. The study included 26 patients who did not qualify for IV thrombolysis. Excellent recanalization (TIMI grade ≥ 2) was achieved in 25 of these patients. Good clinical outcomes were seen in 9 of 16 patients treated for anterior circulation stroke. Two patients had symptomatic hemorrhages after using the Penumbra and there were no treatment-related deaths.

Relevant Training

Several specialists are poised to provide IA stroke therapies. These specialists include interventional neuroradiologists, interventional radiologists, interventional neurosurgeons, interventional neurologists, and interventional cardiologists. Each specialty society has generated training standards that, it feels, are appropriate metrics by which to judge operators.

The Society of Interventional Radiology last published its recommended guidelines for training and performance of IA catheter-directed treatment of acute ischemic stroke in 2009.³³ Six months of cognitive training in neuroanatomy and pathology and neurovascular imaging is recommended, which is satisfied by residency training in diagnostic radiology. The guidelines suggest that physicians desiring to perform IA stroke interventions should have experience with 200 selective vascular catheterizations, of which 50 should be cervicocerebral. The physician should have performed 30 microcatheter procedures including 5 in the internal or external carotid distribution. The practitioner

should also have interpreted 200 cervicocerebral angiograms, 50 CT angiograms, 50 MR angiograms, and 25 CT or MR perfusion studies. Finally, the panel recommends that five stroke interventions be proctored. The Society of Interventional Radiology also hosts a training course, Catheter Lysis of Thrombosis in Stroke (CLOTS), for interested physicians. The course includes didactic instruction as well as hands-on opportunities to experience and become familiar with neurointerventional equipment in a controlled setting. There is also an exam at the end of the course that can be used by the participant to measure their weaknesses and strengths. Short of providing proctored interventions, the course is inclusive and recommended for those interested in performing stroke therapy or those in need of comprehensive review of the topic.

Accepting the gauntlet to treat ischemic stroke means having a system in place to accept consults 24 hours a day, 7 days a week, 365 days a year. The practice of stroke management is not simple. Many patients will not improve despite technical success. However, the natural history of the disease is poor and it is thrilling when a patient improves because of the provided treatment.

The skills needed to perform stroke interventions are already in the general interventional radiologist's tool bag. The devices discussed in this article are microcatheter based, and the newest generation of mechanical devices, the stent-retrievers, is intuitive and highly effective.

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