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Intra-arterial Thrombolysis: Tissue Plasminogen Activator and Other Thrombolytic Agents

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Recanalization rates with the administration of intravenous tissue plasminogen activator in acute ischemic stroke are low. Adjuvant endovascular techniques that achieve recanalization by direct intra-arterial (IA) delivery of thrombolytics, mechanical clot retrieval, clot aspiration, and stenting may complement intravenous pharmacotherapy. IA thrombolytics can be administered within 6 hours of symptom onset in anterior circulation strokes and within 24 hours in posterior circulation strokes. This review describes the indications, patient selection, and technique for IA administration of thrombolytics.
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Partial or complete recanalization with intravenous (IV) tissue plasminogen activator (tPA) in acute ischemic stroke occurs in only 10% of occluded internal carotid arteries (ICAs) and in 25% of occluded proximal middle cerebral arteries (MCAs).[1,2] More than 80% of stroke patients with a National Institutes of Health Stroke Scale (NIHSS) score of 10 or more have persistent arterial occlusion despite IV tPA.[3] Endovascular recanalization therapies for acute ischemic stroke have rapidly evolved during the past decade and now comprise a wide range of pharmacologic and mechanical techniques. Intra-arterial (IA) administration of thrombolytics with or without mechanical thrombectomy is a common treatment for vessel recanalization.

IA thrombolytics can be infused distal, proximal, or directly within the occlusion using a microcatheter delivery system. Compared with standard IV administration, the IA route offers several theoretic advantages, such as higher concentrations of the thrombolytic agent at the obstruction site; reduced systemic exposure to thrombolytics; an opportunity to carry out gentle mechanical disruption of the clot with the delivery microcatheter and microwire; precise imaging of case-specific vascular anatomy, pathology, and collateral patterns; and exact knowledge of the timing and degree of recanalization achieved. Disadvantages of IA thrombolysis include the risk of arterial perforation during microcatheter or microwire manipulation; increased risk of intracerebral hemorrhage (ICH) due to intraprocedural heparin administration to deter catheter-induced thrombosis; limited availability of the procedure, mostly offered at tertiary and secondary hospitals capable of acute endovascular therapy; and exposure to iodinated contrast and radiation. In open clinical series, IA cerebral thrombolysis has yielded higher early recanalization rates than IV therapy. IA thrombolysis has been recommended for treatment of selected patients with major stroke of <6 hours' duration due to MCA occlusion.[4] This recommendation is based on the prospective, randomized, placebo-controlled phase III study testing IA thrombolysis with prourokinase (PROACT II) among patients with MCA occlusion within 6 hours of symptom onset.[5] Five randomized trials of IA thrombolysis versus control have been performed. A meta-analysis of these 5 trials, collectively analyzing 395 patients, found that IA thrombolysis increased the likelihood of good outcome (odds ratio = 2.05; $P = 0.001$).[6] Although symptomatic ICH was increased with IA treatment (8.9% vs 2.3%), the mortality rate was not elevated (20.5% vs 24%).

Patient Selection

Patient selection for IA thrombolysis may be difficult because of the wide variety of stroke presentations and rapid evolving nature of cerebral ischemia. The exclusion criteria used in the PROACT II trial can be used as a general guideline (Table 1). Overall, the eligibility criteria includes:

1. Patients with clinical diagnosis of ischemic stroke and at least a noncontrast computed tomography (CT) that

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Table 1 PROACT II Exclusion Criteria

NIHSS score >30 or <4
Rapidly improving neurological signs
Stroke within the previous 6 wks[a]
Seizures at onset of presenting stroke
Clinical presentation suggestive of subarachnoid hemorrhage
Previous intracranial hemorrhage, neoplasm, or subarachnoid hemorrhage[a]
Septic embolism
Suspected lacunar stroke
Surgery, biopsy of a parenchymal organ, trauma with internal injuries or lumbar puncture within 30 d[a]
Head trauma within 90 d[a]
Active or recent hemorrhage within 30 d[a]
Known hemorrhagic diathesis, INR >1.7, APTT >1.5 times normal and platelet count $<100 \times 10^9$ dL[a]
Sensitivity to contrast agents[a]
BP ≥180 mm Hg systolic or ≥100 mm Hg diastolic × 3 despite antihypertensive medications[a]
CT evidence of ICH, intracranial tumors except for small meningiomas, significant mass effect from the infarction, and acute hypodense parenchymal lesion or effacement of cerebral sulci in more than one-third of the MCA territory
Angiographic evidence of arterial dissection, arterial stenosis precluding safe passage of a microcatheter into the MCA, nonatherosclerotic arteriopathy, no visible occlusion, or occlusion of an artery other than the M1 or M2 segments of the MCA[a]

APTT, activated partial thromboplastin time; BP, blood pressure; CT, computed tomography; ICH, intracerebral hemorrhage; INR, international normalized ratio; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

[a]Relative contraindications that may not be a limiting factors outside a clinical trial.

rules out ICH. IA thrombolysis may be offered if there is a contraindication or failure of IV tPA.

2. Minimum NIHSS score of 4, except for isolated aphasia or hemianopia.
3. Certain patients who do not qualify for IV thrombolysis may benefit from IA therapy. Recent history of major surgical procedures may be an indication for IA therapy.[7] Localized administration of thrombolytics in smaller quantities than IV therapy decreases systemic exposure and the risk of extracranial hemorrhage.
4. Guidelines suggest 6 hours from symptom onset as the treatment window for administration of IA tPA.[4] This may be extended to 24 hours after symptom onset in patients with posterior circulation occlusions.[8]
5. Patients with distal vascular occlusions of vessels <2 mm in diameter (M2, M3, and P1) in whom mechanical thrombectomy devices cannot be used.

Vascular imaging is a valuable aid in patient selection for IA thrombolysis. Helical CT angiography or magnetic resonance angiography are ideal for noninvasive screening of the extracranial and intracranial circulations. It may also provide potentially important information about the presence of vessel occlusions or stenoses.[9]

Additional patient triage with perfusion imaging has demonstrated a high degree of sensitivity and specificity for detecting cerebral ischemia.[10,11] Normal imaging suggests a nonvascular event such as seizures, or resolved ischemia. It also identifies patients with clear large-vessel occlusions and large infarct (≥100 mL). This population has a poor neurological outcome regardless of vessel recanalization.[12] CT perfusion may also differentiate thresholds of reversible and irreversible ischemia, and thus identify the ischemic penumbra.[13] However, neither vascular nor perfusion imaging justifies delays in the administration of IV thrombolysis in patients with <4.5 hours from symptom onset.

A relative contraindication for IA thrombolysis is tortuous vascular anatomy with difficult vascular access. However, new steerable guide catheters have eased distal access despite tortuous supra-aortic vessels.[14,15] Iodine allergy may be a relative contraindication that can be easily overcome. The protocol for iodine desensibilization includes the IV administration of 50 mg of diphenhydramine and 40 mg of methylprednisolone before the procedure to reduce the risk of allergic reactions in patients with history of sensitivity to contrast agents.

Combined Thrombolysis

Combined IV and IA thrombolysis has been investigated in several noncontrolled trials. The Emergency Management of Stroke (EMS) Bridging Trial and the Interventional Management of Stroke (IMS I) trials demonstrated that the combined IV/IA approach had similar rates of mortality and symptomatic ICH compared with matched subjects in the National Institute of Neurological Disorders and Stroke trial.[16,17] In IMS I, 0.6 mg/kg (estimated body weight) IV tPA (maximum 60 mg) was given within 3 hours of symptom onset. Ten percent of the total dose was given as an IV bolus over 1 minute, followed by a controlled 30-minute infusion. During the IA administration, 1 mg of tPA was injected beyond the thrombus. The catheter was then retracted into the proximal thrombus, and 1 mg of tPA was injected directly into the thrombus followed by infusion at a rate of 10 mg/h (10 mg/25 mL normal saline) using an infusion pump. Repeat angiography was performed every 15 minutes, and if the vessel was completely recanalized, the infusion was stopped. If the vessel had partially recanalized, the infusion catheter was introduced further into clot. The infusion was continued for a maximum of 2 hours, with a maximum local IA dose of 20 mg. Good functional outcome was statistically similar to the matched controlled group that only received IV tPA in the National Institute of Neurological Disorders and Stroke trial (43% vs 39%).

The IMS II trial achieved higher recanalization rates than IMS I (73% vs 56%).[18] However, there was no statistically significant difference in good functional outcome at 3 months (46% vs 43%). The IMS II study protocol was similar to the IMS I trial, except for the use of the EKOS microinfusion catheter (EKOS Corporation, Bothell, WA). This catheter uses acoustic streaming to theoretically increase throm-