STROKE

Acute Interventions for Stroke

Mechanical thrombectomy combined with drug therapy may be an effective technique for treating acute stroke.

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There are 750,000 acute strokes in the US each year, resulting in death and varying levels of permanent neurologic deficit.[1] Less than 5% of patients with acute stroke are treated nationally. The remaining untreated patients comprise a wide group whose symptoms are not recognized as strokes, do not present within the time window for treatment, or who are taken to facilities that lack the expertise to treat acute stroke. Some patients improve without treatment. The majority of stroke patients are left to suffer with chronic neurologic problems including speech and language deficits, weakness, paralysis, cognitive impairments, and visual loss.[2] The central nervous system is a unique and unforgiving organ. The death of brain cells can result in devastating loss of function, with multiple and varied signs and symptoms complicating diagnosis and treatment.

The treatment of acute ischemic stroke has evolved during the past 10 years. The use of intravenous thrombolytic therapy ushered in a new era for the treatment of acute stroke.[3] Prior to the use of thrombolytic agents, the treatment of acute stroke was primarily therapy with intravenous heparin. Early trials with intravenous streptokinase resulted in unacceptable levels of intracranial hemorrhage (ICH).[4] The introduction of intravenous tPA and contraction of the time frame (3-hour window vs 6-hour window) for treatment lead to marginal improvement in treatment outcomes.[5] Examples set by the interventional cardiology community for the treatment of acute myocardial infarction encouraged neurointerventionalists to begin microcatheter-based intra-arterial thrombolytic therapy. As a result, thrombolytic agents were delivered directly into intracranial vessels at the site of occlusion. Clot manipulation and maceration soon became an integral part of vessel recanalization, and intracranial mechanical thrombolysis was born. This article reviews material from clinical trials aimed at the catheter-based treatment for acute stoke, outlines treatment modalities, presents some case examples, and discusses perioperative care of this high acuity population with multiple comorbidities.

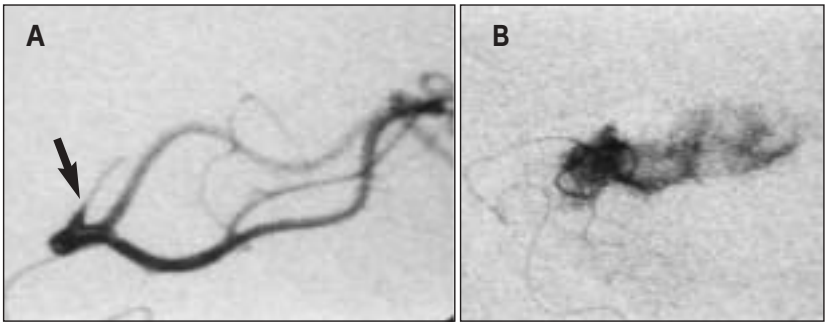

Figure 1. A microcatheter angiogram in the lateral projection (A). An occluded M2 branch is shown (arrowhead). Microcatheter injection in the right lateral projection in the middle cerebral artery (B). The M2 stump demonstrates contrast extravasation into the subarachnoid space.

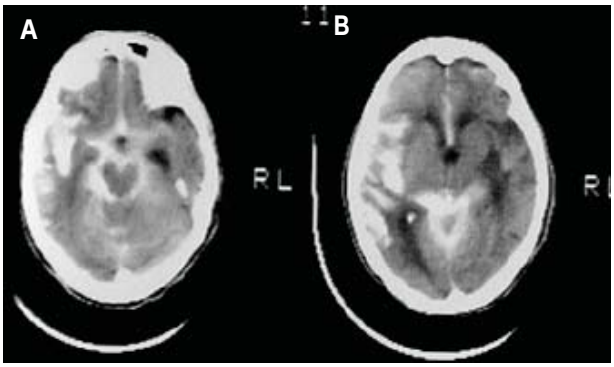

Figure 2. CT scan axial slices at the level of the cerebral peduncles (A) and the sylvian fissure (B). Note the high-density signal from the right sylvian fissure (pictured in both images on the left side of the scan) and the interhemispheric fissure. The brain stem is completely surrounded by high-density signal. The ventricular system is not filled because blood and contrast are in the subarachnoid space.

CLINICAL TRIALS

The National Institute of Neurologic Disease and Stroke (NINDS) trial used intravenous (IV) tPA for the treatment of acute stroke.[6] Patients presenting within 3 hours of the onset of symptoms were treated with 0.9 mg/kg IV tPA, with 10% of the dose given as a bolus and the remainder administered during the following 1 hour. Blood pressure was carefully controlled to maintain the systolic pressure below 180 mm Hg. Patients with systolic pressure >180 mm Hg on three readings were excluded from enrollment.[7] Uncontrolled hypertension was associated with increased risk of intracranial hemorrhage after tPA administration. Six hundred twenty-four patients who presented with acute ischemic stroke were enrolled in the trial and given IV tPA or placebo. Results demonstrated a marginal benefit for the treatment group. At 24 hours, 47% of the treatment group showed improvement compared to 39% of the placebo group. This was not statistically significant. The Rankin score at 3 months indicated a statistically significant improvement in 42% of treated patients and only 27% of the placebo group. ICH rates were 6.4% of the treatment group versus 0.6% of the placebo group. The mortality rate at 3 months was 17% for the IV tPA group and 21% for the placebo group.

The marginal benefits demonstrated by the NINDS IV tPA study revolutionized the treatment of acute ischemic stroke for patients presenting within 3 hours of ictus. Prior to the NINDS IV tPA study, IV heparin was the most popular form of therapy for acute stroke. Despite the proven efficacy of the NINDS study, most neurologists did not adopt this new treatment. Many centers found it difficult to organize hospital teams capable of triaging patients for drug administration within the 3-hour time frame. In addition, the complication of ICH made many neurologists uncomfortable with the process.[7] The steep learning curve associated with acute stroke treatment, labor-intensive clinical responsibilities, and marginal reimbursement prevented wide adoption of IV tPA treatment.

The first trial employing intra-arterial delivery of a thrombolytic agent was sponsored by Abbott Pharmaceuticals using prourokinase. A total of 45 patients were enrolled within 6 hours of the onset of ischemic symptoms.[8] Only patients with middle cerebral artery (MCA) occlusions were enrolled. After placement of the microcatheter proximal to the thrombus in the MCA, either prourokinase or saline was injected. Improved recanalization rates in the prourokinase group were

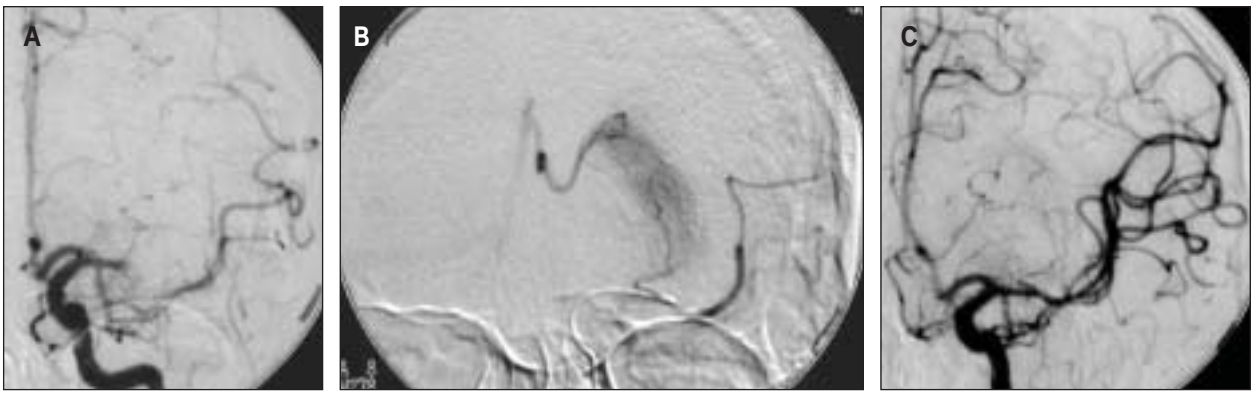

Figure 3. A 42-year-old female smoker who takes birth control pills. Acute onset right hemiplegia and aphasia. Middle cerebral artery occlusion in the M1 segment distal to the take off of the anterior temporal branch (A). Microcatheter angiogram in the AP projection with the catheter positioned in the MCA at the proximal end of the clot (B). Note the catheterization of a lenticulostriate artery and blush of the deep nuclei, as well as the venous drainage. Recanalization of the M1 occlusion after thrombolysis (C).

accompanied by a significant increase in ICH when compared with placebo. Rates of IV heparin infusion had a direct effect on symptomatic ICH. In this study, the "low-dose" heparin group sustained fewer episodes of symptomatic ICH. The results of this pilot study led to development of a larger randomized trial in which 10,000 patients were screened to enroll 180 patients with acute MCA occlusions.[9] Patients were randomized to receive either IV heparin or intra-arterial prourokinase within 6 hours of the onset of symptoms. Patients randomized to the intra-arterial treatment arm received 9 mg of prourokinase proximal to the clot. Mechanical manipulation of the clot was avoided. The recanalization rate was 66% in the prourokinase arm and 18% in the heparin group. Symptomatic intracranial hemorrhage occurred in 10% of the prourokinase group and in only 2% of the heparin group. Favorable outcome was seen in 40% of the prourokinase group and 25% of the heparin group. Although the results indicate only a 15% difference in outcome between the treatment and placebo group, this modest improvement in outcome was statistically significant. With the advent of later-generation thrombolytic agents such as retavase (Centocor, Inc., Malvern, PA), recanalization rates improved dramatically without significant improvements in patient outcome.[10] As a result, alternative and adjunctive therapies were sought that would shorten recanalization times and provide cerebral protection during periods of ischemia.

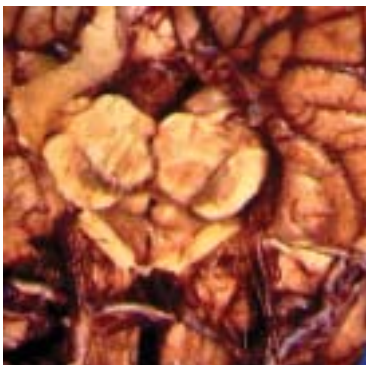

Figure 4. The ventral (under) surface of a cadaver brain showing the cerebral peduncles and brain stem. The lenticulostriate arteries can be seen penetrating the deep structures of the brain. These end arteries measure 100 to 500 µm in diameter.

IMAGING REQUIREMENTS FOR A STROKE CENTER

CT is a requirement for all patients with acute ischemic stroke. The presence of ICH or hypodensities that comprise more than one-third of the affected hemisphere represent exclusion criteria for treatment of acute ischemic stroke using thrombolytic agents. Rapid triage of patients from the emergency room to CT imaging is critical. In our facility, it is complete within 45 minutes. Use of brain perfusion techniques can help differentiate between completed infarcts and ischemic salvageable tissue referred to as the *ischemic penumbra*. Presently, all patients undergo CT perfusion studies at the time of conventional CT multislice imaging. The CT perfusion provides quantitative measurements of cerebral blood flow, cerebral blood volume, and the time required for the IV contrast to reach the intracranial circulation.[11] Serial CT perfusion images have the capability to differentiate between areas of completed infarct and ischemic penumbra. The utility of intra-arterial thrombolysis and associated ICH risk can be inferred from this study. This powerful technique requires only a few additional minutes in the CT scanner. MRI represents the gold standard for intracranial imaging. Diffusion perfusion imaging can identify completed infarcts and define the ischemic penumbra.[12,13] In addition, the age of the infarct can be categorized as acute, subacute, or chronic. This can be very useful when multiple hypodensities are seen on CT or if the timing of the onset of symptoms is in question. Unfortunately, MRI is not available on a 24-hour basis in our facility. Imaging intubated patients can be time-consuming, and motion artifact can be problematic. For these reasons, we depend on CT and CT perfusion to provide rapid imaging in our acute stroke patients. Nuclear medicine cerebral blood flow imaging techniques can be useful, but can consume precious time while cerebral ischemia progresses;[14] as a result, they are of minimal utility.

TRIAGE AND TREATMENT

The time course of symptoms and the severity of stroke signs influence the decision to use IV or intra-arterial

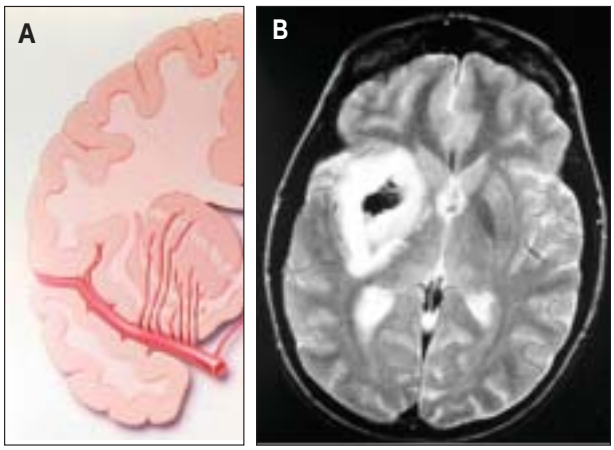

Figure 5. A coronal section of the right hemisphere at the level of sylvian fissure and caudate and putamen (A). The MCA is seen sending lenticulostriate arteries to the deep nuclei. MRI axial section demonstrating increased signal intensity in the right (pictured on the left side of the image) and deep nuclear infarction after M1 occlusion with successful recanalization 4 hours from onset of symptoms (B).

thrombolytic therapy. In the anterior circulation (carotid, ACA, and MCA distribution), patients who present within 3 hours of the onset of symptoms and have a mild-to-moderate stroke (National Institute of Health Stroke Score NIHSS <10) are good candidates for IV therapy with tPA. Patients with an NIHSS <10 with receptive and/or expressive aphasia, associated with an angular artery occlusion of the dominant hemisphere, may be best served by intra-arterial therapy. Patients who present with onset of symptoms between 3 and 6 hours or within 3 hours and have an NIHSS >10 are candidates for intra-arterial thrombolysis. Patients with posterior circulation symptoms (vertebrobasilar symptoms) can be treated up to 12 hours;[15] in these patients, intra-arterial therapy is the treatment modality of choice.

Catheter-based stroke therapy is always preceded by a diagnostic cerebral angiogram. Aortic arch injections using a pigtail catheter can help define tortuous or calcific aortic arches. In addition, aortic arch injections can provide a rapid means of evaluating intracranial vessel occlusion by positioning the image intensifier on the cranial compartment during aortic arch injections. Evaluation of the collateral circulation to the brain is critical and can be easily achieved by selective catheterization of both common carotid arteries and at least one vertebral artery. Once the occluded vessel has been identified, a 6-F guide catheter is placed into the extracranial internal carotid artery ipsilateral to the occluded intracranial vessel. When posterior circulation stroke is suspected, the guide catheter can be placed into the larger of the two vertebral arteries. A microcatheter with a 2.5-F distal tip is navigated into the cerebral circulation using a soft tip microguidewire. This is accomplished with retavase and urokinase. Infusion is halted if recanalization occurs, or after 4 units has been injected in 1-unit intervals.

Intra-arterial thrombolysis procedures can be performed in conscious patients. Repeated neurologic examinations can help provide an endpoint for the intervention. Often, patients are confused and uncooperative. Progression of cerebral ischemia can cause agitation and emesis, resulting in aspiration. As a result, we typically employ endotracheal intubation and neuroleptanalgesia with neuromuscular blockade.

After all thrombolysis procedures, patients undergo CT scanning to rule out ICH. All patients are taken to the neuroscience intensive care unit and are monitored closely for signs of infarction progression, ICH, or increased intracranial pressure.[16]

Intracerebral hemorrhage can occur at any time in the perioperative period during the treatment of acute stroke.[17] Patients experience headaches and agitation. Increases in systolic and mean arterial pressure are also seen. Intraparenchymal bleeding will not always result in neurologic deficit. Vessel perforation with the wire, microcatheter, or a device can also occur, which results in bleeding into the subarachnoid space (Figure 1). In any case, where ICH is suspected, a CT scan of the head should be obtained (Figure 2). In addition heparin should be reversed with protamine. Thrombolysis should be aborted. If increased intracranial pressure is suspected, a ventriculostomy should be placed.

All catheter-based interventions are performed using systemic heparinization. Heparin is administered in an IV bolus of 50 to 100 U/kg and is adjusted using activated clotting time (ACT) to maintain an ACT between 250 and 300 seconds. Throughout the procedure, all devices are attached to rotating hemostatic adapters, which are flushed with pressurized heparin saline flush packs.

Most intra-arterial thrombolytic therapy trials for acute ischemic stroke permitted enrollment of patients within 6 hours after the onset of stroke symptoms. Unfortunately, the deep nuclei of the brain (caudate and putamen) are more vulnerable to ischemia than the cerebral cortex. The deep nuclei are fed by end arteries called *lenticulostriates*

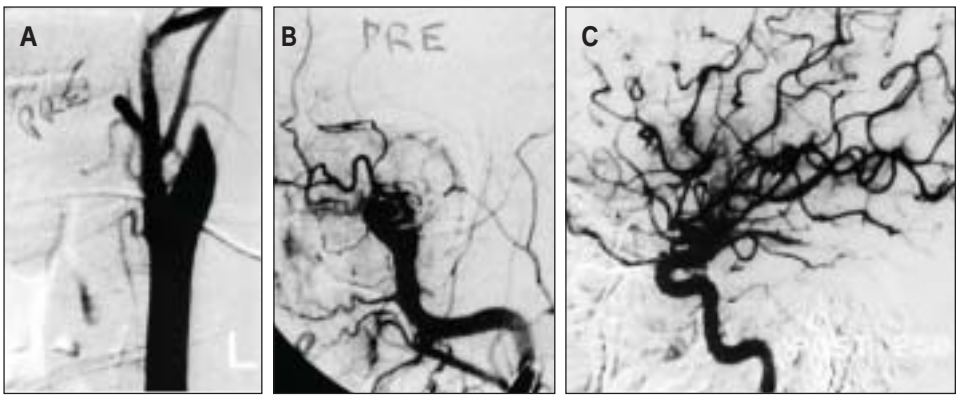

Figure 6. A 32-year-old woman, 8 weeks postpartum with right hemiplegia and aphasia. An angiogram of the left common carotid artery injection shows a left internal carotid occlusion (A). The AP projection of a left common carotid injection demonstrates complete occlusion of the supraclinoid segment of the internal carotid artery blocking both anterior and middle cerebral arteries (B). Common carotid artery injection in the lateral view demonstrates complete recanalization after lysis (C). The patient's hemiplegia and aphasia resolved immediately after recanalization.

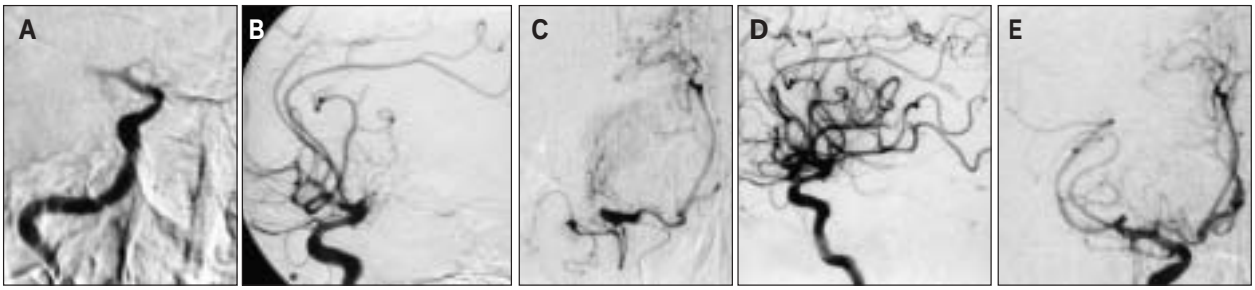

Figure 7. A right common ICA injection in the RAO view (A). The supraclinoid segment of the carotid is patent but the ACA and MCA fill only as stumps. An ICA injection in the lateral projection demonstrates MCA occlusion with recanalization of the anterior cerebral artery (B). Microcatheter injection of the right MCA M1 segment in the AP projection demonstrates M1 occlusion distal to the anterior temporal branch, lenticulostriate filling, and right anterior cerebral artery (C). Right ICA injection in the oblique view (D) and right ICA injection in the AP view (E) demonstrate complete recanalization of the MCA after thrombolysis.

that originate from the proximal portion of the MCA. There is no collateral supply to the deep nuclei. As a result, thrombus in the proximal portion of the MCA can result in infarction even if recanalization of the MCA occurs within the 6-hour time frame. Hemorrhagic transformation or ICH associated with thrombolysis usually occurs in the deep nuclei of the brain. Intra-arterial infusion of thrombolytic agents proximal to an MCA occlusion can result in the majority of the drug dose going into the lenticulostriates arteries directly (Figures 3-5). Careful scrutiny of the microcatheter position prior to infusion of thrombolytic agents can minimize this problem and decrease the incidence of ICH.

Figure 6 depicts a common carotid artery injection in a 32-year-old woman who presented with a complete internal carotid artery (ICA) occlusion 4 hours after onset of right hemiplegia and aphasia. She was 8 weeks postpartum. A microcatheter was placed into the MCA and 250,000 units of urokinase was infused. Shortly after infusion, the MCA recanalized and the patient's symptoms reversed while she was on the table.

Figure 7 depicts a 64-year-old man with a history of chest pain after coronary artery vein bypass grafting. During angioplasty of stenotic vein grafts he developed acute onset of left hemiplegia. Angiography revealed complete occlusion of the supraclinoid segment of the ICA. A microcatheter was placed into the MCA. The anterior cerebral artery opened spontaneously. Infusion of 4 units of retavase resulted in complete recanalization of the MCA after 60 minutes. The patient's neurologic exam returned to baseline after 24 hours.

Patients who present with acute anterior circulation strokes may be found to have complete ICA occlusions originating at the level of the cervical bifurcation. Recanalization in these patients poses increased risk of ICH. Once access is obtained to the occluded ICA, a microcatheter is placed distal to the stenosis. Microcatheter angiography is performed. Long segment disease throughout the length of the intracranial ICA makes sustained recanalization unlikely. Focal stenosis in the cervical carotid and intracranial carotid artery can be treated using angioplasty and stent techniques. Great care should be exercised when microcatheter angiography of the intracranial circulation reveals delayed emptying of contrast in the deep nuclei. This signals progressive infarction in the deep nuclei and poses an increased risk of reperfusion hemorrhage after recanalization, especially when using thrombolytic

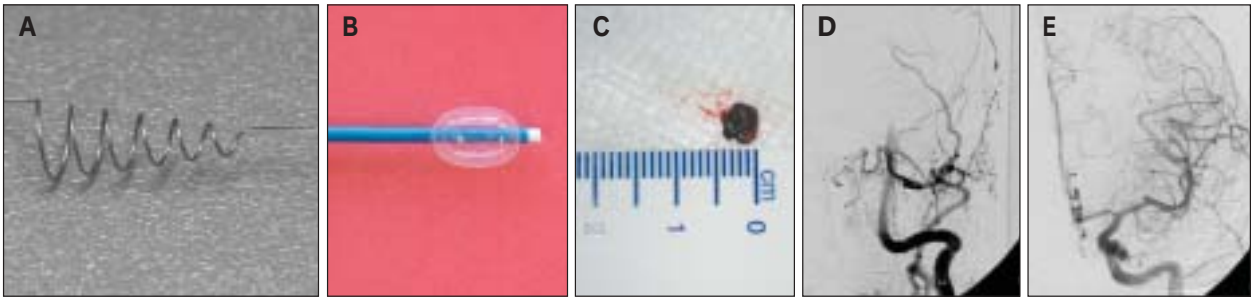

Figure 8. The Merci Clot Retrieval System (Concentric Medical, Inc., Mountain View, CA) (A). The balloon occlusion guide catheter (B) and the clot retrieved from the patient (C). Digital subtraction angiogram left carotid injection in the AP view MCA occlusion (D). DSA left carotid artery after clot removal with concentric device (E).

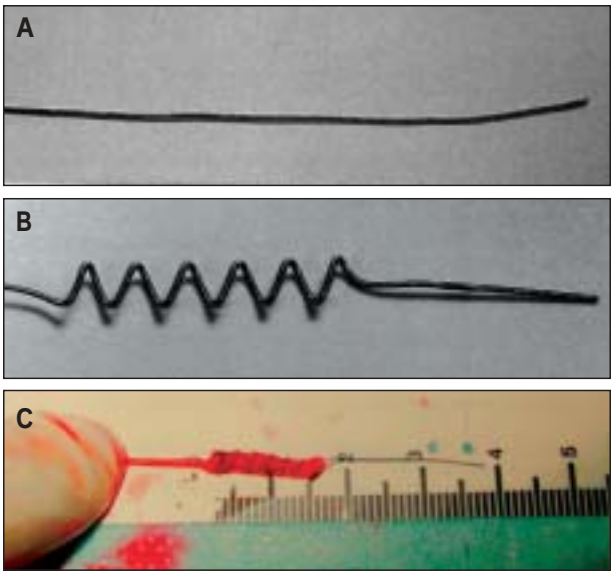

Figure 9. The Primus (Hanover, MA) device straight form used for delivery in a microcatheter (A). After actuation, the spiral shape is formed within the clot after positioning (B). Bottom clot removed with primus device porcine model (C).

agents. These hemorrhages can be fatal.

Mechanical thrombectomy combined with intra-arterial lytic therapy can be an effective technique for treating acute stroke. The Proact I and II trials were designed as drug trials. Maceration of the clot with the wire or microcatheter was discouraged. Early in our revascularization experience, we realized that manipulation of the clot facilitated lysis. We have employed 2-mm and 4-mm snares to help disrupt the clot, with some success. Intracranial clot retrievers have gained popularity during the past few years. The Merci Retrieval System (Figure 8) is an alloy conical spiral that is deployed into the clot with a standard microcatheter. Once the clot is engaged, a balloon on the distal end of the guide catheter occludes the target vessel and the clot is withdrawn. In a large clinical trial, recanalization rates exceeded 50%. The Concentric device awaits FDA approval. Another recent entry on the clot retrieval market is the Primus device (Figure 9). The Primus device is delivered through a standard microcatheter in an unactuated form that is similar to a guidewire. Once inside the clot, the Primus device is actuated to form a spiral that engages the clot. It can be deactivated and repositioned if required. This device has not yet been used in human trials.

CONCLUSION

The use of intra-arterial thrombolytic therapy has been proven efficacious and safe in a narrowly defined population of patients with acute stroke due to MCA occlusions. The use of intra-arterial therapy for acute stroke has been applied over a much wider patient population that includes ICA and vertebrobasilar strokes. Mechanical techniques in conjunction with drug therapies may represent the combination of techniques for fast and effective cerebral revascularization in the setting of acute stroke. ■

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1. Davalos A, Cendra E, Teruel J, et al. Deteriorating ischemic stroke: risk factors and prognosis. *Neurology.* 1990;40:1865-1869.
2. Qureshi AI, Ringer AJ, Suri MF, et al. Acute interventions for ischemic stroke: present status and future directions. *J Endovasc Ther.* 2000;7:423-428.
3. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet.* 1998;352:1245-1251.
4. Albers GW, Bates VE, Clark WM, et al. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA.* 2000;283:1145-1150.
5. Clark WM, Wissman S, Albers GW, et al. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. *JAMA.* 1999;282:2019-2026.
6. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med.* 1995;333:1581-1587.
7. Chamorro A, Vila N, Ascaso C, et al. Blood pressure and functional recovery in acute ischemic stroke. *Stroke.* 1998;29:1850-1853.
8. del Zoppo GJ, Higashida RT, Furlan AJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. *Stroke.* 1998;29:4-11.
9. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA.* 1999;282:2003-2011.
10. Qureshi AI, Ali Z, Suri MF, et al. Intra-arterial third-generation recombinant tissue plasminogen activator (reteplase) for acute ischemic stroke. *Neurosurgery.* 2001;49:41-50.
11. Harrigan MR. Presented at the 3rd International Symposium on CT and MR Brain Perfusion, Washington University Medical Center, St. Louis, MO: October 10-12, 2003.
12. Kidwell CS, Saver JL, Mattiello J, et al. Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging. *Ann Neurol.* 2000;47:462-469.
13. Kidwell CS, Saver JL, Mattiello J, et al. Diffusion-perfusion MRI characterization of post-recanalization hyperperfusion in humans. *Neurology.* 2001;57:2015-2021.
14. Ozgur HT, Kent Walsh T, Masaryk A, et al. Correlation of cerebrovascular reserve as measured by acetazolamide-challenged SPECT with angiographic flow patterns and intra- or extracranial arterial stenosis. *Am J Neuroradiol.* 2001;22:928-936.
15. Levy EI, Firlik AD, Wisniewski S, et al. Factors affecting survival rates for acute vertebrobasilar artery occlusions treated with intra-arterial thrombolytic therapy: a meta-analytical approach. *Neurosurgery.* 1999;45:539-548.
16. Gibbons KJ, Livingston K. Patient management, complications, and intensive care. *Neurosurg Clin North Am.* 1994;5:555-563.
17. Gorter JW. Major bleeding during anticoagulation after cerebral ischemia: patterns and risk factors. Stroke Prevention in Reversible Ischemia Trial (SPIRIT). European Atrial Fibrillation Trial (EAFT) study groups. *Neurology.* 1999;53:1319-1327.