Management of Acute Ischemic Stroke

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The treatment of acute ischemic stroke has evolved from observation and the passage of time dictating outcome to an approach that emphasizes time from ictus, rapid response, and a dedicated treatment team. We review the treatment of acute ischemic stroke from the prehospital setting, to the emergency department, to the inpatient hospital setting. We discuss the importance of prehospital assessment and treatment, including the use of elements of the neurologic examination, recognition of symptoms that can mimic those of acute ischemic stroke, and rapid transport of patients who are potential candidates for thrombolytic therapy to hospitals with that capability. Coordinated management of acute ischemic stroke in the emergency department is critical as well, beginning with non-contrast-enhanced computed tomography of the brain. The advantages of a multidisciplinary dedicated stroke team are discussed, as are thrombolytic therapy and other inpatient treatment options. Finally, we cover evolving management strategies, treatments, and tools that could improve patient outcomes.


MANAGEMENT OF ACUTE ISCHEMIC STROKE

Management of acute ischemic stroke is a multitiered, time-critical process that involves prehospital health care providers, emergency medicine physicians, nurses, neurologists, interventional neuroradiologists, and neurosurgeons. Ideally, patient care is streamlined and timely among these departments. This article discusses the management of acute ischemic stroke from the patient’s first medical attention from the prehospital health care provider through treatment in the stroke unit or the neurologic intensive care unit. Not all of these medical specialties are available for every situation or in all regions. Our goals are to provide a framework for primary care providers who treat patients with acute ischemic stroke, offer guidelines for this care, and outline the infrastructure needed to meet the demands of this care, and, when appropriate, to transfer a patient to a tertiary care center.

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PREHOSPITAL AND EMERGENCY DEPARTMENT CARE

At initial presentation of a patient with acute ischemic stroke, making the diagnosis can be difficult because many patients are unable to give a good history or may report vague symptoms such as malaise or general weakness. Physical examination is essential for making a prompt diagnosis of acute ischemic stroke because diagnostic adjuncts such as electrocardiography for myocardial infarction are not available in the prehospital setting. To overcome these issues, many prehospital medical personnel use elements of the neurologic examination that can be performed easily, such as assessing for facial weakness (facial droop), dysarthria or slurred speech, and limb weakness, to ascertain whether acute ischemic stroke has occurred. Several prehospital stroke scales have been designed specifically for this purpose.1–3 The National Institutes of Health Stroke Scale Score is used widely, not only in the research setting for standardizing treatments and measuring outcomes but also in the clinical setting.

Several disorders have symptoms that can mimic those of acute ischemic stroke and are important to consider when evaluating a patient with sudden onset of focal neurologic signs and symptoms. An important mimic of stroke is hypoglycemia, which can cause not only global weakness but also focal neurologic deficits. All patients in prehospital and emergency department settings should undergo immediate blood glucose testing. Hypoglycemia should be corrected immediately. An often-overlooked symptom that mimics those of acute ischemic stroke is migraine associated with neurologic symptoms and signs. Other diagnoses that should be considered in patients with new neurologic deficits are included in the mnemonic MEDICS (Table 1).

Patients who are potential candidates for thrombolytic therapy should be transported to hospitals with that capability, including the availability of 24-hour computed tomography (CT) of the head.4 Specific algorithms for assessing and treating stroke in a prehospital setting have been developed. The one used by medical transport personnel at the Mayo Clinic in Rochester, Minn, is presented in Table 2.

Time of arrival to medical attention (to the emergency department) is shortened with use of an emergency medical
MANAGEMENT OF ACUTE ISCHEMIC STROKE

TABLE 1. Mnemonic for Differential Diagnosis of Stroke

<table>
<thead>
<tr>
<th>M</th>
<th>Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Epilepsy (postictal)</td>
</tr>
<tr>
<td>D</td>
<td>Dissection, aortic</td>
</tr>
<tr>
<td>I</td>
<td>Intoxication (drug, alcohol); infection</td>
</tr>
<tr>
<td>C</td>
<td>Contusion; trauma</td>
</tr>
<tr>
<td>S</td>
<td>Sodium; electrolytes; glucose</td>
</tr>
</tbody>
</table>

services system and by public education efforts that focus on laypersons regarding the signs and symptoms of stroke. Once the patient arrives at the emergency department, non–contrast-enhanced CT of the brain should be performed immediately. Notification of the estimated time of arrival by emergency medical services personnel allows the CT suite to be ready for the patient’s arrival. Emergency department evaluation of patients with acute ischemic stroke involves several elements that should happen simultaneously. If a neurology consultation has not occurred yet, it should take place as early as possible. If CT scan of the head shows intracranial hemorrhage, blood volume and type of hemorrhage should be assessed quickly, and if surgery is a consideration, a neurosurgeon should evaluate the patient immediately. If acute ischemic stroke is diagnosed and the patient is within a 3-hour window from symptom onset, intravenous thrombolytic therapy should be considered. For appropriate patients and settings, intraarterial thrombolytic therapy is an option (see the “Thrombolytic Therapy” section). The presence of a multidisciplinary dedicated stroke team consisting of emergency physicians, neurologists, nurses, and interventionalists facilitates an expedited evaluation. The role of the nurse is critical because he or she initiates triage of the patient with acute stroke in the emergency department, monitors vital signs, expedites necessary studies, and coordinates communication between specialists involved with the patient’s care. This team approach has been shown to reduce the length of time between the patient’s arrival at the emergency department and completion of the evaluation, CT scan of the head, and possible initiation of thrombolytic therapy.

Brain optimization measures consist of assessing and addressing vital signs and initiating treatment plans. Patients should be given nasal cannula oxygen therapy with transcutaneous oxygen saturation monitoring per Advanced Cardiac Life Support protocol. Unless an allergy exists or patients are candidates for thrombolytic therapy, all patients should receive aspirin in the emergency department. Results of a systematic review of 41,325 patients showed that early use of aspirin for acute ischemic stroke reduced the rate of death or dependence and the number of early recurrent strokes. Interestingly, many patients had favorable outcomes, despite the 771 patients with intracra-

nal hemorrhage who were given aspirin before the CT scan was obtained. Patients with an allergy to aspirin can be given clopidogrel at a loading dose of 300 mg by mouth. Of note, although aspirin is withheld from patients who are candidates for thrombolytic therapy, having received aspirin is not of itself a contraindication to thrombolytic therapy.

Prompt ancillary evaluations should be performed in parallel. Reasonable initial evaluation in the emergency department setting includes blood glucose level, electrolyte panel including creatinine level, complete blood cell count, and coagulation studies (prothrombin time, international normalized ratio, activated partial thromboplastin time). Often, the serum erythrocyte sedimentation rate is determined, and liver function tests are performed. Chest radiography should be performed as well. Because atherosclerosis is a major etiology for both ischemic coronary disease and cerebrovascular disease, electrocardiography should be performed to rule out atrial fibrillation or acute myocardial infarction, and a cardiac biomarker panel should be obtained. A patient with atrial fibrillation should receive anticoagulants unless the patient is a candidate for thrombolytic therapy.

While waiting for results of CT of the brain to exclude hemorrhage or other structural lesions, the differential diagnosis (Table 1) should be reviewed again. Trauma is an important consideration. In patients who are unable to provide their history (either by themselves or via surrogate), head and neck injury must be assumed, and precautions to protect the cervical spine must be in place. Aortic dissection is another important consideration. Blood pressure should be measured in both arms, and a difference of more than 10 mm Hg should prompt a search for aortic dissection, including CT of the chest and CT angiography as appropriate. An immediate surgical consultation is indicated if the patient is hemodynamically unstable. Additional physical examination findings that may be helpful are external signs of trauma and cardiac murmurs or bruits.

THROMBOLYTIC THERAPY

INTRAVENOUS THROMBOLYTIC THERAPY FOR ACUTE ISCHEMIC STROKE

To treat patients presenting with ischemic stroke, ensure that patients are medically stable and confirm the diagnosis. As noted previously, symptoms that can mimic those of acute ischemic stroke must be considered and excluded. Subsequently, timely restoration of blood flow to the uninfarcted brain is paramount, ie, preserving the ischemic penumbra or brain that is “stunned” but will be viable if blood flow is reestablished.
Intravenous recombinant tissue-type plasminogen activator (r-tPA) has been proved effective at restoring blood flow to ischemic myocardium in acute coronary syndromes, and a natural extension was to apply the principle of thrombolytic therapy to ischemic stroke. Multiple trials have tested this hypothesis, but results were inconclusive for many reasons, including variable dosing of the thrombolytic agent, timing of the intervention, concomitant use of antiplatelet agents, and violations of study protocol.\textsuperscript{11-14} In 1995, the National Institute of Neurological Disorders and Stroke (NIHDS) published the results of a clinical trial that used r-tPA to treat ischemic stroke within 3 hours from symptom onset.\textsuperscript{15} This study consisted of 625 patients assigned randomly to placebo or intravenous r-tPA (alteplase). When results were assessed at 3 months, there was an 11% absolute increase in the number of patients with little or no deficits among those receiving alteplase compared with those receiving placebo. Although there was a 6% increase in symptomatic intracerebral hemorrhage in those receiving alteplase, there was no increase in the number of patients with severe morbidity and no increased mortality in the alteplase arm of the study vs the placebo arm.

As a result of the NIHDS trial, the Food and Drug Administration (FDA) approved the use of alteplase for treatment of acute ischemic stroke. To reproduce the results of the NIHDS study and to ensure patient safety, a rigorous protocol must be followed. The protocol outlined in Table 2 was followed at the Mayo Clinic since 1996. Adherence to the 3-hour time limit from ictus to treatment is important because treatment after a longer time interval has not shown benefit.\textsuperscript{11,15} Although the treatment window is 3 hours long, treatment should be initiated as early as possible for optimal results. Patients treated within 90 minutes from ictus have better outcomes than those treated within 90 to 180 minutes from ictus.\textsuperscript{16} Currently, the use of alteplase as a bridge to endovascular intervention is being explored.\textsuperscript{17}

A non–contrast-enhanced CT scan of the head is essential for deciding whether to proceed to thrombolytic therapy. Evidence of intracranial hemorrhage is an absolute contraindication to thrombolytic therapy. Similarly, thrombolysis in a large territory of infarction (ie, \(>1/3\) of the distribution of the middle cerebral artery) increases the likelihood of hemorrhagic conversion of an ischemic infarction or may lead to a parenchymal hemorrhage. Several subtle signs of ischemia can be recognized on CT of the head, including loss of the insular ribbon, loss of gray-white differentiation, and subtle local mass effect (Figure 1). These subtle signs are of themselves not a contraindication for thrombolytic therapy unless they encompass a large territory of infarction. Contraindications for intravenous thrombolytic therapy are summarized in Table 3.

**TABLE 2. Stroke Protocol for Mayo Medical Transport Personnel**

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose: To provide guidelines for the care of a patient with acute stroke</td>
</tr>
<tr>
<td>1. Establish and maintain an open airway</td>
</tr>
<tr>
<td>Insert nasal or oral airway as tolerated if patient is unconscious</td>
</tr>
<tr>
<td>Suction secretions as needed</td>
</tr>
<tr>
<td>2. Transport patient as soon as possible</td>
</tr>
<tr>
<td>3. Place patient recumbently on left side if patient is vomiting or having</td>
</tr>
<tr>
<td>problems with secretions, provided no spinal trauma is suspected</td>
</tr>
<tr>
<td>4. Start intravenous lactated Ringer injection or normal saline and run to</td>
</tr>
<tr>
<td>keep vein open. Initiation of intravenous solutions should not delay</td>
</tr>
<tr>
<td>transport of patient with recent stroke symptoms. Attempt to obtain</td>
</tr>
<tr>
<td>venous access en route to hospital</td>
</tr>
<tr>
<td>5. Assess vital signs</td>
</tr>
<tr>
<td>6. Perform blood glucose test</td>
</tr>
<tr>
<td>If blood glucose is (&lt;80) mg/dL and patient is conscious and</td>
</tr>
<tr>
<td>cooperative, administer juice, pop, milk with sugar, or 1 tube oral</td>
</tr>
<tr>
<td>glucose, 30 g/tube</td>
</tr>
<tr>
<td>Repeat blood glucose testing as needed</td>
</tr>
<tr>
<td>7. Determine and record initial Glasgow Coma Score</td>
</tr>
<tr>
<td>8. Perform brief neurologic examination including arm strength, facial</td>
</tr>
<tr>
<td>droop, and impaired speech</td>
</tr>
<tr>
<td>9. Alert receiving hospital early if patient meets stroke criteria</td>
</tr>
<tr>
<td>10. Transport patient as soon as possible</td>
</tr>
<tr>
<td>11. If diastolic blood pressure is (&gt;140) mm Hg, contact medical control</td>
</tr>
<tr>
<td>for possible order of 0.4 mg sublingual nitroglycerin, physician order</td>
</tr>
</tbody>
</table>

After receiving thrombolytic therapy, patients will require monitoring in the intensive care unit for at least 24 hours, including frequent neurologic assessments and blood pressure measurements. Blood pressure is recorded usually via a pneumatic blood-pressure cuff rather than from an arterial line. Anticoagulant and antithrombotic therapies are withheld for at least 24 hours, until a post-treatment CT scan of the head shows no hemorrhage. As the protocol in Table 3 states, patients with minimal deficits and those with extremely severe deficits are not candidates for thrombolytic therapy because risks of treatment outweigh potential benefits. Figure 2 reviews the steps to take if intracerebral bleeding is suspected during or after the infusion of r-tPA. In the NIHDS trial, the risk of intra-cerebral hemorrhage was highest in the first 36 hours after onset of ischemic stroke symptoms.\textsuperscript{15}

**Intra-arterial Thrombolytic Therapy for Ischemic Stroke**

No drugs or devices are approved by the FDA for intraarterial treatment of acute ischemic stroke; thus, such therapy is not standard. Currently, intra-arterial treatment is an option to consider when intravenous thrombolytic therapy is contraindicated. Intra-arterial therapy is used most commonly for patients who have an occlusion of a
The safety and efficacy of r-tPA in patients whose CT scan shows early findings of small cerebral infarction such as a small area of low attenuation without evidence for notable early infarction, hemispheric swelling, or hemorrhage.

‡The risk of hemorrhagic complication in the setting of a recent lumbar puncture or arterial puncture at a noncompressible site is uncertain. Treatment in these situations should be considered cautiously for selected patients after review of the findings of the lumbar puncture or arterial puncture, the clinical circumstances, and review with the consulting neurologist.

§The risk of hemorrhagic complication in the setting of a recent lumbar puncture or arterial puncture at a noncompressible site is uncertain. Treatment in these situations should be considered cautiously for selected patients after review of the findings of the lumbar puncture or arterial puncture, the clinical circumstances, and review with the consulting neurologist.

The following should be obtained as soon as possible after patient admission to the emergency department:

- Baseline laboratory tests (complete blood cell count, electrolyte panel, activated partial thromboplastin time, prothrombin time, aspartate aminotransferase, blood glucose level)
- Electrocardiogram, chest x-ray
- Non–contrast-enhanced CT of the head
- Body weight

2. Pretreatment management guidelines

<table>
<thead>
<tr>
<th>Consider r-tPA</th>
<th>No r-tPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>&gt;3 h from onset of focal anterior or posterior circulation ischemic symptoms†</td>
</tr>
<tr>
<td>Fixed major or progressive deficit</td>
<td>Rapidly resolving or minor deficit</td>
</tr>
<tr>
<td>Alert or somnolent patient</td>
<td>Obtunded or comatose patient</td>
</tr>
<tr>
<td>No seizure(s) in association with stroke</td>
<td>Seizure(s) at onset of stroke</td>
</tr>
<tr>
<td>No history of intracranial hemorrhage or bleeding diathesis</td>
<td>History of intracranial hemorrhage or bleeding diathesis</td>
</tr>
<tr>
<td>No history of large ischemic stroke within 2 mo</td>
<td>Large ischemic stroke within 2 mo</td>
</tr>
<tr>
<td>Elevations in blood pressure rapidly responsive to use of labetalol and similar agents and maintained at 185 mm Hg systolic, &gt;110 mm Hg diastolic pretreatment</td>
<td>Elevations in blood pressure persistently &gt;185 mm Hg systolic, &gt;110 mm Hg diastolic despite antihypertensive therapy. Patients requiring aggressive therapy to maintain above levels (eg, sodium nitroprusside) excluded</td>
</tr>
<tr>
<td>Absence of gastrointestinal, urinary tract hemorrhage within 21 d</td>
<td>Gastrointestinal or urinary tract hemorrhage within 21 d</td>
</tr>
<tr>
<td>No major surgery within 14 d</td>
<td>Major surgery within 14 d</td>
</tr>
<tr>
<td>No recent arterial puncture at a noncompressible site</td>
<td>Recent arterial puncture at a noncompressible site‡</td>
</tr>
<tr>
<td>No recent lumbar puncture</td>
<td>Recent lumbar puncture‡</td>
</tr>
<tr>
<td>Female patient who is not pregnant</td>
<td>Pregnant female patient</td>
</tr>
<tr>
<td>Normal activated partial thromboplastin time, international normalized ratio &lt;1.7</td>
<td>Elevated activated partial thromboplastin time, heparin within 48 h, oral anticoagulants, and international normalized ratio &gt;1.7</td>
</tr>
<tr>
<td>Platelet count, ≥100 × 10⁹</td>
<td>Platelet count, &lt;100 × 10⁹</td>
</tr>
<tr>
<td>Glucose, 50–400 mg/dL</td>
<td>Glucose, &lt;50 mg/dL or &gt;400 mg/dL</td>
</tr>
<tr>
<td>CT scan of the head</td>
<td>Evidence for notable early infarction with focal mass effect, hemispheric swelling, or hemorrhage</td>
</tr>
<tr>
<td>Absence of intracranial tumor</td>
<td>Intracranial tumor</td>
</tr>
</tbody>
</table>

3. Treatment guidelines

A. If patient eligibility is confirmed, r-tPA is to be administered in the recommended dose of 0.9 mg/kg of body weight (maximum, 90 mg), 10% given as a bolus, followed by the remaining 90% as a constant infusion over 60 min

B. All patients given r-tPA will be admitted to the intensive care unit

4. Posttreatment management guidelines

A. Antithrombotic and antiplatelet agents should not be used for the first 24 h after r-tPA administration

B. Monitor blood pressure for the first 24 h after initiation of r-tPA treatment

Every 15 min for 2 h after initiation of infusion, then
Every 30 min for 6 h, then
Every hour from the eighth hour until 24 h after initiation of r-tPA

If for 2 readings 5–10 min apart, systolic blood pressure is between 180 and 230 mm Hg or diastolic pressure is between 105 and 120 mm Hg
Give labetalol, 10 mg intravenously over 1 to 2 min. The dosage may be repeated and/or doubled every 10–20 min up to 300 mg. Monitor blood pressure every 15 min during treatment. Observe for hypotension

If systolic blood pressure is >230 mm Hg or diastolic pressure is between 121 and 140 mm Hg
Give labetalol, 10 mg intravenously over 1 to 2 min. The dosage may be repeated and/or doubled every 10 min up to 300 mg. If satisfactory response is not obtained, use sodium nitroprusside. Monitor blood pressure every 10 min during treatment. Observe for hypotension

If diastolic blood pressure is >140 mm Hg
Infuse sodium nitroprusside (0.5-10.0 µg/kg per minute). Monitor blood pressure every 15 min during treatment. Observe for hypotension

C. Nursing observation

Neurologic observations are obtained at the same time that vital signs are checked
Every 15 min for 2 h after initiation of infusion, then
Every 30 min for 6 h, then
Every hour from the eighth hour until 24 h after initiation of r-tPA

Particular attention is paid to possible markers of bleeding changes in neurologic function, nausea or vomiting, or increases in blood pressure
Patients are also observed for signs of external bleeding, particularly from puncture sites

TABLE 3. Guidelines for the Administration of r-tPA for Acute Ischemic Stroke, Mayo Clinic Division of Cerebrovascular Diseases*  

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline laboratory tests</td>
<td>Complete blood cell count, electrolyte panel, activated partial thromboplastin time, prothrombin time, aspartate aminotransferase, blood glucose level</td>
</tr>
<tr>
<td>Electrocardiogram, chest x-ray</td>
<td>No evidence for notable early infarction, hemispheric swelling, or hemorrhage</td>
</tr>
<tr>
<td>Non–contrast-enhanced CT of the head</td>
<td>Evidence for notable early infarction with focal mass effect, hemispheric swelling, or hemorrhage</td>
</tr>
<tr>
<td>Body weight</td>
<td>Absence of intracranial tumor</td>
</tr>
</tbody>
</table>

*CT = computed tomography; r-tPA = recombinant tissue-type plasminogen activator.
†For patients who awaken with stroke symptoms, the time they went to sleep defines the time of symptom onset.
‡The risk of hemorrhagic complication in the setting of a recent lumbar puncture or arterial puncture at a noncompressible site is uncertain. Treatment in these situations should be considered cautiously for selected patients after review of the findings of the lumbar puncture or arterial puncture, the clinical circumstances, and review with the consulting neurologist.
§The safety and efficacy of r-tPA in patients whose CT scan shows early findings of small cerebral infarction such as a small area of low attenuation without focal mass effect is still controversial and its use in these patients should be decided by the consulting neurologist. In most patients with early findings suggestive of a major cerebral infarction (ie, >1/3 of the middle cerebral artery distribution), r-tPA is not used because of hemorrhage risk and low likelihood of efficacy.
MANAGEMENT OF ACUTE ISCHEMIC STROKE

major anterior circulation artery (internal carotid or middle cerebral artery) or the basilar artery. The amount of time a patient can tolerate an arterial occlusion without sustaining a permanent neurologic deficit depends primarily on the presence of residual circulation to the affected area. Variability in degree of occlusion and collateral circulation probably accounts for much of the variability in outcome in patients treated with thrombolytic techniques. As more time passes after onset of symptoms, the chance of neurologic improvement decreases and the chance of hemorrhagic complication increases. Intra-arterial therapy for anterior circulation ischemia should begin within 6 hours after symptom onset. Because of the dire consequences of not recanalizing an acutely occluded basilar artery, a higher risk can be tolerated, and intra-arterial thrombolytic therapy has been advocated up to 12 hours after symptom onset with good clinical outcomes. To receive intra-arterial stroke interventions, a patient must be at an experienced stroke center that provides immediate access to cerebral angiography and interventional neuroradiology.

Urokinase was the most commonly used drug for intra-arterial thrombolytic therapy until it was removed from the market in 1999. Recently, it has been reintroduced and therefore may again become an intra-arterial treatment of acute stroke. The use of urokinase in stroke therapy is supported by only a few case series.

Trials have been performed to evaluate the efficacy of the urokinase precursor prourokinase. The Prolyse in Acute Cerebral Thromboembolism I (PROACT I) trial was a phase 2 prospective, randomized, double-blind, placebo-controlled study to evaluate the intra-arterial administration of recombinant prourokinase for treatment of acute ischemic stroke due to middle cerebral artery occlusion. Recanalization was significantly associated with prourokinase treatment ($P=0.017$). Intracerebral hemorrhage occurred in 15% of patients treated with prourokinase and in 7% of control patients (not statistically significant). High-dose adjuvant heparin therapy was associated with a high risk of intracerebral hemorrhage compared with low-dose heparin therapy.

PROACT II was a phase 3, randomized, placebo-controlled trial to evaluate the efficacy of intra-arterial prourokinase in patients with stroke of less than 6 hours’ duration secondary to occlusion of the middle cerebral artery. Low-dose heparin was used during the intervention. A significant improvement in outcome was associated with prourokinase treatment, with 40% of the 121 patients treated with prourokinase and 25% of the 59 control patients having modified Rankin scores of 0 to 2 at 90 days ($P=0.043$). Recanalization of the middle cerebral artery occurred in 66% of patients treated with prourokinase and in 18% of patients in the control group ($P<0.001$). Intracranial hemorrhage with neurologic deterioration within 24 hours of treatment occurred in 10% of patients treated with prourokinase and in 2% of control patients. No difference in overall mortality was observed between patients treated with urokinase and placebo. Currently,
prourokinase is not available for clinical use because it is not FDA approved.

Because urokinase and prourokinase have been unavailable, most medical centers have been using r-tPA for intra-arterial stroke therapy. The intra-arterial use of r-tPA is based primarily on its easy availability and its acceptance as an intravenous therapy for acute ischemic stroke. It is unclear whether PROACT II results can be extrapolated to the use of intra-arterial r-tPA. The Emergency Management of Stroke phase 1 bridging trial evaluated the feasibility of combined intravenous and local intra-arterial r-tPA.17 Angiographic recanalization rates 2 hours after initiation of intra-arterial infusion of r-tPA suggest that combined intravenous and intra-arterial infusions may be more effective than intra-arterial infusions alone. However, the efficacy of such a regimen remains to be proved.
Thromboemboli in the cerebral circulation are undoubtedly variable in time and place of origin. The material that embolizes to the cerebral circulation may be a thrombus that formed suddenly, one that formed a long time previously, or a mixture of both. The composition of the thromboembolus definitely affects its response to intraarterial thrombolytic therapy. Intra-arterial stroke therapy in the future will likely consist of several interventional options. Most likely, lytic drugs will be more effective for treatment of recent thrombi, and mechanical devices will be more effective for treatment of older thrombi or atheroemboli. Unfortunately, the composition of a thromboembolus usually cannot be determined at the time that therapeutic decisions are being made.

Patients who develop thromboemboli during endovascular procedures and are treated with thrombolytics are an interesting subset of patients because the thromboemboli almost certainly developed recently and are platelet-rich. In a recent series of 9 patients with such intraprocedural thromboemboli, intra-arterial thrombolytic therapy with r-tPA resulted in successful recanalization in only 4 patients (44%). This study indicates that fibrinolytic drugs such as r-tPA are not ideal for treatment of platelet-rich, acute, intra-arterial emboli. Early experience in similar cases with intravenous abximab, a potent anti-platelet agent, suggests that the recanalization rate is higher with this agent than with r-tPA. These data are preliminary, and a large randomized clinical trial is necessary.

Because intra-arterial administration of thrombolytic drugs is not always successful in recanalizing an artery, attempts are being made to remove emboli mechanically. Angioplasty of clot with balloons and retrieval of emboli with various devices have been successful for recanalizing arteries in small case series. Devices specifically designed to remove thromboemboli from the cerebral circulation are being developed.

**Medical Management of Acute Ischemic Stroke**

Although the introduction of thrombolytic agents appears to be the most important contribution to improving outcome in stroke, notable strides have been made in medical management as well. Several important issues should be considered at the initial patient assessment and may involve triage of the patient to a stroke unit or intensive care unit. The criteria for admission to the intensive care unit (and preferably a neurologic/neurosurgical intensive care unit) include any evidence of oxygen desaturation by pulse oximeter, recent aspiration, cardiac arrhythmia, electrocardiographic changes with increased troponin levels, and recent administration of intravenous or intra-arterial r-tPA. Management of severe hypertension requiring intravenously administered drugs is another indication for admission to an intensive care unit.

**Table 4. Blood Pressure Management in Patients With Acute Ischemic Stroke**

<table>
<thead>
<tr>
<th>Blood Pressure Management</th>
<th>MAP ≤ 130 mm Hg</th>
<th>Systolic pressure ≤ 220 mm Hg</th>
<th>Diastolic pressure ≤ 120 mm Hg</th>
<th>Thrombolytic therapy (first 24 h)</th>
<th>MAP ≤ 120 mm Hg</th>
<th>Systolic pressure ≤ 180 mm Hg</th>
<th>Diastolic pressure ≤ 105 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No thrombolytic therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*MAP = mean arterial blood pressure.

The treatment of patients with acute ischemic cerebral infarction in either the anterior or the posterior circulation should include the “6 norms”: normoglycemia, normoolemia, normothermia, normoxemia, normocapnia, and normotension. Normotension is more difficult to identify than the other norms in patients with acute ischemic stroke because acceptable blood pressure depends on many factors, including prior treatment with thrombolytic agents or the presence of comorbidities that would require changes in blood pressure parameters (Table 4). The definitions of these normal states are open to debate, not supported by rigorous trials, and primarily empirical. Nonetheless, they represent a consensus among stroke experts that should be used in clinical practice.

Airway management is important in patients with ischemic stroke. The airway often becomes compromised, primarily as a result of a decreased level of consciousness and decreased muscle tone; such patients are unable to protect their airway, which becomes obstructed when the tongue falls back. In patients with infarctions in the brainstem due to occlusive disease in the posterior circulation, oropharyngeal dysfunction—pharyngeal weakness and the inability to move the tongue—may cause airway obstruction. The decision to intubate patients with ischemic stroke depends primarily on the failure of oxygenation despite supplemental oxygen to control tachypnea, respiratory compromise due to fatigue, the inability to clear secretions, or the occurrence of a prolonged seizure requiring medication that causes marked sedation. Many patients have an adequate respiratory drive, and supplemental oxygen can be noninvasive with use of nasal cannula, a close-fitting face mask, or continuous positive airway pressure and pressure support. An arterial line is needed for patients in unstable condition and allows for frequent determination of blood gas values. The criteria for intubation are ambiguous; thus, outcomes of patients receiving mechanical ventilation may range widely. However, most studies have reported poor outcome once intubation and mechanical ventilation are needed, a reflection of secondary brain edema and swelling surrounding the infarction.
Blood pressure levels often are elevated in patients with acute ischemic stroke, and the decision to treat and the goals of treatment are at best uncertain. Complicating the decision to treat blood pressure is the physiology in the region of the infarction, with blood flow being pressure dependent due to vasomotor paralysis and loss of normal autoregulation. Patients with preexisting hypertension are at increased risk of infarction extension when blood pressure is decreased suddenly because the normal autoregulatory curve is shifted to the right. Reducing blood pressure in either situation may precipitate further ischemic injury. Normal blood pressure can be defined as a mean arterial blood pressure between 100 and 120 mm Hg. Below this range, intravenous fluids, often augmented with 5% albumin or other plasma expanders, should be used.

When the mean arterial blood pressure is greater than 120 mm Hg and the patient has received thrombolytic therapy, the NINDS guidelines should be followed for blood pressure management (Table 3). Systolic pressure should be 180 mm Hg or less and diastolic pressure should be 105 mm Hg or less after thrombolytic therapy. Above this range, labetalol or esmolol are preferred to control hypertensive surges (labetalol, 10-20 mg intravenously and may be repeated every 10 to 20 minutes to a maximum of 300 mg total dose; esmolol, 500 µg/kg intravenously as a loading dose over 1 minute, then 50 µg/kg/min and dosage is titrated to blood pressure parameters). When notable bradycardia exists, enalapril is considered, starting at 0.625 mg intravenously every 6 hours; the dosage is titrated to the desired effect. In patients not receiving thrombolytics, blood pressure should not be treated unless the mean arterial blood pressure is greater than 130 mm Hg, systolic pressure is greater than 220 mm Hg, diastolic pressure is greater than 120 mm Hg, or there is evidence of hemorrhagic transformation of the cerebral infarction, myocardial ischemia, hypertensive encephalopathy, arterial dissection, acute renal failure, or end-organ injury due to blood pressure. Patients with diastolic pressure greater than 120 mm Hg, or there is evidence of hemorrhagic transformation of the cerebral infarction, myocar-

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important; use of intermittent pneumatic compression devices on the lower limbs is probably sufficient to prevent this condition. Subcutaneous heparin can be considered for those unable or unwilling to use pneumatic compression devices. Patients with a paralyzed leg are at high risk of deep venous thrombosis (and pulmonary emboli) and should undergo screening ultrasonography 1 week after admission. It is also necessary to frequently put the paralyzed or paretic upper limb through its range of motion to prevent upper extremity deep venous thrombosis. The need for gastric prophylaxis is uncertain. The risk of gastrointestinal hemorrhage is low (1%-3%) except in patients taking anticoagulants and patients using a mechanical ventilator. When gastric prophylaxis is used, proton pump inhibitors are preferred.

**Future of Acute Ischemic Stroke Treatment**

The goal of acute ischemic stroke treatment is to minimize damage to the brain by preserving cells and restoring blood flow. This requires early recognition of symptoms, assessment, and treatment. We have summarized available management options in this article. Future goals and experimental treatments are aimed at each of these levels of intervention.

In humans, normal cerebral blood flow is approximately 50 to 60 mL/100 g of brain tissue per minute. When flow decreases to less than 10 to 15 mL/100 g per minute, irreversible tissue damage occurs. Irreversible cellular damage occurs within the central core. Around this core is a region of decreased flow in which the threshold for cell death has not yet been reached, the so-called ischemic penumbra. Restoration of blood flow may preserve the penumbra, limiting irreversible damage.

Cells in the penumbra can be preserved either by preventing or limiting cellular death or by restoring blood flow. The latter is the presumed mechanism of intravenous thrombolytic therapy. Other ways to restore blood flow include intra-arterial thrombolytic therapy, intra-arterial mechanical disruption of clot, and use of intravenous antithrombotics such as abciximab. These strategies are currently in phase 1, 2, or 3 trials.

Preservation of cellular viability has been the theoretical goal of using neuroprotectant agents, hyperbaric oxygen, and hypothermia. In the past 15 years, more than 114 clinical trials testing 49 neuroprotective agents have been unsuccessful, despite promising animal data. Similarly, hyperbaric oxygen has shown no harm or benefit in humans with ischemic stroke. Two randomized clinical trials suggested that mild hypothermia improves neurologic outcome and reduces overall mortality in witnessed cardiac arrest. Early studies evaluating the safety and feasibility of mild hypothermia in focal ischemia are ongoing, with early reports that hypothermia can reduce intracerebral pressure. Various methods of cooling patients are being assessed, as are methods to overcome adverse effects including thrombocytopenia, bradycardia, infection, and increased intracerebral pressure after hypothermia.

Some researchers have hypothesized that the time to treatment and the inability to select patients at risk (ie, with persistent penumbra) are the reasons the “neuroprotection” therapies failed. Early recognition and assessment of symptoms need to improve for optimal selection of patients for therapy. Early recognition cannot be overemphasized. The longer the time to treatment, the more extensive is the brain damage, and continued educational campaigns aimed at potential patients, emergency medical services, and physicians will be important. Also, centralizing the care of patients with acute ischemic stroke to centers capable of intervention can improve patient outcome.

Tools to assess and select which patients may benefit most from early intervention are evolving. Immediate use of transcranial Doppler ultrasonography and CT angiography has been promoted for the selection of patients with persistent clot who may benefit from thrombolytic therapy, specifically intra-arterial therapy. A combination of early diffusion-weighted imaging and perfusion-weighted imaging has been suggested as a potential tool to assess patients who may benefit from neuroprotectant agents or agents that restore blood flow such as thrombolytics. This combination of magnetic resonance sequences can help define the ischemic penumbra. Diffusion-weighted imaging of the brain provides a signal inversely proportional to the molecular diffusion of water molecules. With cytotoxic edema, influx of water from the extracellular to intracellular space occurs, and thus there is restriction in the diffusion of water molecules. This results in markedly increased signal intensity in the ischemic brain compared with the normal brain (Figure 3). Diffusion-weighted imaging is extremely sensitive for detecting acute infarction. Perfusion-weighted imaging measures relative cerebral blood flow. Thus, a perfusion defect that is larger than a diffusion defect suggests there is brain tissue at risk of infarction. These tools are being evaluated for use in selecting patients for early intervention.

Hemicraniectomy is a life-saving procedure performed in some patients with malignant middle cerebral artery infarctions. The premise is that with the substantial edema associated with these infarctions, allowing the brain to herniate outward prevents downward herniation and death. Although this procedure may prevent death, morbidity may be considerable, especially in elderly persons. The appropriate selection of patients and timing of surgery are unclear. Ongoing studies will address these issues.

Continued efforts toward early recognition of symptoms, appropriate selection of patients, treatments aimed at
MANAGEMENT OF ACUTE ISCHEMIC STROKE

Figure 3. Magnetic resonance image of the head within 4 hours after acute left hemiplegia. Left, Subtle increased T2 signal on the fluid-attenuated inversion recovery (FLAIR) imaging sequences (small arrows) in the right hemisphere. Large arrow shows a remote left hemispheric infarction. Right, Diffusion-weighted image reveals a large area of restricted water diffusion in the right cerebral hemisphere.

restoration of blood flow, and limitation of neuronal damage are necessary to reduce the morbidity and mortality from acute ischemic stroke. Evolving tools for the selection of patients with a substantial amount of viable tissue that is at risk of infarction (ie, a penumbra) will allow better treatment trials to assess the efficacy of neuroprotectant agents and agents or devices that restore blood flow.

CONCLUSION

Ongoing scientific research will provide new tools that will result in more therapeutic options to improve outcomes of patients with acute ischemic stroke. Presently, however, patients rely on medical practitioners having protocols in place to provide rapid assessment and treatment in the prehospital setting and after admission. Care must be viewed as a continuum with many steps occurring simultaneously and involving many specialists. Equally important is public awareness that “time is brain.” All efforts are for naught if people have a nihilistic attitude toward brain ischemia. Dispelling this attitude among patients and some medical practitioners is perhaps the most daunting task confronting those who care for patients with stroke.

REFERENCES

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The Symposium on Cerebrovascular Diseases will continue in the December issue.