ASA Scientific Statement

Guidelines for the Early Management of Patients With Ischemic Stroke

A Scientific Statement From the Stroke Council of the American Stroke Association

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In 1994, a panel appointed by the Stroke Council of the American Heart Association authored guidelines for the management of patients with acute ischemic stroke.[1] After the approval of the use of intravenous recombinant tissue plasminogen activator (rtPA) for treatment of acute ischemic stroke by the Food and Drug Administration, the guidelines were supplemented by a series of recommendations 2 years later.[2] Several promising interventions for the treatment of acute ischemic stroke have subsequently been tested in clinical trials, and other components of acute management have been evaluated since the previous guidelines were published. These new data have prompted the present revision of the prior guideline statement.

The goal of these guidelines is to provide updated recommendations that can be used by primary care physicians, emergency medicine physicians, neurologists, and other physicians who provide acute stroke care from admission to an emergency department through the first 24 to 48 hours of hospitalization by addressing the diagnosis and emergent treatment of the acute ischemic stroke in addition to the management of its acute and subacute neurological and medical complications.

Several groups have now written statements about management of stroke.[3–7] These statements also include recommendations about public educational programs, the organization of stroke resources, and other aspects of patient management. For example, the Brain Attack Coalition published recommendations for organizing stroke services in a community, and the recommendations of the American Heart Association Emergency Cardiovascular Care Committee provide an outline for emergency medical services.[6] The current panel elected not to duplicate these recent efforts.

Therapies to prevent recurrent stroke, also a component of acute management, are similar to prophylactic medical or surgical therapies used for patients with transient ischemic attacks and other high-risk patients. The reader is referred to relevant recent statements for additional information.[8,9]

In developing the present guidelines, the panel applied the Rules of Evidence[10] and formulation of strength of recommendations used by other American Heart Association (AHA) guidelines panels (Table 1). If the panel concluded that the data support or do not support the use of a particular intervention, appropriate recommendations to use or to not use a specific therapy were made. If data were not definitive, the panel made no specific recommendation. In some cases, supporting evidence based on clinical research is not available for a specific intervention, but nonetheless represents current customary practice. In such circumstances, the panel has provided a recommendation but indicated that the recommendation was based on customary practice.

In addition, for assessing the status of brain imaging tests, the panel used the rules of evidence adapted from the quality of evidence ratings for diagnostic tests developed by the American Academy of Neurology Therapeutics and Technology Subcommittee (Table 2).[11]

Immediate Diagnosis and Evaluation

The first goal of the initial diagnostic evaluation is to confirm that the patient's impairments are due to ischemic stroke and not due to another systemic or neurological illness, especially intracranial hemorrhage. Second, the evaluation helps determine advisability for acute treatment with thrombolytic agents. Third, diagnostic studies are carried out to screen for acute medical or neurological complications of stroke. Fi-

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TABLE 1. Levels of Evidence

Level of evidence	
Level I	Data from randomized trials with low false-positive and low false-negative errors
Level II	Data from randomized trials with high false-positive or high false-negative errors
Level III	Data from nonrandomized concurrent cohort studies
Level IV	Data from nonrandomized cohort studies using historical controls
Level V	Data from anecdotal case series
Strength of recommendation	
Grade A	Supported by level I evidence
Grade B	Supported by level II evidence
Grade C	Supported by level III, IV, or V evidence

nally, the evaluation provides historical data or other information that can be used to establish the vascular distribution of the stroke and to provide clues about its likely pathophysiology and etiology. These data are essential for further rational decisions about prevention of recurrent stroke.

History and Physical Examination

Obtaining a history and performing general medical and neurological examinations rapidly provide the foundation of the urgent evaluation. The clinical assessment is supplemented with selected diagnostic tests.

The physician must first determine the reason for the patient's neurological impairments. Stroke patients usually present with a history of sudden or rapid onset of focal neurological symptoms. Some patients may have a stepwise or gradual worsening or waxing and waning of symptoms. Most patients are alert, although patients with major hemispheric infarctions, basilar artery occlusion, or cerebellar strokes with edema causing brain stem compression can have a decreased level of consciousness. Headaches occur in approximately 25% of cases. Nausea and vomiting can occur with strokes in the brain stem or cerebellum.

TABLE 3. Common Patterns of Neurological Impairments Among Patients With Acute Ischemic Stroke

Left (dominant) hemisphere—major or branch cortical infarction:
Aphasia
Right hemiparesis
Right-sided sensory loss
Right-sided spatial neglect
Right homonymous hemianopia
Impaired right conjugate gaze
Right (nondominant) hemisphere—major or branch cortical infarction:
Left hemiparesis
Left-sided sensory loss
Left-sided spatial neglect
Left homonymous hemianopia
Impaired left conjugate gaze
Deep (subcortical) hemisphere or brain stem
Hemiparesis (pure motor stroke) or sensory loss (pure sensory stroke)
Dysarthria, including dysarthria-clumsy hand
Ataxic-hemiparesis
No abnormalities of cognition, language, or vision
Brain stem
Motor or sensory loss in all 4 limbs
Crossed signs (signs on same side of face and other side of body)
Dysconjugate gaze
Nystagmus
Ataxia
Dysarthria
Dysphagia
Cerebellum
Ipsilateral limb ataxia
Gait ataxia

Common patterns of neurological abnormalities among patients with ischemic stroke are listed in Table 3. In general, the diagnosis of stroke is straightforward. The accuracy (the degree to which a diagnosis agrees with a perceived "standard") of physicians' diagnosis of stroke generally is good. In one study, emergency department physicians correctly iden-

TABLE 2. Quality of Evidence Ratings for Radiological Diagnostic Tests

Level of evidence	
Class A	Evidence provided by a prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where test is applied in a blinded evaluation, and enabling the assessment of the appropriate tests of diagnostic accuracy.
Class B	Evidence provided by a prospective study of a narrow spectrum of persons with a suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by the "gold standard") is compared to a broad spectrum of controls, where test is applied evaluation and enabling the assessment of appropriate tests of diagnostic accuracy.
Class C	Evidence supplied by a retrospective study where either persons with an established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation.
Class D	Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls).
Strength of recommendation	
Grade I	Established as useful/predictive or not useful/predictive for the given condition in the specified population.
Grade II	Probably useful/predictive or not useful/predictive for the given condition in the specified population.
Grade III	Possibly useful/predictive or not useful/predictive for the given condition in the specified population.
Grade IV	Data are inadequate or conflicting. Given current knowledge, the test/predictor is unproven.

TABLE 4. Immediate Diagnostic Studies: Evaluation of a Patient With Suspected Acute Ischemic Stroke

All patients:
Brain CT (brain MRI could be considered at qualified centers)
Electrocardiogram
Blood glucose
Serum electrolytes
Renal function tests
Complete blood count, including platelet count
Prothrombin time/international normalized ratio
Activated partial thromboplastin time
Selected patients:
Hepatic function tests
Toxicology screen
Blood alcohol determination
Pregnancy test
Oxygen saturation or arterial blood gas tests (if hypoxia is suspected)
Chest radiography (if lung disease is suspected)
Lumbar puncture (if subarachnoid hemorrhage is suspected and CT is negative for blood)
Electroencephalogram (if seizures are suspected)

CT indicates computed tomography; MRI, magnetic resonance imaging.

tified 152 of 176 consecutive stroke patients (sensitivity, 86.4%) and 1818 of 1835 patients without stroke (specificity, 99.1%).[12] However, errors in clinical diagnosis can occur.

In one series of 821 consecutive patients initially diagnosed with stroke, 13% were later determined to have other conditions.[13] Several conditions mimic stroke. Frequent alternative diagnoses include unrecognized seizures, confusional states, syncope, toxic or metabolic disorders, including hypoglycemia, brain tumors, and subdural hematoma. These stroke mimics are commonly, but not always, associated with global rather than focal neurological symptoms and are usually readily detected with standard laboratory tests (Table 4).

Differentiation of ischemic or hemorrhagic stroke is especially important, because of the marked difference in the management of these conditions. Some studies show that features on the history and physical examination can be used to help distinguish hemorrhagic from ischemic strokes.[14–16] For example, one study found that the chance of intracranial hemorrhage was more than doubled with the presence of at least one of the following findings: coma on arrival, vomiting, severe headache, current warfarin therapy, systolic blood pressure >220 mm Hg, or glucose level >170 mg/dL in a nondiabetic patient.[15] The absence of these features decreases the odds of hemorrhage by approximately one third. Scales to differentiate ischemic or hemorrhagic stroke have been developed based on these types of studies. However, diagnostic errors based solely on clinical features still occur and the level of accuracy is insufficient to guide treatment decisions.[17] Because clinical findings overlap, a brain imaging study is mandatory to distinguish ischemic stroke from hemorrhage or other structural brain lesions that may imitate stroke.[18]

Anatomic localization based on clinical features can help determine the vascular distribution of the ischemic lesion. A stroke in the distribution of the middle cerebral artery can result from cardioembolism, carotid occlusion, arterial dissection, or local arterial thrombosis. Small subcortical hemisphere or brain stem infarctions can occur through a variety of mechanisms and are not necessarily due to local small-vessel disease.[19]

Specific features of the history are important when considering treatment with thrombolytic agents. Among these, the time of symptom onset is most critical. For the purposes of treatment, the onset is assumed as the time that the patient was last known to be symptom-free. Because ischemic stroke is often painless, most patients are not awakened by its occurrence. Thus, for a patient with symptoms of stroke on awakening, the time of onset is assumed to be the time the patient was last known to be symptom-free before retiring. If a patient had mild impairments but then had worsening over the subsequent hours, the time the first symptom began is assumed to be the time of onset. In contrast, if a patient has symptoms that completely resolved (TIA) and then has a second event, the time of onset of the new symptoms is used. Other important information includes a report of any recent medical or neurological events, including trauma, hemorrhage, surgery, myocardial infarction, or previous stroke. Patients also should be queried about their use of medications, especially oral anticoagulants and antiplatelet agents. If the patient is confused, aphasic, or unconscious, historical information might be available from family, friends, or emergency medical service personnel. A coworker, shop owner, apartment manager, or other observer might be reached by phone. They might be able to provide information about the time of onset of stroke.

Particular attention should be paid to the patient's vital signs. Issues related to the importance of disorders of breathing, arrhythmias, hypertension, or fever and their treatment are discussed subsequently. However, the vital signs also provide clues about the cause of stroke and prognosis. An irregularly irregular heart rhythm might suggest atrial fibrillation. Severe elevations of blood pressure might point to hypertensive encephalopathy or increase the likelihood of a primary intracranial hemorrhage. Fever can point toward an infectious cause of stroke or it may be secondary to an acute complication of the neurological illness. In addition, the general examination includes an assessment for signs of trauma and a cardiovascular evaluation. Specific contraindications for treatment with thrombolytic agents such as clinical evidence of active bleeding should also be sought.

The severity of stroke, based on the findings detected by neurological examination, is a strong indicator of prognosis. Several reliable and well-validated scoring systems have been developed; each has strengths and limitations.[20,21] Among these scales, the National Institutes of Health Stroke Scale (NIHSS) has come into widespread use in the United States (Table 5).[22,23] The initial NIHSS score provides important prognostic information.[17,24,25] Approximately 60% to 70% of patients with an acute ischemic stroke and a baseline NIHSS score <10 will have a favorable outcome after 1 year as compared with only 4% to 16% of those with a score >20.[25] The NIHSS score can also help identify those patients at greatest risk for intracranial hemorrhage associated with

TABLE 5. National Institutes of Health Stroke Scale

Tested Item	Title	Responses and Scores
1A	Level of consciousness	0—alert
		1—drowsy
		2—obtunded
		3—coma/unresponsive
1B	Orientation questions (two)	0—answers both correctly
		1—answers one correctly
		2—answers neither correctly
1C	Response to commands (two)	0—performs both tasks correctly
		1—performs one task correctly
		2—performs neither
2	Gaze	0—normal horizontal movements
		1—partial gaze palsy
		2—complete gaze palsy
3	Visual fields	0—no visual field defect
		1—partial hemianopia
		2—complete hemianopia
		3—bilateral hemianopia
4	Facial movement	0—normal
		1—minor facial weakness
		2—partial facial weakness
		3—complete unilateral palsy
5	Motor function (arm)	0—no drift
	a. left	1—drift before 5 seconds
	b. right	2—falls before 10 seconds
		3—no effort against gravity
		4—no movement
6	Motor function (leg)	0—no drift
	a. left	1—drift before 5 seconds
	b. right	2—falls before 5 seconds
		3—no effort against gravity
		4—no movement
7	Limb ataxia	0—no ataxia
		1—ataxia in one limb
		2—ataxia in two limbs
8	Sensory	0—no sensory loss
		1—mild sensory loss
		2—severe sensory loss
9	Language	0—normal
		1—mild aphasia
		2—severe aphasia
		3—mute or global aphasia
10	Articulation	0—normal
		1—mild dysarthria
		2—severe dysarthria
11	Extinction or inattention	0—absent
		1—mild (loss 1 sensory modality)
		2—severe (loss 2 modalities)

There are 15 items in this version of the National Institutes of Health Stroke Scale (NIHSS).[36] This version contains a rating of the unaffected (contralateral) arm and leg and emphasizes the recording of observations without neuroanatomic interpretation. The actual form for recording the data contains detailed instructions for the use of the scale. The complete scale with instructions can be obtained from the National Institute of Neurological Disorders and Stroke.

thrombolytic treatment. In the NINDS trial of rtPA, those with a score of 20 or greater on the NIHSS had a 17% chance of intracranial hemorrhage, whereas the risk of bleeding was only 3% among those with a score <10.[26]

Brain Imaging

As therapeutic options evolve, brain imaging strategies are playing an increasingly important role in patients' initial evaluation. Brain imaging findings, including the size, location, and vascular distribution of the infarction as well as the presence of bleeding, affect both acute and long-term treatment decisions. In addition, information about the possible degree of reversibility of ischemic injury, the status of intracranial vessels, and cerebral hemodynamic status can be obtained from modern imaging studies.[27] Neuroimaging tests might improve selection of patients who could be treated with thrombolytic agents by identifying those with regions of salvageable brain tissue, a low risk for hemorrhagic transformation, or occlusions of large arteries that might or might not be amenable to therapy.

At present, the usual brain imaging test is computed tomography (CT). The diagnostic yield and clinical utility of other newer neuroimaging procedures must be weighed against the time cost of acquiring the data, as well as the availability and financial costs of these tests. At present, the clinical utility of these techniques in the emergent evaluation of patients with ischemic stroke is not fully demonstrated and additional research is required.[28] As a result, there is a general agreement that the performance of these tests should not delay treatment with intravenous rtPA (grade C).[29]

Noncontrast-Enhanced Computed Tomographic Scan of the Brain

Emergent, noncontrast-enhanced CT of the brain is currently the most commonly employed initial neuroimaging study. There is a uniform agreement that CT accurately identifies most cases of intracranial hemorrhage and helps discriminate nonvascular causes of neurological symptoms, eg, brain tumor (grade B).[30] The prior guidelines recommended that CT be the primary diagnostic brain imaging study for evaluation of patients with suspected stroke.[1,31] Although no randomized trials have tested the utility of CT, most trials testing interventions in acute stroke, including those that involved the administration of rtPA, required the test prior to treatment. While CT is the "gold standard" to which other brain imaging studies are compared, it is relatively insensitive in detecting acute and small cortical or subcortical infarctions, especially in the posterior fossa. In most cases, the use of a contrast infusion does not provide additional information and is not necessary unless it is required for CT angiography (and more recently CT perfusion) or there is a concern about a brain tumor or infectious process.

With the advent of rtPA treatment, interest has grown in using CT to identify subtle, early signs of ischemic brain injury (early infarct signs) or arterial occlusion that might affect decisions about treatment. These findings include the hyperdense middle cerebral artery sign that is indicative of a thrombus or embolus in the first portion of the middle cerebral artery. In addition, the loss of the gray-white differ-

entiation in the cortical ribbon (particularly at the lateral margins of the insula) or the lentiform nucleus, and sulcal effacement appear to be important.[32] These signs may be detected within 6 hours of onset of symptoms in up to 82% of patients with ischemia in the territory of the middle cerebral artery (class C).[33] The presence of these signs is associated with poor outcomes (class A).[34,35]

In addition, the presence of widespread signs of early infarction is correlated with a higher risk of hemorrhagic transformation following treatment with thrombolytic agents (level I). In one trial of intravenous rtPA administered within 3 hours of symptom onset, CT evidence of early edema or mass effect was accompanied by an 8-fold increase in the risk of symptomatic hemorrhage.[36] A second report from this same trial analyzed outcome in patients with evidence of both mild and major early infarction, including loss of gray-white matter distinction, hypodensity or hypoattenuation, and sulcal effacement or compression of CSF spaces (focal and/or diffuse brain swelling). In this second analysis, early infarct signs involving more than one third of the territory of the middle cerebral artery were not independently associated with increased risk of adverse outcome after rtPA treatment, and as a group these patients still benefited from therapy.[37] In a European trial in which thrombolytic therapy was administered within 6 hours of symptom onset, patients estimated to have involvement of more than one third of the territory of the middle cerebral artery had an increased risk of intracerebral hemorrhage, whereas those with less involvement benefited the most from thrombolytic treatment.[35,38] Unfortunately, the physician's ability to reliably and reproducibly recognize the early CT changes is variable (class B).[39–42] The accuracy in detecting ischemic areas involving more than one third of the territory of the middle cerebral artery is approximately 70% to 80%.[43] Use of scoring systems for early CT changes may improve identification of cerebral ischemia and might provide valuable prognostic information, but are not validated for outcome.[44]

For patients who are candidates for treatment with rtPA, the goal is to complete the CT examination within 25 minutes of arrival to the emergency department with the study interpreted within an additional 20 minutes (door to interpretation time of 45 minutes).[45]

A subsequent CT often is obtained if the patient worsens neurologically and may be especially helpful in identifying hemorrhagic transformation following administration of rtPA.[2,36]

Multimodal MRI

The standard MRI sequences (T1-weighted, T2-weighted, and proton density) are relatively insensitive to the changes of acute ischemia within the first hours after onset of stroke. These sequences will show abnormalities in <50% of patients (class A).[46] Because of early changes of decreased water diffusion within ischemic brain tissue, diffusion-weighted imaging (DWI) allows visualization of ischemic regions within minutes of onset of symptoms.[47,48] Perfusion-weighted imaging (PWI), usually performed with the rapid administration of an intravenous paramagnetic contrast agent, provides relative measures of cerebral hemodynamic status.

Several studies provide preliminary data about the potential clinical utility of DWI in the evaluation of patients with suspected stroke. It allows early identification of the lesion size, site, and age. It can detect relatively small cortical or subcortical lesions, including those in the brain stem or cerebellum, areas often poorly visualized with standard CT scan techniques. It provides information about the involved vascular territory and has a high sensitivity (88% to 100%) and specificity (95% to 100%) for detecting acute ischemia, even at very early time points (class B).[49–56] The initial volumes of the lesions seen on DWI and PWI correlate well with the final size of the stroke found on follow-up brain imaging.[52,57,58] In addition, these lesion volumes correlate well with both severity of stroke as rated by clinical scales and outcomes. These findings suggest that DWI might provide helpful early prognostic information (class C).[50,57–59]

The ischemic penumbra has been characterized on MRI as regions of perfusion change without a corresponding diffusion abnormality (diffusion-perfusion mismatch). However, a recent study indicates that at least in some circumstances the initial diffusion abnormality might be reversible.[60] Sequential MRI studies performed in patients being treated with thrombolytic therapy have shown that the technique can detect diffusion and perfusion thresholds for irreversible ischemia and visualize salvage of penumbral tissue with smaller volumes of infarction among those patients who had successful recanalization (class D).[61,62]

Efforts are under way to develop specific MRI criteria that could identify regions of irreversible infarction from potentially reversible ischemia as well as MRI signatures that portend a high risk of hemorrhagic complications following thrombolytic therapy.[62–68] For example, the addition of MR spectroscopy might improve selection of patients for treatment, but this procedure will need considerable testing before it is used in patient care.[69] These diagnostic studies offer the possibility of identifying patients who might be successfully treated with rtPA or other agents outside the current time-based therapeutic windows.[70,71]

An important limitation of the use of MRI is the potential difficulty in reliably identifying acute intracranial hemorrhage. However, several recent reports suggest that intraparenchymal blood can be detected very soon after the ictus by using gradient-recalled echo (GRE) MRI sequences or echo-planar susceptibility-weighted MRI (class D).[72,73] Additional research is needed to determine the utility of MRI in place of CT for identifying hemorrhage among patients with suspected stroke. Other limitations of MRI in the acute setting include cost, relatively limited availability of the test, and patient contraindications such as claustrophobia, cardiac pacemakers, or metal implants.

Other Brain Perfusion Techniques

Oxygen-15 positron-emission tomography (PET) can quantify regional brain perfusion and oxygen consumption. PET provided the first evidence of a penumbra in stroke patients by identifying regions of decreased cerebral blood flow (CBF) and increased oxygen extraction fraction (OEF) with relatively preserved oxygen metabolism (ie, misery perfusion; class D).[74–76] PET ligands that specifically identify

penumbral regions also show promise.[77,78] However, logistical and pragmatic considerations limit the application of PET in the setting of acute stroke.

Xenon-enhanced CT provides a quantitative measurement of CBF by employing inhaled xenon. Perfusion CT measures CBF by mapping the appearance of a bolus of iodinated contrast. Both can be used to screen for thresholds of reversible or irreversible ischemia among patients with acute stroke.[79–81] These techniques have the advantages of acquiring data relatively rapidly and can be performed with conventional CT equipment. The techniques of CT perfusion imaging discussed are being developed using the more accessible CT scanner to track a bolus of x-ray contrast through brain tissue. CT perfusion is more readily quantitative as compared with MR and can be completed within 3 to 5 minutes following the standard noncontrast CT scan.[82,83] Further studies are needed to determine the clinical utility of these methods.

Single photon-emission computed tomography (SPECT) is minimally invasive and measures relative CBF. SPECT might be able to identify thresholds for reversible ischemia and could be helpful in predicting outcomes or monitoring responses to treatment.[84–86] Limitations include lack of availability, expense, and the difficulty associated with tracer preparation.

Cardiac Tests

A clinical cardiovascular examination and a 12-lead ECG should be performed in all stroke patients (Table 4). Cardiac abnormalities are prevalent among patients with stroke and the patient can have an acute cardiac condition that mandates urgent treatment. For example, acute myocardial infarction can lead to stroke, and acute stroke can lead to myocardial ischemia.[87–91] In addition, cardiac arrhythmias can occur among patients with acute ischemic stroke.[87,88,92,93] Atrial fibrillation, an important potential cause of stroke, can be detected in the acute setting.[94] Cardiac monitoring often can be conducted after stroke to screen for serious cardiac arrhythmias.[95]

Blood Tests

Several blood tests should be routinely performed to identify systemic conditions that may mimic or cause stroke, or that may influence choices for acute treatment. These include blood glucose, electrolytes, complete blood count with platelet count, prothrombin time, activated partial thromboplastin time, and renal and hepatic function studies (Table 4). Because time is critical, therapy involving the use of rtPA in particular should not be delayed while waiting for the results of the prothrombin time or activated partial thromboplastin time unless there is clinical suspicion of a bleeding abnormality or unless the patient has been taking warfarin and heparin or their use is uncertain.

Hypoglycemia may mimic the symptoms and signs of stroke, and hyperglycemia is associated with unfavorable outcomes. Determination of the platelet count and, in patients taking warfarin, the prothrombin time/international normalized ratio (INR) are required prior to administration of thrombolytic agents.[2] A toxicology screen, blood alcohol level, and pregnancy test should be obtained if the physician is uncertain about the patient's history and/or suggested by findings on examination. Arterial blood gas levels should be obtained if hypoxia is suspected.

Chest radiography was previously recommended for the evaluation of all patients with acute ischemic stroke.[1] A subsequent study found that clinical management was altered in only 3.8% of patients having routine chest radiographs at the time of admission for stroke,[96] suggesting that the test is of little use in the absence of an appropriate clinical indication (grade B).

Examination of the cerebrospinal fluid is indicated if the patient has symptoms suggestive of subarachnoid hemorrhage and a CT does not demonstrate blood. Fortunately, the clinical features of subarachnoid hemorrhage differ considerably from those of ischemic stroke. Electroencephalography may be helpful for evaluating patients in whom seizures are suspected as the cause of the neurological deficits or in whom seizures could have been a complication of the stroke.[97] Seizure is a relative contraindication for the use of rtPA in acute ischemic stroke.

Vascular Imaging

A wide variety of imaging techniques have been used to assess the status of the large cervicocephalic vessels. Choices depend on availability, individual patient characteristics, and the type of information being sought. Transcranial Doppler ultrasonography, magnetic resonance angiography, CT angiography, and catheter angiography have been used to detect intracranial or extracranial arterial occlusions.[98] Transcranial Doppler ultrasonography and angiography have been employed to monitor the effects of thrombolytic therapy over time and can help determine prognosis.[99,100] The necessity of obtaining these tests on an urgent basis has not been established.

A variety of ancillary tests are available to help clinicians reach accurate pathophysiological and etiological stroke diagnosis and provide information that can be critical for effective prevention of recurrent stroke.[9,101] Vascular imaging is a key component of the evaluation. The selection of tests needs to be tailored to the individual patient and clinical setting.

Recommendations

The evaluation of patients with acute ischemic stroke should be performed immediately. The medical history and the general and neurological examinations form the cornerstone of emergent evaluation of patients with suspected ischemic stroke. The clinical evaluation provides clues about the cause of the neurological symptoms and screens for potential contraindications for treatment with thrombolytic agents (grade I).

Patients generally require a limited number of diagnostic tests as part of the emergent evaluation (Table 4) (grade I). Because time is of the essence in acute stroke care, institutions should have these diagnostic studies available on a 24-h/day and 7-d/week basis. If the tests are not readily available, and if time and the patient's condition permit, the patient's transfer to another medical facility equipped to do so should be considered.

Brain imaging is required to guide acute intervention (grade A). For most cases and at most institutions, CT remains the most important brain imaging test. A physician skilled in assessing CT studies should be available to interpret the scan (grade B). The study should be formally evaluated for evidence of early signs of infarction. The presence of early infarct signs on CT (even if they involve greater than one third of the middle cerebral artery territory) in patients with a well established stroke onset time of <3 hours does not preclude treatment with IV rtPA or suggest an unfavorable response to therapy (grade I).[37,102] There are insufficient data to make a strong recommendation regarding the use of IV rtPA treatment in the rare patient whose CT reveals extensive (greater than one third of the middle cerebral artery territory) and clearly identifiable hypodensity in patients with a well-established stroke onset time of <3 hours. While differences of opinion exist, some experts would recommend that thrombolytic therapy not be administered in these patients because they suspect that the risk/benefit ratio is unlikely to be favorable.[102] For patients beyond 3 hours of symptom onset, intravenous tissue plasminogen activator is not of proven benefit and is best contemplated only in the setting of a clinical trial, regardless of CT findings.[102] In patients seen within <6 hours of onset, CT currently may be preferred as the first imaging study because MRI detection of acute intracerebral hemorrhage has not been fully validated (grade A). While there is general agreement that PWI and DWI brain imaging studies might be helpful in diagnosis and management of patients with acute stroke, there are insufficient data at this time to recommend these tests for most patients. There is general agreement that their use, outside of clinical research programs, must not significantly delay treatment of a patient who is otherwise eligible for intravenous rtPA treatment (grade B).

Other diagnostic studies, including imaging of intracranial and extracranial arteries and the heart, can be obtained after the patient receives initial treatment. If intra-arterial thrombolysis becomes a standard treatment approach, vascular imaging could become a key component of the initial evaluation.

General Supportive Care and Treatment of Acute Complications

Airway, Ventilatory Support, and Supplemental Oxygen

Maintaining adequate tissue oxygenation is of great importance during periods of acute cerebral ischemia in order to prevent hypoxia and potential worsening of the neurological injury. The most common causes are partial airway obstruction, hypoventilation, aspiration pneumonia, or atelectasis. Patients with a decreased level of consciousness or brain stem stroke have an increased risk of airway compromise due to impaired oropharyngeal mobility and loss of protective reflexes.[103,104] In general, the prognosis of patients who need endotracheal intubation is very poor; approximately 50% of these patients die within 30 days of stroke.[105,106]

Elective intubation might help in the management of patients with severely increased levels of intracranial pressure or who have severe brain edema.[105] Although no clinical trial has tested the utility of endotracheal intubation in this situation, there is general agreement that an endotracheal tube should be placed if the airway is threatened (level V).[103,107] Following stroke, some patients develop Cheyne-Stokes respiration with decreases in oxygen saturation that can be readily reversed with oxygen supplementation.[108] The results of a recent quasirandomized controlled trial do not support the use of supplemental oxygen therapy at 3 L/min for most patients with acute ischemic stroke (level V).[109] However, patients with acute stroke should be monitored with pulse oximetry with a target oxygen saturation level of ≥95% (level V).[110] Supplemental oxygen should be administered if there is evidence of hypoxia by blood gas determination, desaturation detected by pulse oximetry, or there are other specific reasons. Hyperbaric oxygen therapy might be useful for treatment of selected patients with ischemic neurological symptoms secondary to air embolism or Caisson disease (level V).[111] Data are lacking to support its general use in patients with acute ischemic stroke (levels III and IV).[112–114]

Fever

Increased body temperature in the setting of acute ischemic stroke has been associated with poor neurological outcome, possibly due to increased metabolic demands, enhanced release of neurotransmitters, and increased free radical production.[115–118] A recent meta-analysis suggested that fever after stroke onset is associated with a marked increase in morbidity and mortality (level I).[119] The source of any fever following stroke should be ascertained, and the fever should be treated with antipyretic agents.[3,119–121] Lowering an acutely elevated body temperature might improve the prognosis of patients with severe events.[122] Measures can include antipyretic medications and cooling devices. Hypothermia has been shown to be neuroprotective after experimental global and focal hypoxic brain injury (levels II to V).[123] Small clinical studies have addressed the feasibility of inducing modest hypothermia for treatment of patients with acute ischemic stroke; however, the efficacy of this approach has been established (levels III and IV).[124–126]

Cardiac Rhythm

Myocardial infarction and cardiac arrhythmias are potential complications of acute ischemic stroke.[127] Patients with infarctions in the right hemisphere may have a high risk of arrhythmias, presumably due to disturbances in sympathetic and parasympathetic nervous system function (level V).[88,128–131] Electrocardiographic changes secondary to stroke include ST segment depression, QT interval prolongation, inverted T waves, and prominent U waves.[132–134] Acute or subacute myocardial infarction is a potential complication related to a release of catecholamines.[134,135] The most common arrhythmia detected in the setting of stroke is atrial fibrillation. While life-threatening cardiac arrhythmias are relatively uncommon, sudden death can occur.[87,136]

Arterial Hypertension

Despite the prevalence of arterial hypertension following stroke, its optimal management has not been established.[137–142] An

TABLE 6. Approach to Elevated Blood Pressure in Acute Ischemic Stroke

Blood Pressure Level (mm Hg)	Treatment
A. Not eligible for thrombolytic therapy	
Systolic <220 OR Diastolic <120	Observe unless other end-organ involvement, eg, aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy Treat other symptoms of stroke such as headache, pain, agitation, nausea, and vomiting Treat other acute complications of stroke, including hypoxia, increased intracranial pressure, seizures, or hypoglycemia
Systolic >220 OR Diastolic <121–140	Labetalol 10–20 mg IV over 1–2 min May repeat or double every 10 min (maximum dose 300 mg) or Nicardipine 5 mg/hr IV infusion as initial dose; titrate to desired effect by increasing 2.5 mg/hr every 5 min to maximum of 15 mg/hr Aim for a 10% to 15% reduction of blood pressure
Diastolic >140	Nitroprusside 0.5 μg/kg/min IV infusion as initial dose with continuous blood pressure monitoring Aim for a 10% to 15% reduction of blood pressure
B. Eligible for thrombolytic therapy	
Pretreatment	
Systolic >185 OR Diastolic >110	Labetalol 10–20 mg IV over 1–2 min May repeat × 1 OR Nitropaste 1–2 inches If blood pressure is not reduced and maintained at desired levels (systolic ≤185 and diastolic ≤110), do not administer rtPA
During and after treatment	
1. Monitor BP	Check BP every 15 min for 2 hours, then every 30 min for 6 hours, and then every hour for 16 hours
2. Diastolic >140	Sodium nitroprusside 0.5 μg/kg/min IV infusion as initial dose and titrate to desired blood pressure
3. Systolic >230 OR Diastolic 121–140	Labetalol 10 mg IV over 1–2 min May repeat or double labetalol every 10 min to a maximum dose of 300 mg or give the initial labetalol bolus and then start a labetalol drip at 2 to 8 mg/min or Nicardipine 5 mg/hr IV infusion as initial dose; Titrate to desired effect by increasing 2.5 mg/hr every 5 min to maximum of 15 mg/hr. If BP is not controlled by labetalol, consider sodium nitroprusside
4. Systolic 180–230 OR Diastolic 105–120	Labetalol 10 mg IV over 1–2 min May repeat or double labetalol every 10 to 20 min to a maximum dose of 300 mg or give the initial labetalol bolus and then start a labetalol drip at 2 to 8 mg/min

elevated blood pressure can result from the stress of the stroke, a full bladder, pain, preexisting hypertension, a physiological response to hypoxia, or increased intracranial pressure. Theoretical reasons to lower the blood pressure include reducing the formation of brain edema, lessening the risk of hemorrhagic transformation of the infarction, preventing further vascular damage, and forestalling early recurrent stroke. However, aggressive treatment of elevated blood pressure could be detrimental because of secondary reduction of perfusion in the area of ischemia, which could expand the size of the infarction.[143]

Because of these conflicting issues and the lack of unambiguous data, the appropriate treatment of the blood pressure in the setting of acute ischemic stroke remains controversial. In a majority of patients, a decline in blood pressure without any specific medical treatment will occur.[60,140] The blood pressure often falls spontaneously when the patient is moved to a quiet room, the bladder is emptied, pain is controlled, and the patient is allowed to rest. In addition, treatment of increased intracranial pressure can result in a decline in arterial blood pressure.

Although there are no definitive data from controlled clinical trials, in the absence of other organ dysfunction necessitating rapid reduction in blood pressure, or in the setting of thrombolytic therapy, there is little scientific basis and no clinically proven benefit for lowering blood pressure among patients with acute ischemic stroke.[143] In most circumstances, the blood pressure should generally not be lowered. Situations that might require urgent antihypertensive therapy include hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, or acute myocardial infarction.[144]

Although severe hypertension might be considered as an indication for treatment, there are no data to define the levels of arterial hypertension that mandate emergent management.[143] The consensus is that antihypertensive agents should be withheld unless the diastolic blood pressure is >120 mm Hg or unless the systolic blood pressure is >220 mm Hg (level V) (Table 6).

When treatment is indicated, lowering the blood pressure should be done cautiously. Parenteral agents such as labetalol that are easily titrated and that have minimal vasodilatory effects on cerebral blood vessels are preferred. In some cases, an intravenous infusion of sodium nitroprusside may be necessary for adequate blood pressure control. Patients also can be treated with oral agents, such as captopril or nicardipine. Sublingual use of a calcium antagonist, such as nifedipine, should be avoided because of rapid absorption and a secondary precipitous decline in blood pressure (level V).[145]

Among patients who are candidates for treatment with thrombolytic agents, careful management of blood pressure is critical before and during the administration of rtPA and during the ensuing 24 hours[137] because excessively high blood pressure is associated with parenchymal hemorrhage.[26,37,38] Thrombolytic therapy is not given to patients who have a systolic blood pressure >185 mm Hg or a diastolic blood pressure >110 mm Hg at the time of treatment (Table 6).

Arterial Hypotension

Persistent arterial hypotension is rare in patients with acute ischemic stroke, but if present, the cause should be sought.[146] Causes include aortic dissection, volume depletion, and decreased cardiac output secondary to myocardial ischemia or cardiac arrhythmias. Correction of hypovolemia and optimization of cardiac output are important priorities during the first hours after stroke. Treatment includes volume replacement with normal saline and correction of arrhythmias—such as slowing ventricular response to rapid atrial fibrillation. If these measures are ineffective, vasopressor agents such as dopamine may be used. Trials have tested the utility of volume expansion and drug-induced hypertension for treatment of acute ischemic stroke and are discussed later in this report.

Hypoglycemia

Because hypoglycemia can cause focal neurological signs that mimic stroke and because severe hypoglycemia can itself lead to brain injury, prompt measurement of the serum glucose concentration and rapid correction of a low serum glucose concentration is important. A finger stick can be done to rapidly measure glucose levels.

Diabetes mellitus is an important risk factor for ischemic vascular disease. The severity of strokes may be increased among diabetic patients. In addition, several clinical studies have associated hyperglycemia with poor outcomes.[147,148] However, hyperglycemia can be a consequence of a severe stroke and thus, the elevated blood sugar can be a marker of a serious vascular event.[149] The detrimental effects of hyperglycemia are not clearly understood but can include increasing tissue acidosis secondary to anaerobic glycolysis and increased blood-brain barrier permeability.

Still, there is uncertainty whether hyperglycemia worsens stroke outcomes.[150] For example, outcome after stroke is not worse among patients with elevated levels of glycosylated hemoglobin as compared with persons with normal levels.[151] There are no data evaluating the impact on outcomes of maintaining euglycemia during the period of acute stroke. A small randomized trial showed that a glucose and an insulin infusion could be safely given to patients with mild to moderate hyperglycemia.[152] However, the efficacy of this approach is not established (level II). A randomized trial testing management of blood sugar levels in this setting is currently in progress.

Conclusions

As in other serious, acute medical conditions, urgent management of patients with acute ischemic stroke should begin with the assessment and treatment of the airway, breathing, circulation, temperature, and glucose concentration.

Recommendations

There is general agreement to strongly recommend airway support and ventilatory assistance in the treatment of patients with acute stroke who have depressed levels of consciousness or airway compromise (grade C).

There is general agreement to strongly recommend supplemental oxygen to hypoxic patients (grade C). Nonhypoxic patients with acute ischemic stroke do not need supplemental oxygen therapy (grade B). There are insufficient data about the utility of hyperbaric oxygen to recommend this therapy for most patients with stroke.

There is general agreement to recommend treatment of sources of fever and the use of antipyretics to control elevated temperatures in the setting of acute stroke (grade B). There are insufficient data about the usefulness of induced hypothermia to recommend this treatment.

There is general agreement to recommend cardiac monitoring during the initial evaluation of patients with acute ischemic stroke to detect atrial fibrillation and potentially life-threatening cardiac arrhythmias (grade C).

There is general agreement to recommend a cautious approach toward the treatment of arterial hypertension in the acute setting (grade C). Although the level of arterial hypertension that mandates treatment is not known, there is consensus that antihypertensive agents should be avoided unless the systolic blood pressure is >220 mm Hg or the diastolic blood pressure is >120 mm Hg (grade C). Agents that have a short duration of action and little effect on cerebral blood vessels are preferred (grade C). Because some patients can have neurological worsening with rapid lowering of the blood pressure, the use of sublingual nifedipine and other antihypertensive agents causing precipitous reductions in blood pressure should be avoided (grade C).

Patients with elevated blood pressure and who are otherwise eligible for treatment with rtPA can have their blood pressures lowered cautiously so that their systolic blood pressure is ≤185 mm Hg and their diastolic blood pressure is ≤110 mm Hg (grade C). Because the maximum interval from stroke onset until treatment of stroke is short, most patients with sustained hypertension above recommended levels cannot be treated with intravenous rtPA.

There is general agreement to recommend control of hypoglycemia or hyperglycemia following stroke. Until further data become available, a judicious approach to management of hyperglycemia is recommended. By consensus, a reasonable goal would be to lower markedly elevated glucose levels to <300 mg/dL (<16.63 mmol/L) (grade C).[120] Management of an elevated blood glucose level following stroke should be similar to that given to treatment of other acutely ill patients who have hyperglycemia. Blood glucose concentrations should be monitored. Intravenous administration of glucose-containing solutions should be avoided. However, fluids and insulin should be administered if the blood glucose concentrations are markedly elevated. Overly aggressive therapy should be avoided because it can result in fluid shifts,

electrolyte abnormalities, and hypoglycemia, all of which can be detrimental to the brain.

Treatment of the Acute Ischemic Stroke

Measures to Restore or Improve Perfusion

Because most strokes are due to thromboembolic occlusion of an intracranial artery, restoration or improvement of perfusion to the ischemic area is a key therapeutic strategy. The concept of the existence of an ischemic penumbra is fundamental to the current approach to treatment of ischemic stroke: although a core of infarcted tissue might not be salvageable, adjacent dysfunctional tissue might be saved if the circulation is restored and metabolism is normalized. A number of strategies have been employed to improve blood flow to the ischemic region. Because of the dynamic consequences of acute stroke, the interval from onset of symptoms until treatment appears to be critical for success of any therapy. Thus, restoration of blood flow needs to be achieved as quickly as possible. To date, only intravenous administration of rtPA has been proven to be effective.

Intravenous Thrombolysis With rtPA

Five phase III trials of intravenous rtPA have been reported.[35,36,153,155] Approval of this treatment by the FDA in 1996 was based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study, in which 624 patients with ischemic stroke were treated with placebo or rtPA (0.9 mg/kg IV, maximum 90 mg) within 3 hours of symptom onset with approximately one half treated within 90 minutes.[36] The study was conducted in two parts. In part I, the primary endpoint was neurological improvement at 24 hours as indicated by complete neurological recovery or an improvement of 4 points or more on the NIH Stroke Scale. In part II, the pivotal efficacy trial, the primary end point was a global odds ratio for a favorable outcome defined as complete or nearly complete neurological recovery at 3 months after stroke. Favorable outcomes were achieved in 31% to 50% of patients treated with rtPA as compared with 20% to 38% of patients given placebo. The benefit was similar at 1 year after stroke (level I).[25,36] The major risk of treatment was symptomatic brain hemorrhage, which occurred in 6.4% of patients treated with rtPA and 0.6% of patients given placebo (level I). However, the mortality rate in the two treatment groups was similar at 3 months (17% versus 20%) and 1 year (24% versus 28%).[25,36] While the presence of edema or mass effect on baseline CT were associated with higher risk of symptomatic intracranial hemorrhage, follow-up study demonstrated that presence of early ischemic changes on CT were not associated with adverse outcome.[36,37] The likelihood of favorable outcome also was affected by the severity of deficits and the patient's age. Those with mild-to-moderate strokes (NIHSS score <20) and those persons younger than 75 had the greatest possibility for a favorable response to treatment.[36,156] Although the chances of a complete or nearly complete recovery among patients with severe stroke (NIHSS score ≥ 20) improved with treatment, overall success in this group of critically ill patients was low.[156]

In two large trials, the European Cooperative Acute Stroke Study (ECASS) and ECASS-II, intravenous rtPA was not more effective than placebo in improving neurological outcomes at 3 months after stroke (level I).[36,154] The dosage of rtPA used in ECASS was marginally higher than that used in the NINDS trials and patients were treated up to 6 hours after stroke. Patients with CT evidence of low attenuation (edema and/or ischemia) involving more than one third of the territory of the middle cerebral artery were less likely to have a good outcome after treatment with rtPA than did those who received placebo.[157] However, the numbers were small and the difference did not reach statistical significance (level II). A post-hoc analysis concluded that the patients treated within 3 hours appeared to benefit from rtPA.[158]

In the ECASS-II trial, 800 patients were assigned randomly to treatment with either rtPA (0.9 mg/kg IV) or placebo (level I).[153] More than one third of the patients in each group made an excellent recovery, and no significant benefit was noted from treatment. A post-hoc analysis of ECASS-II showed that the combination of death or dependency was less among the patients treated with rtPA (level II). The trial included vigorous methodology to avoid recruitment of patients with CT changes consistent with multilobar infarctions.[159] As a result, the severity of strokes among the patients admitted in ECASS-II was less than in the other studies, and the generally more favorable prognosis among patients may have reduced the likelihood of detecting a therapeutic effect. Still, the rate of symptomatic intracranial hemorrhage was increased with rtPA treatment (8.8% versus 3.4%) (level I). An American trial tested rtPA up to 5 hours following stroke.[154] Results were similar in that approximately one third of the patients in both treatment groups made an excellent recovery. The rate of symptomatic hemorrhage was higher in the treatment group (7% versus 1.1%). Another American trial found no benefit from rtPA when given up to 6 hours following stroke (level I).[160]

Subsequent to the approval of rtPA for treatment of patients with acute ischemic stroke, several groups reported on the utility of the treatment in a community setting (level V).[161–169] A recent study showed that favorable responses to treatment with rtPA were highest among patients with a NIHSS score <10 and a normal baseline CT scan.[170] Some groups reported rates of intracranial hemorrhage and favorable outcomes that are similar to those found in the NINDS trials. Others have not. Several problems have been identified. Besides a risk of intracranial hemorrhage, other potential adverse experiences include systemic bleeding, myocardial rupture if the agent is given within a few days of acute myocardial infarction, and allergic reactions including anaphylaxis.[171] In addition, patients are given rtPA even though they have one or more reasons that should preclude treatment, including many who are treated outside the required time window.[161,162,172] Violations of the FDA-approved protocol occur frequently, and these violations may increase the likelihood of treatment-related complications (level V).[173–176]

Debate regarding time of initiation of rtPA treatment merits attention. The NINDS investigators reported a time to treatment interaction in a subgroup analysis of the NINDS rt-PA Trial.[177] Treatment with rtPA initiated within 90

minutes of symptom onset was associated with an odds ratio of 2.11 (1.33 to 3.55, 95% confidence interval)—for favorable outcome at 3 months as compared with placebo. In comparison, the odds ratio for good outcome at 3 months for treatment with rtPA initiated within 90 to 180 minutes was 1.69 (1.09 to 2.62). The investigators concluded that the earlier treatment is initiated, the better. However, 19% of the patients treated with rtPA between 91 and 180 minutes after stroke onset had an NIHSS score of ≤5 compared with 4% of the placebo patients. On the basis of this observation, it has been suggested that the relative preponderance of mild strokes with a likely good outcome in the rtPA treatment group may explain the entire benefit reported for patients treated between 91 and 180 minutes.

Even though this time-to-treatment subgroup analysis was prespecified, it must be considered exploratory. The NINDS rt-PA Trial was stratified to address time-to-treatment in two categories, 0 to 90 and 91 to 180. It was not also stratified by baseline NIHSS. Data obtained from the investigators indicate that the beneficial effect of rtPA in the patients treated 91 to 180 minutes is not entirely explained by the imbalance in baseline stroke severity. The adjusted odds ratio for 3-month favorable outcome (odds ratios for treatment as compared with placebo) for that subgroup of patients from the NINDS rt-PA Stroke Trial with NIHSS >5 at baseline and time from stroke onset to treatment of 91 to 180 minutes (n=286) is 1.68 (95% confidence limits 1.02 to 2.77, probability value = 0.041). The "adjusted" odds ratio is the odds ratio after adjusting for the variables shown to be significantly related to 3-month favorable outcome (age, baseline NIHSS, admission mean blood pressure [AMBP], diabetes, early CT findings [as defined in the paper], age × NIHSS, age × AMBP) as well as for center as described in the NINDS trial paper on generalized efficacy.[156] This is a less powerful analysis than the analysis of the entire trial data set randomized 91 to 180 minutes after stroke onset that indicates similar results.[177]

Intravenous Administration of Streptokinase

Three trials of streptokinase were halted prematurely because of an excess of poor outcomes or deaths among treated patients (level I).[178–181] The dose of streptokinase was 1.5 million units, the same given to patients with myocardial infarction, and may have been too high for treatment of patients with stroke. In addition, treatment was initiated up to 6 hours after the onset of symptoms. The trials also enrolled seriously ill patients, who were at high risk of bleeding complications. However, there remains no evidence that intravenous streptokinase is of benefit in patients with acute ischemic stroke.

Other Thrombolytic Agents

Other intravenously administered thrombolytic agents, including reteplase, urokinase, anistreplase, and staphylokinase might have been considered for treatment of patients with acute ischemic stroke. None of these agents have been tested extensively.

Defibrinating Enzymes

Ancrod, an enzyme derived from snake venom that degrades fibrinogen, was tested in a series of clinical studies. A preliminary trial found that ancrod treatment improved outcomes after stroke in those patients with blood fibrinogen levels <100 mg/dL having the best responses (level I).[182] A subsequent study found a favorable benefit-risk profile for patients (level I).[183]

Conclusions

Intravenous administration of rtPA is currently the only FDA-approved therapy for treatment of patients with acute ischemic stroke. Its use is associated with improved outcomes for a broad spectrum of carefully selected patients who can be treated within 3 hours of onset of stroke (level I). Earlier treatment (ie, within 90 minutes) may be more likely to result in a favorable outcome (level II). Later treatment, at 90 to 180 minutes, is also beneficial (level I). Treatment with rtPA is associated with symptomatic intracranial hemorrhage, which can be fatal (level I). Management of intracranial hemorrhage following treatment with rtPA is problematic. The best methods for preventing bleeding complications are careful selection of patients and scrupulous ancillary care. Close observation and monitoring of the patient and early management of arterial hypertension are critical. The use of anticoagulants and antiplatelet agents should be delayed for 24 hours after treatment.

Recommendations

Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is strongly recommended for carefully selected patients who can be treated within 3 hours of onset of ischemic stroke (grade A).

The decision for treatment with rtPA is based on several features (Table 7). The physician should review each of the criteria to determine the patient's eligibility. The safety and efficacy of rtPA for treatment of pediatric patients are not established. Patients with major strokes (NIHSS score >22) have a very poor prognosis whether or not they are treated with rtPA.[24] Because of this, and because the risk of hemorrhage is considerable among this population, caution should be exercised. However, they may still benefit from treatment. A patient whose blood pressure can be lowered without an intravenous infusion of sodium nitroprusside might be eligible for treatment, and the physician needs to assess the stability of the blood pressure prior to starting treatment. Because time is limited, most patients with markedly elevated blood pressures cannot be managed adequately and still meet the <3-hour requirement. A patient with a seizure at the time of onset of stroke might be eligible for treatment as long as the clinician is convinced that the residual impairments are due to stroke and not the seizure. Although a written consent is not necessary, patients and their families should be informed about the potential risks and benefits as with any other approved medical or surgical intervention.

To date, no other thrombolytic agent has been established as a safe and effective alternative to rtPA. Currently available data do not support the clinical use of either streptokinase or ancrod (grade A).

Recommendations for Ancillary Care and Treatment of Bleeding Complications

The ancillary care of patients treated with rtPA is outlined in Table 8. These components of care as well as the other

TABLE 7. Characteristics of Patients With Ischemic Stroke Who Could Be Treated With rtPA

Diagnosis of ischemic stroke causing measurable neurological deficit
The neurological signs should not be clearing spontaneously
The neurological signs should not be minor and isolated
Caution should be exercised in treating a patient with major deficits
The symptoms of stroke should not be suggestive of subarachnoid hemorrhage
Onset of symptoms <3 hours before beginning treatment
No head trauma or prior stroke in previous 3 months
No myocardial infarction in the previous 3 months
No gastrointestinal or urinary tract hemorrhage in previous 21 days
No major surgery in the previous 14 days
No arterial puncture at a noncompressible site in the previous 7 days
No history of previous intracranial hemorrhage
Blood pressure not elevated (systolic <185 mm Hg and diastolic <110 mm Hg)
No evidence of active bleeding or acute trauma (fracture) on examination
Not taking an oral anticoagulant or if anticoagulant being taken, INR ≤1.5
If receiving heparin in previous 48 hours, aPTT must be in normal range
Platelet count ≥100 000 mm^3
Blood glucose concentration ≥50 mg/dL (2.7 mmol/L)
No seizure with postictal residual neurological impairments
CT does not show a multilobar infarction (hypodensity >⅓ cerebral hemisphere)
The patient or family understand the potential risks and benefits from treatment

TABLE 8. Regimen for Treatment of Acute Ischemic Stroke Intravenous rtPA

- Infuse 0.9 mg/kg (maximum of 90 mg) over 60 minutes with 10% of the dose given as a bolus dose over 1 minute.
- Admit the patient to an intensive care unit or a stroke unit for monitoring.
- Perform neurological assessments every 15 minutes during the infusion of rtPA and every 30 minutes for the next 6 hours and then every hour until 24 hours from treatment.
- If the patient develops severe headache, acute hypertension, nausea, or vomiting, discontinue the infusion (if agent is still being administered) and obtain a CT scan of brain on an emergent basis.
- Measure blood pressure every 15 minutes for the first 2 hours, every 30 minutes for the next 6 hours, and then every hour until 24 hours from treatment.
- Increase the frequency of blood pressure measurements if a systolic blood pressure ≥180 mm Hg or diastolic blood pressure of ≥105 mm Hg is recorded. Administer antihypertensive medications to maintain blood pressure at or below these levels.
- If diastolic blood pressure 105–120 mm Hg or systolic blood pressure 180–230 mm Hg, intravenously administer 10 mg labetalol over 1–2 minutes. May repeat or double the dosage or labetalol every 10 to 20 minutes to a maximum dose of 300 mg. As an alternative, can start with the initial bolus dose of labetalol and then follow with a continuous labetalol infusion given at a rate of 2–8 mg/min.
- If diastolic blood pressure 121–140 mm Hg or systolic blood pressure >230 mm Hg, intravenously administer 10 mg labetalol over 1–2 minutes. May repeat or double labetalol every 10 minutes to a maximum dose of 300 mg. As an alternative, can start with the initial bolus dose of labetalol and then follow with a continuous labetalol infusion given at a rate of 2–8 mg/min. If the blood pressure is not controlled, consider starting an infusion of sodium nitroprusside.
- If diastolic blood pressure >140 mm Hg, start infusion of sodium nitroprusside at a rate of 0.5 mg/kg/min.
- Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters.

aspects of general management are crucial for success of treatment with rtPA. Much of the ancillary care is aimed at lowering the risk of symptomatic intracranial hemorrhage or other serious bleeding complications.

Intra-arterial Thrombolysis

The 1996 supplement to these guidelines concluded that intra-arterial administration of thrombolytic agents was experimental, and should be used only within a clinical trial setting.[2] This recommendation was based on the results of uncontrolled or small anecdotal studies that had evaluated a variety of thrombolytic agents (urokinase, streptokinase, rtPA) in treatment of patients with acute stroke, including those with basilar artery occlusion. Several additional studies have been completed since 1996, and intra-arterial therapy has been given to an increasing number of patients (level V).[184–190]

Although recanalization rates for patients with occlusion of the middle cerebral arteries presumably would be superior with intra-arterial thrombolysis, there are no studies directly comparing intravenous and intra-arterial administration of thrombolytic agents for patients with acute ischemic stroke. Diffusion and perfusion MRI studies provide some pathophysiological evidence linking recanalization in the middle cerebral artery with a smaller volume of infarction and improved clinical outcomes.[191] Conversely, an advantage in recanalization with intra-arterial administration might be offset to an unknown degree by inherent risks of catheterization and the delays required to mobilize the resources to perform the intra-arterial procedure.

A prospective, randomized, placebo-controlled phase II study evaluated the utility of intra-arterial administration of recombinant prourokinase (r-proUK) in combination with heparin and demonstrated that the combination was successful in achieving recanalization more frequently, but increased the risk of intracranial bleeding (level I).[192] The results prompted a second randomized, controlled, multicenter trial testing the efficacy of intra-arterial thrombolysis with r-proUK among patients with stroke of <6 hours' duration secondary to occlusion of the middle cerebral artery.[184] Heparin was given to both patients who received r-proUK and those in the control group. In the primary intent-to-treat analysis, 40% of the 121 patients treated with r-proUK and 25% of the 59 control patients had modified Rankin Score=0 to 2 at 90 days ($P=0.043$) (level I).

Recanalization of the middle cerebral artery was achieved in 66% of the patients treated with r-proUK and 18% of the patients in the control group ($P<0.001$). Intracranial hemorrhage with neurological deterioration within 24 hours of treatment occurred in 10% of patients treated with r-proUK and in 2% of the control group ($P=0.06$) (level I). There was no difference in overall mortality between the 2 groups. The

FDA has not approved the drug, and r-proUK is not currently available for clinical use.

The feasibility of combining intravenous and intra-arterial rtPA in treatment of ischemic stroke was examined in the Emergency Management of Stroke (EMS) Bridging Trial (level III).[193] The study suggested that this strategy, which included early intravenous administration of rtPA in a lower dose followed by arterial administration, could achieve recanalization and might be associated with a reasonable degree of safety. A trial testing the efficacy of combined intravenous and intra-arterial thrombolysis with rtPA is now in progress.

Physicians with expertise in endovascular therapy are using intra-arterial techniques to treat patients with acute ischemic stroke secondary to occlusion of large intracranial arteries including the basilar or middle cerebral arteries. Most centers that are performing intra-arterial thrombolysis are using rtPA although there are limited or no data demonstrating the efficacy or safety of the intra-arterial administration of this agent.

Conclusions

Intra-arterial administration of at least one specific thrombolytic agent appears to be of some benefit in treatment of carefully selected patients with acute ischemic stroke secondary to occlusion of the middle cerebral artery (level I). The relative utilities of intra-arterial or intravenous administration of thrombolytic agents is not established. In addition, the resources (equipment and physician expertise) required to administer intra-arterial thrombolytic agents are not widely available. The time to transfer a patient to an institution that has these resources or to mobilize these services means that lags in treatment are likely to occur. In addition, the implementation of ancillary diagnostic tests, such as diffusion and perfusion MRI, to select the patients to treat might engender additional delays and affect outcomes. These delays may lessen the utility of intra-arterial thrombolysis in treating acute ischemic stroke.

Recommendations

Intra-arterial thrombolysis is an option for treatment of selected patients with major stroke of $<$6 hours' duration due to large vessel occlusions of the middle cerebral artery (grade B).[194] It should be recognized that intra-arterial thrombolysis is not FDA approved. Further, the drug (recombinant prourokinase) tested in the referenced prospective randomized trial of intra-arterial thrombolysis is not available for clinical use. Therefore, extrapolation to the available thrombolytic drug (rtPA) is based on consensus as supported by case series data. Case series data suggest this approach may also be of benefit in patients with basilar artery occlusion treated at longer intervals. Treatment requires the patient to be at an experienced stroke center with immediate access to cerebral angiography and interventional neuroradiology. Importantly, the availability of intra-arterial thrombolysis should generally not preclude the administration of intravenous rtPA in otherwise eligible patients.

Anticoagulants

The usefulness of emergent anticoagulation for acute stroke care has been the subject of debate, prompting a recent joint guideline statement from the AHA and the American Academy of Neurology (AAN).[195] There have been disagreements about the best agent to use, the level of anticoagulation required, the route of administration, the duration of treatment, and the use of a bolus dose to start therapy. In 1994, the panel concluded that data about the usefulness of heparin in management of acute ischemic stroke was uncertain and that no recommendation could be made.[1] Furthermore, the panel stated that the use of heparin was a matter of personal preference of the treating physician but with the understanding that the use of the medication (or its nonuse) might not alter outcomes. Since then, several clinical trials tested the safety and efficacy of heparin, low-molecular-weight heparins, and a heparinoid.[196] Physicians have been uncertain about the severity of neurological impairments or the CT finding that would contraindicate the early use of heparin. The primary safety issue is that urgent anticoagulation might lead to symptomatic intracranial bleeding.

Anticoagulants often are prescribed to patients with recent stroke in an effort to prevent early recurrent stroke and to improve neurological outcomes. The Cerebral Embolism Study Group estimated that the risk of early recurrent embolism was approximately 12% among untreated patients with embolic stroke.[197,198] This estimate appears to have been too high. Recent clinical trials show much lower rates (0.3% to 0.5%/d).[199–201] The relatively low rates of early recurrent stroke mean that detection of a therapeutic effect in prevention of recurrences by anticoagulation will be difficult.

The International Stroke Trial tested two doses of subcutaneously administered heparin.[199] While the trial included randomization in its design, investigators and patients knew the nature of treatment. Patients were enrolled up to 48 hours after stroke. Heparin was given subcutaneously in doses of 5000 U or 25 000 U per day without dose adjustment rather than via an intravenous infusion. Monitoring the level of anticoagulation and adjusting dosages to biological responses were not done. Thus, some patients may have received excessive doses of the anticoagulant with an increased risk of bleeding complications while others may have received inadequate dosages with a resultant loss of efficacy. In addition, patients enrolled in the trial did not need to have a brain imaging study prior to treatment. Although heparin was effective in lowering the risk of early recurrent stroke, including among patients with atrial fibrillation, an increased rate of bleeding complications negated this benefit (level I).

Low-Molecular-Weight Heparins

Several trials tested low-molecular-weight (LMW) heparins in treatment of patients with acute ischemic stroke. Results have varied. A small trial from Hong Kong tested two doses of nadroparin given subcutaneously for 10 days following stroke.[196] Although no net benefit from treatment was found at the end of the treatment period or at 3 months, those patients who received the larger dose of nadroparin had a significantly lower mortality at 6 months as compared with the control group (levels I and II). Another trial of nadroparin did not find any improvement in the rates of favorable outcomes with treatment with either of two doses of the LMW heparin.[202] On the other hand, the risk of serious

bleeding was increased with administration of nadroparin, especially with the larger dose (level I). A Norwegian trial compared the utility of dalteparin or aspirin in prevention of early recurrent stroke or improvement in neurological outcome among patients with presumed cardioembolic stroke.[203] Although no significant differences in outcomes or the rates of recurrent stroke were noted, the patients receiving aspirin had fewer second strokes (level I). The rate of bleeding also was higher among those patients who were treated with dalteparin than among those given aspirin. A German trial compared four different doses of certoparin (level I).[204] The highest dose of certoparin was associated with the highest rate of bleeding with no differences in the rates of favorable outcomes noted among the four groups.

Heparinoid

A randomized, double blind, placebo-controlled trial tested the usefulness of danaparoid (ORG 10172) in improving outcomes after acute ischemic stroke.[201] It was the only recent trial that tested intravenous therapy, and it included administration of a bolus dose and dosage adjustments in response to the level of anticoagulation. The trial halted treatment of patients with moderate-to-severe stroke (NIHSS scores of 15 or greater) because of an increased rate of symptomatic hemorrhagic transformation of the infarction (level I). The use of danaparoid did not lessen the risk of neurological worsening or the rate of recurrent stroke, including among the patients with cardioembolism, during the 7-day treatment period. No improvement in the likelihood of favorable or very favorable outcomes was found with treatment (level I). The trial design included prespecified subgroup analyses among patients with different subtypes of ischemic stroke. The only subgroup that showed benefit were those patients with stroke attributed to large artery atherosclerosis (level II).

Anticoagulants as an Adjunctive Therapy

The administration of anticoagulants and platelet antiaggregants is currently contraindicated during the first 24 hours following treatment with intravenous rtPA. This restriction is based on the regimen used in the NINDS trial.[36] The two trials of prourokinase previously discussed included heparin as part of the acute treatment regimen with the control patients receiving only heparin.[160,193] In the first study, recanalization and the risk of hemorrhagic transformation were greater among the patients who received the higher of two doses of heparin than among the patients receiving the lower dose (level II).[193] Two small studies examined the use of intravenously administered heparin immediately following treatment with rtPA (level V).[165,205] The rates of favorable outcomes were satisfactory and the rates of major bleeding complications were not higher than expected with treatment with rtPA alone.

Additional trials of heparin are under way. For example, a European trial is testing intravenously administered heparin given within 12 hours of onset of stroke.[206]

Conclusions

Parenterally administered anticoagulants (heparin, LMW heparins, or heparinoid) are associated with an increased risk of serious bleeding complications (level I). These medications increase the risk of symptomatic hemorrhagic transformation of ischemic strokes, especially among patients with severe strokes, and increase the risk of serious bleeding in other parts of the body. While the risk of hemorrhage appears to be less than that associated with the administration of thrombolytic agents, it is sufficiently high to require evidence for efficacy in order to justify urgent anticoagulation. Bleeding can complicate either subcutaneously or intravenously administered anticoagulants. Monitoring of the level of anticoagulation and adjustment of the dosage/treatment regimen increase the safety of treatment with these agents.

Present data indicate that the early administration of the tested rapidly acting anticoagulants does not lower the risk of early recurrent stroke, including among patients with cardioembolic stroke (level I). Early administration of anticoagulants does not lessen the risk of neurological worsening (level I). There are no adequate data to demonstrate efficacy of anticoagulants in potentially high-risk groups such as those patients with intracardiac or intra-arterial thrombi. The efficacy of urgent anticoagulation is not established for treatment of patients with vertebrobasilar artery disease or arterial dissection.

Urgent administration of the tested anticoagulants does not increase the likelihood of a favorable outcome following acute ischemic stroke (level I). A subgroup analysis from one trial found that an anticoagulant might improve the chances of favorable outcomes among patients with stroke secondary to large artery atherosclerosis (level II). Additional information about the utility of urgent anticoagulant treatment is needed before the therapy can be considered as effective in this setting.

Additional research is needed to define the role of adjunctive anticoagulation in addition to mechanical or pharmacological thrombolysis for treatment of acute ischemic stroke (levels II to V).

Recommendations

In agreement with the independent recent Joint Guideline Statement from the AHA and AAN,[195] the present panel recommends the following:

Urgent routine anticoagulation with the goal of improving neurological outcomes or preventing early recurrent stroke is not recommended for the treatment of patients with acute ischemic stroke (grade A). More studies are required to determine if certain subgroups (large-vessel atherothrombosis or patients perceived to be at high risk of recurrent embolism) may benefit from urgent anticoagulation.

Urgent anticoagulation is not recommended for treatment of patients with moderate-to-severe stroke because of a high risk of serious intracranial bleeding complications (grade A).

Initiation of anticoagulant therapy within 24 hours of treatment with intravenously administered rtPA is not recommended (grade A).

Parenteral anticoagulants should not be prescribed until a brain imaging study has excluded the possibility of a primary intracranial hemorrhage. The level of anticoagulation should be closely monitored if a patient is receiving one of these medications. Adjustment in the dosage of medication should be done if the level of anticoagulation is outside the desired range.

Antiplatelet Agents

Data about the usefulness of aspirin or other antiplatelet agents in patients with acute stroke are less certain than those for treatment of acute myocardial ischemia. Recent clinical trials have evaluated the potential utility of antiplatelet agents in the setting of acute stroke, and additional research is in progress.

Aspirin

Aspirin was tested alone and in combination with streptokinase in the Multicentre Acute Stroke Trial-Italy.[183] Aspirin alone was not superior to placebo in preventing early recurrent events or reducing death or disability (level II). The trial was halted prematurely because of an unacceptably high incidence of early mortality and intracranial hemorrhage among the patients who received the combination of aspirin and streptokinase (level I).

The International Stroke Trial tested aspirin alone (300 mg/d) or in combination with one of two doses of subcutaneously administered heparin in comparison to heparin alone or control.[199] The trial demonstrated a significant reduction in recurrent events by aspirin within the first 2 weeks, but acute mortality was not reduced (level I). A modest but significant increase in serious systemic hemorrhages was noted with aspirin during the 14-day treatment period, and a small (0.1% absolute) significant increase in the incidence of intracranial hemorrhage was noted (level I). At 6 months, patients assigned aspirin had a significantly lower incidence of death and dependency, but there was no significant improvement in the proportion of patients free from disability (level I).

The Chinese Acute Stroke Trial tested aspirin, 160 mg/d, in a randomized, placebo-controlled trial.[200] A significant reduction in mortality and recurrent stroke was noted with aspirin during the 28 days of treatment (level I). A modest but not significant increase in the risk of intracranial hemorrhage and a significant increase in systemic hemorrhage were found. At the time of discharge, mortality was significantly reduced with aspirin, but the rates of long-term complete recovery or death and disability were not significantly improved (level I).

A preplanned combined analysis showed that early administration of aspirin was associated with a small but significant increase in the risk of hemorrhagic transformation of the infarction (level I). On the other hand, aspirin was effective in reducing recurrent ischemic stroke, death, or dependency (level I). It should be noted that the authors of the combined analysis also acknowledge that the differences in populations studied and the differences in rates of favorable outcomes may lead some to question the appropriateness of combining the two trials.

Other Antiplatelet Agents

Potent inhibitors of the glycoprotein IIb/IIIa receptor are being used alone or in combination with other medications to treat patients with acute myocardial ischemia or as an adjunct to cardiovascular procedures.[207,208] A small, randomized, placebo-controlled dose-escalation trial of one of these agents, abciximab, demonstrated that the agent was relatively safe (level II).[209]

Conclusions

Two large trials of aspirin give somewhat conflicting results. Although the International Stroke Trial demonstrated a benefit from aspirin in preventing recurrent stroke within 14 days, the results were not definitive at 30 days in the Chinese Acute Stroke Trial. The trials each showed a nonsignificant trend in preventing death and disability with aspirin, and only when the data were combined was the small beneficial result statistically significant.

The risk of serious bleeding complications with urgent use of aspirin is relatively low and much less than that which accompanies the use of anticoagulants or thrombolytic agents. The adjunctive use of aspirin may increase the risk of bleeding from the thrombolytic agents (level II). The primary benefit of aspirin seems to be in preventing recurrent events. On this basis, the use of aspirin within 24 to 48 hours after stroke in attempts to reduce death and disability is reasonable (level I).

Data reflecting the efficiency of other platelet antiaggregants are too limited to support any conclusions.

Recommendations

In agreement with the independent recent Joint Guideline Statement from the AHA and the AAN,[195] the present panel recommends the following:

Aspirin should be given within 24 to 48 hours of stroke onset in most patients (grade A).

The administration of aspirin as an adjunctive therapy, within 24 hours of the use of thrombolytic agents, is not recommended (grade A).

Aspirin should not be used as a substitute for other acute interventions, especially intravenous administration of rtPA, for the treatment of acute ischemic stroke (grade A).

No recommendation can be made about the urgent administration of other antiplatelet aggregating agents (grade C).

Volume Expansion, Vasodilators, and Induced Hypertension

Drug-induced hypertension and isovolemic or hypervolemic hemodilution have been used successfully to prevent ischemia secondary to vasospasm following subarachnoid hemorrhage.[210] This treatment involves the use of colloid solutions and often the intravenous administration of vasopressors, such as phenylephrine or dopamine. Because of the risk of myocardial ischemia, congestive heart failure, pulmonary edema, intracranial hemorrhage, hypertensive encephalopathy, or increased brain edema, this treatment regimen requires close observation and cardiovascular monitoring. Studies of these approaches in the setting of acute ischemic stroke have been inconclusive, but generally negative (levels II to V).[211–218]

Two trials of hemodilution therapy for treatment of patients with acute stroke showed no improvement in outcomes (level I).[219,220] New strategies to improve collateral flow by improving the rheological characteristics of the blood are being studied (level V).[221] The cross-linked hemoglobin oxygen carrier, diaspirin, was tested in a small clinical trial. Unfortunately, the agent was associated with an increased mortality and other poor outcomes (level I).[222]

Conclusions

At present, strategies to improve blood flow by changing the rheological characteristics of the blood or by increasing perfusion pressure are not established as useful (level I). These therapies are associated with a risk of serious neurological or cardiovascular complications, and treated patients require very close monitoring.

Recommendations

Strategies to improve blood flow by changing the rheological characteristics of the blood or by increasing perfusion pressure are not recommended outside a clinical trial setting for the treatment of most patients with acute ischemic stroke (grade A).

Surgical Interventions

Carotid Endarterectomy

Little information exists about the efficacy of surgical treatment of patients with acute ischemic stroke. Most cases of immediate operation are performed in the setting of an acute stroke following carotid endarterectomy. Emergency carotid endarterectomy generally is not performed in other settings of acute ischemic stroke because the risks of the procedure are perceived to be high. The sudden restoration of blood flow might increase the development of brain edema or lead to hemorrhagic transformation, especially among patients with major infarctions. In addition, the time required for detecting the arterial lesion and mobilizing the operating room limits the utility of surgery.

However, some surgeons report encouraging results from emergent operations for patients with severe stenosis or occlusion of the internal carotid artery existing for 24 hours or less (level V).[223–231] In general, improvement following surgery was found among patients with mild-to-moderate neurological impairments. Still, the data are limited and the usefulness of urgent surgery among patients with severe neurological deficits is even less clear.

The indications for immediate carotid endarterectomy in a patient with an acute ipsilateral ischemic stroke and an intraluminal thrombus associated with an atherosclerotic plaque at the carotid bifurcation are controversial. The morbidity of operation appears to be high among patients with an intraluminal thrombus demonstrated by cerebral angiography.[232–235] Although some groups report low rates of complications and good neurological outcomes with immediate surgery (level V),[219,233,234] others have reported better results when the patients are treated initially with anticoagulants followed by delayed operation (level V).[235]

EC-IC Bypass

Immediate extracranial-intracranial (EC-IC) arterial bypass for treatment of ischemic stroke failed to improve outcomes and was associated with a high risk of intracranial hemorrhage (level V).[236] Some surgeons have reported favorable results with emergent bypass procedures (level V).[237,238] In an occasional patient with an acute neurological deficit secondary to an embolus of the middle cerebral artery, outcome might be improved by an emergent microsurgical embolectomy of the middle cerebral artery (level V).[239,240] Experience with immediate surgical procedures for treatment of acute ischemic stroke in the vertebrobasilar circulation is extremely limited.

Conclusions

There are no definitive data about either the efficacy or safety of acute surgical procedures in the treatment of patients with ischemic stroke. Data about the safety and efficacy of carotid endarterectomy for treatment of patients with acute ischemic stroke are not sufficient to permit a recommendation (level V). Surgical procedures may have serious risks and may not favorably alter the outcome of the patient.

Recommendations

Because of the lack of evidence about the safety and efficacy of emergent carotid endarterectomy or other surgical procedures, these procedures are not recommended for treatment of most patients with acute ischemic stroke outside of a research setting (grade C).

Endovascular Treatment

Several new interventional neuroradiological techniques designed to speed or augment vascular recanalization have been examined. Reports are from individual case series from single institutions (level V).[241–248] Techniques include direct mechanical balloon angioplasty of the thrombus, mechanical removal of clot from the middle cerebral artery, intravascular stenting of the underlying occlusive atherosclerotic lesion for restoring arterial patency, suction thrombectomy, laser-assisted thrombolysis of emboli, and power-assisted Doppler thrombolysis. Intravenous or intra-arterial administration of glycoprotein IIb/IIIa inhibitors has been used to enhance the effects of clot lysis.[208,209,249] No controlled clinical trials have been performed to test the efficacy and safety of these procedures.

Conclusions

Although anecdotal reports describe the potential utility of mechanical endovascular procedures for treatment of patients with acute ischemic stroke, no controlled data on the safety and efficacy of these interventions are available.

Recommendations

Because of the lack of evidence about the safety and efficacy of these procedures, they are not recommended for treatment of most patients with acute ischemic stroke outside of a research setting (grade C).

Neuroprotective Agents

A large number of clinical trials testing a variety of putative neuroprotective agents have been completed. These trials have produced negative or disappointing results. Although some of these trials were small and had other significant methodological limitations, others have been sufficiently large and were well designed. To date, no consistent benefit of these approaches has been demonstrated, and, in some cases, treated patients had poorer outcomes or an unacceptable rate of adverse experiences.

Nimodipine is approved for the prevention of ischemic neurological impairments following subarachnoid hemorrhage.[210] Because of that success, several groups tested the usefulness of nimodipine in treating patients with acute brain ischemia, but the results are largely negative (level I).[250–256] In some of these trials, outcomes were worse among patients treated with nimodipine presumably due to its antihypertensive effects. A trial of another calcium channel blocker, flunarizine, also was negative (level I).[257] Clinical studies of the NMDA receptor antagonists, aptiganel and YM-90K, also were inconclusive because of unacceptable effects attributed to the agent (levels I and II).[258] Lubeluzole was tested in clinical trials with negative results (levels I and II).[259–261] Trials of glutamate antagonist, selfotel, the GABA agonist, clomethiazole, and glycine site antagonists, gavestinel, also have been negative (levels I and II).[262–274] Although a preliminary study of citicoline suggested that the agent might improve outcomes, a subsequent trial was negative (level I).[275,276] None of these agents have demonstrated the capacity to improve clinical outcomes among treated patients.[277–279] Trials of magnesium suggest that this agent may have some neuroprotective effect, and it is relatively safe.[280–282]

Neurotrophic factors were shown to decrease the volume of infarction in experimental models, but a clinical trial of basic-FGF failed to be completed because of safety and efficacy concerns (level I). Trials of gangliosides also have produced negative results (level I).[283,284] Hypothermia is a promising form of neuroprotection just entering clinical trials in acute stroke.[285]

Secondary neuronal injury can result from free radical generation and by the participation of activated leukocytes in the inflammatory phase of the ischemic injury.[286] Tirilazad mesylate, an inhibitor of lipid peroxidation, was shown to reduce residual injury in animal models of focal cerebral ischemia (level VI). However, low doses were not efficacious based on an interim analysis of prospective trials in ischemic stroke. A trial at higher doses was terminated when concerns about safety arose (level I).[287,288] Similar results occurred in the trial of the murine monoclonal antibody to human ICAM-1, enlimomab.[289] The 90-day disability, mortality, and adverse experiences were significantly increased among those patients receiving the agent compared with those receiving placebo (level I).

There is reason to believe that most of the trials have not adequately tested their underlying hypotheses.[290] A number of limitations have been identified. Some trials have not adhered to preclinical testing paradigms and have had inadequate power. Others have been curtailed because of dose-limiting effects (eg, hypotension or somnolence). Trials have also been limited by inadequate or inappropriate dosing, inadequate preclinical testing, flawed clinical trial design, thresholding of outcome events, and other issues. Therefore, the results of those trials should not be considered to show unequivocal evidence of the lack of efficacy of neuroprotective agents.

Finally, the hypotheses that neuroprotective agents can reduce cellular injury, enhance the efficacy of an intravenously delivered thrombolytic agent, or improve blood flow have not been rigorously tested.[291]

Conclusions

Considerable work remains before an agent with identified neuroprotective properties in preclinical models can be applied to successful treatment of patients with acute ischemic stroke. Trials testing a number of neuroprotective agents are under way. It is hoped that their results will demonstrate the efficacy and safety of the neuroprotective agents, alone or in combination, with thrombolytic agents or other therapies.

Recommendations

No agent with putative neuroprotective effects can be recommended for the treatment of patients with acute ischemic stroke at this time (grade A). No such agents are available for clinical use.

Admission to the Hospital and Treatment of Neurological Complications

Approximately 25% of patients can worsen during the first 24 to 48 hours after stroke. However, it is difficult to predict which patients will deteriorate.[148,292–294] The potential for preventable medical or neurological complications also means that patients should be admitted to the hospital in most circumstances.[3] The goals of early posttreatment care after admission are to (1) observe for changes in the patient's condition that might prompt initiation of medical or surgical interventions, (2) facilitate medical or surgical measures aimed at improving outcome after stroke, (3) begin measures to prevent subacute complications, (4) plan for long-term therapies to prevent recurrent stroke, and (5) start efforts to restore neurological function through rehabilitation and good supportive care.

Several studies performed in Europe have demonstrated the utility of comprehensive stroke units in lessening mortality and morbidity from stroke with positive effects persisting for years (level I).[295–303] The benefits from treatment in this type of a stroke unit are comparable to the effects achieved with intravenous administration of rtPA. There is no strict definition of what constitutes a stroke unit but, in general, the units evaluated had a geographically defined facility staffed by a group of skilled professionals, including physicians, nurses, and rehabilitation personnel. The units can have monitoring capabilities, which permit close observation for neurological worsening or other complications. Regular communications and coordinated care also are key components of the stroke unit. An advantage of stroke units is that this specialized care can be given to a broad spectrum of patients regardless of the interval after stroke or severity of neurological impairments. It should be noted that most stroke units in the United States have much shorter lengths of stay than do the units evaluated in the European studies, and most do not incorporate comprehensive rehabilitative care.

General Care

Most of the individual components of general medical management have not been tested by clinical studies (level V).[103,304–306] Thus, recommendations are based on customary care. The patient's neurological status and vital signs should be assessed frequently during the first 24 hours after admission. Most patients are first treated with bed rest, but

mobilization should begin as soon as the patient's condition is judged to be stable. Some patients can have neurological worsening on movement to an upright position. Thus, close observation should be included during the transition to sitting and standing. Early mobilization is favored because it lessens the likelihood of major complications such as pneumonia, deep vein thrombosis, pulmonary embolism, and pressure sores.[307] Immobility also can lead to contractures, orthopedic complications, and pressure palsies.[308,309] Passive and full-range-of-motion exercises for paralyzed limbs can be started during the first 24 hours. Frequent turning, the use of alternating pressure mattresses, and close surveillance of the skin help prevent pressure sores. Measures to avoid falls are an important part of mobilization.[310]

Alimentation

Sustaining nutrition is important because the malnutrition that can develop after stroke might interfere with recovery.[311–313] There is some evidence that nutritional supplementation can improve outcome after stroke, but a definitive trial has not been performed. Many patients cannot receive food or fluids by mouth because of impairments in swallowing or mental status, and intravenous fluids are needed.[314–316] Persons with infarctions of the brain stem, multiple strokes, large hemispheric lesions, or depressed consciousness are at the greatest risk for aspiration. Swallowing impairments are associated with an increased mortality. An abnormal gag reflex, impaired voluntary cough, dysphonia, or cranial nerve palsies should alert the physician of the risk. An assessment of the ability to swallow is important before the patient is allowed to eat or drink. A wet voice after swallowing, incomplete oral-labial closure, or a high NIHSS score also are independent predictors of aspiration risk. A preserved gag reflex might not indicate safety from aspiration. A water swallow test performed at the bedside is a useful screening test, and a videofluoroscopic modified barium swallow examination can be performed later if indicated.[317–319] When necessary, a nasogastric or nasoduodenal tube can be inserted to provide feedings and to expedite administration of medications.[320] Intravenous hyperalimentation is rarely necessary. Some research indicates that percutaneous placement of an endogastric tube is superior to nasogastric tube feeding if a prolonged need for devices is anticipated (level II).[321–323]

Infections

Pneumonia is an important cause of death following stroke.[324] It usually occurs among patients who are immobile or who are unable to cough. The appearance of a fever after stroke should prompt a search for pneumonia and appropriate antibiotic therapy should be administered early.

Urinary tract infections are common and secondary sepsis can develop in approximately 5% of patients.[325] An indwelling bladder catheter is sometimes needed to treat incontinence or urinary retention. It should be avoided if possible because of the risk of infection. Acidification of the urine or intermittent catheterization might lessen the risk of infection and help avoid the need for prophylactic antibiotics. Anticholinergic agents may help in recovery of bladder function.

Venous Thrombosis

Pulmonary embolism accounts for approximately 10% of deaths after stroke, and the complication can be detected in approximately 1% of persons who have had a stroke.[326] With prophylaxis, proximal deep vein thrombosis can be detected by plethysmography in one third to one half of patients who have moderately severe stroke.[327] Advanced age, immobility, paralysis of the lower extremity, severe paralysis, and atrial fibrillation are associated with an increased risk of deep vein thrombosis.[328] In addition, continued use of hormone replacement therapy may increase the risk of deep venous thrombosis in immobilized patients.[329] Anticoagulants are given to prevent deep vein thrombosis and pulmonary embolism among bedridden patients with recent stroke. A meta-analysis of studies of anticoagulants demonstrated that these agents are effective in preventing deep vein thrombosis (level I).[330–332] Subcutaneous administration of heparin or low-molecular-weight heparins and heparinoids (level I)[320,333–340] as well as the use of alternating pressure stockings (level II)[341,342] are effective in preventing deep vein thrombosis. Aspirin also may be effective for patients who have contraindications to the use of anticoagulants (level I).[343,344] Support stockings are of unproven value.

After Care

After stabilization of the patient's condition, rehabilitation, measures to prevent long-term complications, family support, and treatment of depression can be started when appropriate. In addition, the patient should have an evaluation to determine the most likely cause of the stroke, and medical or surgical therapies to prevent recurrent ischemic events can be initiated.

Recommendations

The use of comprehensive specialized stroke care units (stroke units), incorporating comprehensive rehabilitation, is recommended (grade A).

Early mobilization and measures to prevent subacute complications of stroke (aspiration, malnutrition, pneumonia, deep vein thrombosis, pulmonary embolism, pressure sores, orthopedic complications, and contractures) are strongly recommended (grades B and C).

The subcutaneous administration of anticoagulants (grade A) or the use of intermittent external compression stockings or aspirin for patients who cannot receive anticoagulants (grades A and B) is strongly recommended to prevent deep vein thrombosis among immobilized patients.

Antibiotics to treat infectious complications of stroke are strongly recommended (grade A). Treatment of concurrent medical conditions also is strongly recommended (grade A).

Treatment of Acute Neurological Complications

The most important acute neurological complications of stroke are (1) cerebral edema and increased intracranial pressure, which can lead to herniation or brain stem compression, (2) seizures, and (3) hemorrhagic transformation of the infarction with or without formation of a hematoma.

Brain Edema and Increased Intracranial Pressure

Brain edema and increased intracranial pressure largely occur with occlusions of major intracranial arteries that lead to multilobar infarctions.[304,345–348] Brain edema usually peaks at 3 to 5 days after stroke. It usually is not a problem within the first 24 hours of the ictus except among patients with large cerebellar infarctions. Less than 10% to 20% of patients develop clinically significant edema that could warrant medical intervention.[349] Increased intracranial pressure also can result from acute hydrocephalus secondary to obstruction of cerebrospinal fluid pathways by a large cerebellar lesion.

The goals of management of brain edema are to (1) reduce intracranial pressure, (2) maintain adequate cerebral perfusion to avoid worsening of the brain ischemia, and (3) prevent secondary brain injury from herniation. Initial care includes mild restriction of fluids (levels III to V).[103,304,350] Hypoosmolar fluids, such as 5% dextrose in water, may worsen edema.[351] Factors that exacerbate raised intracranial pressure (eg, hypoxia, hypercarbia, and hyperthermia) should be treated. The head of the bed can be elevated by 20 to 30 degrees in an attempt to help venous drainage. An elevation of the arterial blood pressure may be a compensatory response to maintain adequate cerebral perfusion pressure in a patient with a markedly elevated intracranial pressure. Antihypertensive agents, particularly those that induce cerebral vasodilation, should be avoided in this setting (levels III to V).[351–353]

Patients with raised intracranial pressure whose neurological condition is deteriorating can be treated with hyperventilation, osmotic diuretics, drainage of cerebrospinal fluid, or surgery. Although anecdotal case reports and small case series report success with such measures, there are no trials that address the efficacy of such aggressive management following stroke (levels III to V). Furthermore, the value of continuous intracranial pressure monitoring in this population has not been established, although the results can help predict the patient's outcome and guide the choice of therapies.[354]

Hyperventilation is an emergency measure that acts almost immediately; a reduction of the P_{CO_2} by 5 to 10 mm Hg can lower intracranial pressure by 25% to 30% (levels III to V).[105,355–357] Hyperventilation is a temporizing measure and should be supplemented by another intervention to definitively control brain edema and intracranial pressure. Maintaining adequate brain perfusion is necessary since hyperventilation can lead to vasoconstriction that might aggravate ischemia.

Conventional or large doses of corticosteroids have been tested in clinical trials, but no improvement of outcomes after stroke was found (level I).[358–361] In addition, infections were more common among patients treated with corticosteroids.

Although furosemide or mannitol often are prescribed to treat cerebral edema after stroke, no trials of these agents prove their value in improving outcomes after stroke (levels III to V). An acute intravenous bolus of 40 mg of furosemide has been used as an adjunct in the care of patients whose condition is rapidly deteriorating, but it is not used in long-term care. Mannitol (0.25 to 0.5 g/kg) intravenously administered over 20 minutes lowers intracranial pressure and can be given every 6 hours.[362,363] The usual maximum daily dose is 2 g/kg. Glycerol has been examined in clinical trials and can lower mortality among patients with larger strokes (level II).[364–366] However, it has not been widely used because glycerol is not well tolerated orally and it can induce hemolysis when given intravenously. Barbiturates can be used to reduce intracranial pressure, but benefit from treatment has not been shown (level II).[367–368] Hypothermia also has been used to treat elevated intracranial pressure and is being tested in clinical trials.[124,125,369]

If hydrocephalus is present, drainage of cerebrospinal fluid via an intraventricular catheter can rapidly lower intracranial pressure. Hemicraniectomy and temporal lobe resection have been used to control intracranial pressure and prevent herniation among those patients with very large infarctions of the cerebral hemisphere (levels III to V).[370–379] Hemicraniectomy to remove the skull and relieve dural compression has been used to treat malignant brain edema. Further information is needed about the quality of life among persons who survive these aggressive therapies for multilobar infarctions.

Ventriculostomy and suboccipital craniectomy, especially in concert with aggressive medical therapies, appear to be effective in relieving hydrocephalus and brain stem compression caused by large cerebellar infarctions (levels III to V).[380–385]

Seizures

The reported frequency of seizures during the first days after stroke ranges from 4% to 43% depending on study designs (levels III to V).[97,304,386–391] The true risk of seizures appears to be toward the lower end of the estimates. Seizures are most likely to occur within 24 hours of stroke and are usually partial with or without secondary generalization. Recurrent seizures develop in approximately 20% to 80% of patients. Intermittent seizures seem not to alter the overall prognosis after stroke. However, status epilepticus can be life-threatening.[392] Fortunately, it is uncommon. There are no data about the utility of prophylactic administration of anticonvulsants after stroke. There are few data concerning the efficacy of anticonvulsants in the treatment of stroke patients who have experienced seizures; thus, recommendations are based on the established management of seizures that may complicate any acute neurological illness.

Hemorrhagic Transformation

There is considerable information about the natural rate of early hemorrhagic transformation of ischemic stroke.[393–401] Some studies suggest that almost all infarctions have some element of petechial hemorrhage. Using CT, one prospective study estimates that approximately 5% of infarctions will spontaneously develop symptomatic hemorrhagic transformation or frank hematomas.[393] The location, size, and etiology of stroke can influence the development of this complication. Further information about the influence of hemorrhagic transformation on outcome after stroke is needed. Small asymptomatic petechiae are much less important than hematomas, which can be associated with neurological decline. The use of all antithrombotics, but especially anticoagulants and thrombolytic agents, increases the likelihood of serious hemorrhagic transformation.[26,36,38,182,183,201,402] The

early use of aspirin also is associated with a small increase in the risk of clinically detectable hemorrhage.[199,200] Management of patients with hemorrhagic infarction depends on the amount of bleeding and its symptoms.

Recommendations

Corticosteroids are not recommended for the management of cerebral edema and increased intracranial pressure following ischemic stroke (grade A).

Osmotherapy and hyperventilation are recommended for patients whose condition is deteriorating secondary to increased intracranial pressure, including those with herniation syndromes (grade B).

Surgical interventions, including drainage of cerebrospinal fluid, can be used to treat increased intracranial pressure secondary to hydrocephalus (grade C).

Surgical decompression and evacuation of large cerebellar infarctions that are leading to brain stem compression and hydrocephalus is recommended (grade C).

Surgical decompression and evacuation of a large infarction of the cerebral hemisphere can be a life-saving measure, but survivors have severe residual neurological impairments (grade C).

Recurrent seizures should be treated as with any other acute neurological condition (grade C). Prophylactic administration of anticonvulsants to patients who have had stroke but not seizures is not recommended (grade C).

Summary Statement

The management of patients with acute ischemic stroke is multifaceted, and indications for specific therapies vary among patients. There is strong evidence that outcomes after stroke can be improved and that death or disability from stroke can be reduced with appropriate treatment. This statement aims to provide guidance to physicians for the early treatment of patients.

1. Patients with acute ischemic stroke should be evaluated and treated immediately. Stroke should be approached as the life-threatening emergency it is. A regional or local organized program to expedite stroke care is recommended. This organized approach can increase the number of patients who can be treated.
2. Urgent evaluation is aimed primarily at determining that ischemic stroke is the likely cause of the patient's symptoms and whether the patient can be treated with intravenous rtPA.
3. Urgent treatment should include measures that protect the airway, breathing, and circulation (life support), especially among seriously ill or comatose patients. An elevated blood pressure should be lowered cautiously.
4. Intravenous administration of rtPA (0.9 mg/kg; maximum 90 mg) is strongly recommended for treatment of carefully selected patients who can receive the medication within 3 hours of onset of stroke. Safe use of rtPA requires adherence to NINDS selection criteria, close observation, and careful ancillary care. Intravenous administration of streptokinase or other thrombolytic agents cannot be substituted safely for rtPA.
5. The intra-arterial administration of thrombolytic agents is being given to an increasing number of patients. While intra-arterial thrombolysis holds promise for treating patients at time periods longer than 3 hours after the onset of stroke, the patient selection criteria and effectiveness of this form of therapy have not been fully established.
6. Urgent administration of anticoagulants has not yet been associated with lessening of the risk of early recurrent stroke or improving outcomes after stroke. Because urgent anticoagulation can increase the risk of brain hemorrhage, especially among patients with moderately severe strokes, the routine use of this therapy cannot be recommended. Aspirin can be administered within the first 48 hours because of reasonable safety and a small benefit.
7. No medication with putative neuroprotective effects has yet been shown to be useful for treatment of patients with acute ischemic stroke.
8. Comprehensive stroke unit care, including comprehensive rehabilitation, can be given to a broad spectrum of patients.
9. Subsequent treatment in the hospital should include measures to prevent or treat medical or neurological complications of stroke. An evaluation to determine the most likely cause of the patient's stroke should lead to institution of medical or surgical therapies to lessen the risk of recurrent stroke. Rehabilitation and plans for care after hospitalization also are important components of acute management of patients with stroke.

Statement

The American Heart Association/American Stroke Association has received funding from a number of pharmaceutical companies through its Pharmaceutical Roundtable program. The American Stroke Association also has received funding to help promote Operation Stroke, a program that aims at increasing public awareness of stroke and urging early treatment of stroke. Individual members of the panel have interacted with a large number of pharmaceutical companies through their research and consultation or by giving lectures.

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