Editorial
Perspectives in the management of acute stroke

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Approximately 186 000 Italians have a stroke annually; a rate that is approximately twice the frequency of acute myocardial infarction[1]. Stroke is a life-threatening disease that also is an important cause of disability. Due to the fact that many stroke survivors might need prolonged rehabilitation, have permanent disability, or require long-term institutionalized care, the economic consequences of stroke are considerable. Stroke affects men and women of all ages and it is among the leading neurological causes of death in children. Approximately 80% of strokes are ischemic events, which are secondary to arterial thromboembolism. Prevention of stroke is the most cost-effective form of management of patients with ischemic cerebrovascular disease. Medical and surgical interventions, including antiplatelet agents, oral anticoagulants, and carotid endarterectomy, are of proven utility in lowering the chance of stroke among high-risk persons[2,3]. In addition, aggressive management with cholesterol-lowering medications (statins) and antihypertensive agents (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) can reduce the likelihood of stroke[4,5]. Unfortunately these interventions do not eliminate the risk of stroke. Thus, measures are needed to lessen the neurological consequences of stroke and improve outcomes.

Management of acute stroke involves several components of care including 1) treatment of the ischemic event itself, 2) prevention or control of medical and neurological complications of the stroke, 3) rehabilitation and other restorative interventions to improve outcomes, and 4) prevention of recurrent stroke[6,7]. With advances in the understanding about the pathophysiology of ischemic stroke, a number of promising therapeutic interventions have been developed. Most of these therapies have been tested in clinical trials that use modern methodology including randomization and blinding. These trials' results provide the data for panels from around the world to write guidelines about the management of stroke, including acute treatment, prevention of recurrent stroke, and rehabilitation[8-12]. While neither clinical trials nor guidelines can provide definitive information about every nuance in the management of a complex illness such as stroke, they provide the framework on which physicians can make decisions about the evaluation and treatment of their patients.

Time is the key to success of management; thus, there is a sense of urgency in the evaluation and treatment of patients with suspected stroke. Much of the early management of stroke (brain attack) is modeled after the approach used to treat patients with myocardial infarction (heart attack). A limited number of diagnostic studies, which should be available in most hospitals, are done to exclude alternative causes of the neurological symptoms, to assess eligibility for treatment with thrombolytic agents, and to screen for acute medical and neurological complications (Table I). While magnetic resonance imaging might become the preferred brain imaging study in the future, computed tomography currently is recommended because of its ability to exclude hemorrhage with high degree of certainty and because it can be done rapidly[13,14].

General emergent management of stroke is similar to that applied to other acutely ill

Table I. Diagnostic studies in the early evaluation of patients with suspected ischemic stroke.

Computed tomography of the brain
Electrocardiogram
Complete blood count including platelet count
Prothrombin time (international normalized ratio)
Activated partial thromboplastin time
Blood chemistries (blood glucose in particular)
Pulse oximetry or arterial blood gases

patients including those with myocardial ischemia. Initial measures include protecting the airway and monitoring of oxygenation[7,15]. Intubation to protect the airway might be needed if the patient has decreased consciousness or evidence of bulbar dysfunction. Patients with stroke do not need supplemental oxygen unless there is evidence of oxygen desaturation detected by oximetry[16]. Because elevation of body temperature is associated with increased metabolic demands, the presence of fever predicts neurological worsening and poor outcomes following stroke[17,18]. The cause of the fever should be sought and antipyretics should be given[19]. Lowering the patient's temperature might improve the prognosis of patients with stroke. Preliminary clinical studies testing cooling devices that are used to induce hypothermia in patients with stroke show promising results[20,21].

The relationship between heart disease and stroke is strong. The patient's cardiac status should be assessed for an underlying cardiac lesion that leads to embolization. In addition, the patient should be monitored for acute cardiac complications, especially serious arrhythmias[22]. Cardiac imaging studies often are required to screen for a cardiac lesion that could be a source of emboli.

Arterial hypertension is common following stroke. Often, patients will have a spontaneous decline in blood pressure during the first hours after stroke. An elevated blood pressure can be from preexisting hypertension or be secondary to the stress of the stroke (secondary to release of catecholamines), headache, a full bladder, or nausea. Arterial hypertension also can represent a physiological response to the acute ischemia or increased intracranial pressure[23]. Lowering the blood pressure might reduce the risk of hemorrhagic transformation of the infarction or malignant brain edema. On the other hand, a drop in blood pressure might cause a reduction in perfusion pressure, which might increase the size of the infarction. Neither the level of blood pressure that mandates treatment nor the medications that should be administered in the setting of stroke has been established[24]. The presence of concomitant acute myocardial ischemia, renal insufficiency or aortic dissection will prompt aggressive antihypertensive treatment. The blood pressure may need to be lowered in order to administer recombinant tissue-type plasminogen activator (rt-PA)[25] (Table II). Neurological worsening

Table II. Management of hypertension following acute ischemic stroke.

General management
SBP < 220 mmHg and DBP < 120 mmHg
Treat other symptoms or complications
Delay treatment with antihypertensives
Higher blood pressure values
Labetalol 10-20 mg i.v. over 1-2 min - may increase as needed (maximum dose 300 mg)
Nicardipine 5 mg/hour i.v. titrated (maximum 15 mg/hour)
Nitroprusside 0.5 μg/kg/min i.v. infusion
Continuously monitor blood pressure
Possible treatment with rt-PA
SBP > 185 mmHg or DBP > 110 mmHg
Blood pressure precludes treatment with rt-PA
Can treat with rt-PA if pressure is reduced
Labetalol 10-20 mg i.v. over 1-2 min (repeat × 1) or
Nitropaste 1-2 inches
If desired blood pressure not achieved, do not treat with rt-PA

DBP = diastolic blood pressure; rt-PA = recombinant tissue-type plasminogen activator; SBP = systolic blood pressure.

can follow the administration of a potent antihypertensive agent that dramatically lowers blood pressure, agents, such as sublingually administered nifedipine, should be avoided[26].

Hypoglycemia can mimic ischemic stroke and hyperglycemia can worsen prognosis of stroke, the blood glucose concentration should be measured[27]. While patients with marked hyperglycemia should receive insulin to treat the elevated glucose concentrations, the utility of this approach in improving neurological outcomes is not established. There is evidence that an insulin infusion can be administered safely following stroke to patients with mild-to-moderate hyperglycemia[28].

Therapies aimed at limiting the neurological injury involve medications that protect the neurons from the effects of ischemia and interventions that could restore or improve perfusion to the ischemic areas. The existence of the ischemic penumbra, a dysfunctional but not yet necrotic area of brain tissue adjacent to more severely injured brain, which could be salvaged with prompt treatment provides the scientific rationale for therapies aimed at treating the stroke itself[29]. Clinical trials tested a number of medications that have putative neuroprotective effects including calcium channel blockers, antagonists of excitatory amino acids, membrane stabilization agents, free radical antagonists, and anti-inflammatory agents. To date, no neuroprotective agent has been shown to be effective[30]. Additional research on these therapies is underway. These medications could be given to patients with either ischemic or hemorrhagic stroke, which is a potential advantage because of initiation of treatment prior to admission to a hospital.

While urgent anticoagulation is a traditional treatment for management of patients with ischemic stroke,

recent clinical trials do not provide supporting data[31-33]. Anticoagulants are associated with an increased risk of intracranial bleeding complications, particularly among patients with moderate-to-severe strokes. Evidence is lacking for efficacy in preventing early recurrent stroke, or improving outcomes. Two large trials tested the utility of aspirin when first administered within 48 hours following stroke[34,35]. Aspirin was associated with a minimal increase in bleeding risk and a modest improvement in the rate of favorable outcomes. Starting aspirin within 48 hours after stroke is recommended, but it is not a substitute for treatment with rt-PA or other emergently administered medications. The combination of aspirin and streptokinase was associated with a very high risk of major bleeding complications[36]. Thus, aspirin should not be given within 24 hours after treatment with thrombolytic agents. The success of aspirin has prompted evaluation of other rapidly acting antiplatelet agents such as abciximab. While preliminary results are promising, additional research is necessary[37]. While anecdotal reports of success with emergent surgery or endovascular procedures are available, there are no data to support the use of these procedures in the treatment of patients with acute ischemic stroke. Measures, such as induced hypertension or hemodilution, also are not recommended.

At present, intravenous rt-PA is the only therapy that has been approved for treatment of acute ischemic stroke (Table III). The chances of symptomatic intracranial hemorrhagic complications are much higher with thrombolytic treatment for stroke than for treatment of myocardial ischemia. While intravenous rt-PA is associated with an approximately 6% risk of hemorrhagic transformation of the stroke within 36 hours of treatment, the agent is associated with a significant increase (approximately 30% relative improvement) in the likelihood of favorable outcomes[38]. The medication is recommended for treatment of carefully selected patients who can be treated within 3 hours of onset of stroke[9]. The patient and family should be informed about the potential risks and benefits of treatment.

Table III. Thrombolytic treatment of acute ischemic stroke.

Intravenous rt-PA (0.9 mg/kg - maximum 90 mg/kg) is recommended
Treatment initiated < 3 hours of the first symptom
No recent illness (myocardial infarction, trauma, hemorrhage, surgery, or stroke) that would be associated with high bleeding risk
Not using an oral anticoagulant, such as warfarin, that would be associated with high bleeding risk - check coagulation studies - patients taking antiplatelet agents can be treated
Systolic blood pressure < 185 mmHg
Diastolic blood pressure < 110 mmHg
Computed tomography - no hemorrhage
Severity of neurological impairments
Mild strokes (NIHSS score < 4) - usually do well
Very severe strokes (NIHSS score ≥ 20) - higher risk of bleeding
Patient and family informed of potential bleeding risks
Care after intravenous thrombolytic treatment
Monitor blood pressure closely and treat aggressively
Delay placement of bladder catheters and nasogastric tubes
Monitor neurological status closely
Do not start antiplatelet agents and anticoagulants for 24 hours
Be prepared to treat bleeding complications

NIHSS = National Institutes of Health Stroke Scale; rt-PA = recombinant tissue-type plasminogen activator.

Additional advances in the urgent treatment of patients with stroke are likely. Intra-arterial thrombolysis, which involves pharmacological or mechanical measures, is being tested. Intravenous thrombolysis followed by intra-arterial treatment is another potential option. Current guidelines advise against initiation of antiplatelet agents or anticoagulants within 24 hours of treatment with rt-PA (Table III). However, the potential for reocclusion of the artery with neurological deterioration exists and the use of interventions to maintain patency following thrombolysis would be welcomed[39]. Combining a neuroprotective medication with the thrombolytic agents could be potential treatment approach.

Patients with acute stroke should be admitted to the hospital for subsequent care. Stroke centers provide coordinated, expert management[40]. Admission to a specialized treatment unit (stroke unit) is associated with an increased likelihood of favorable outcomes. Most of the data demonstrating the utility of stroke unit care, which can be recommended to a broad spectrum of patients, comes from studies performed in Europe[41,42]. Subsequent treatment in the hospital should include evaluation for the cause of stroke and initiation of medical and surgical interventions to prevent recurrent stroke, rehabilitation, and measures to prevent or treat subacute complications. Additional research is needed on all aspects of general management of patients with stroke.

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