CRITICAL CARE MANAGEMENT OF ACUTE ISCHEMIC STROKE

Allyson R. Zazulia

ABSTRACT

Although most patients with acute ischemic stroke can be managed in an inpatient stroke ward or urgent care setting, about 15% to 20% will need admission to an intensive care unit. These patients require attention to airway and respiratory status, blood pressure, glucose, temperature, cardiac function, and in some cases, management of life-threatening cerebral edema. This review will discuss general principles in the critical care management of patients with acute ischemic stroke and apply these principles to common clinical scenarios.

INTRODUCTION

Powerful evidence supports the benefit of organized inpatient stroke unit care to prevent complications and reduce the risk of death after acute ischemic stroke. Some stroke units are able to provide an intermediate level of care, such as that required after thrombolytic administration, but about 15% to 20% of patients require admission to a critical care setting for more intensive monitoring or treatment. These may include patients with difficulty controlling blood pressure, acute arrhythmias or myocardial infarction, impaired level of consciousness (or impaired lower cranial nerve function) resulting in inability to maintain an airway, or massive hemispheric or cerebellar infarction creating risk for developing life-threatening cerebral edema, and those undergoing some experimental treatments, such as therapeutic hypothermia. New data have emerged in recent years that have changed the critical care management of acute ischemic stroke, particularly in the areas of glycemic control and aggressive management of cerebral edema.

Of course, patient and family values must be considered before the decision is made to admit a patient to the intensive care unit (ICU). Patients with ischemic stroke are often elderly and may have an advanced directive that specifies that aggressive interventions be withheld. In this situation, ICU admission may not be consistent with the patient’s wishes or an appropriate use of limited resources.

AIRWAY AND RESPIRATORY MANAGEMENT

Respiratory impairment may complicate ischemic stroke in three settings.
(1) It may occur as a direct result of lesions impacting brainstem control of respiration, with loss of pharyngeal tone as well as cough, swallow, and gag reflexes. (2) Consciousness may be diminished, resulting in relaxation of the pharyngeal musculature and tongue and suppression of cough and gag reflexes (Case 4-1).

Case 4-1
A 61-year-old woman was admitted to the neurology floor after the sudden onset of left-sided weakness, dysarthria, and confusion. Blood pressure was 178/96 mm Hg, heart rate 80 beats per minute, and respiratory rate 16 breaths per minute with 100% oxygen saturation on room air. She failed a bedside swallow evaluation because of coughing with intake of liquids and solids and was noted to frequently need to clear her secretions. Over the next 24 hours, she became less responsive with sonorous respirations. Vital signs and oxygen saturation remained stable. Head CT showed hypodensity in the right middle cerebral artery (MCA) territory.

Comment. This patient with MCA infarction has signs of impaired airway protection with depressed level of consciousness, difficulty managing secretions, and impaired swallow. It is not prudent to wait for oxygen saturation to begin to fall before intervening. Initial airway management in ischemic stroke includes repeated assessments for sonorous respirations and inability to manage oral secretions. If such signs develop, conservative measures, including proper positioning, frequent suctioning, and placement of an oral or nasal airway, are indicated. If conservative measures are ineffective, intubation may be necessary. In the setting of large hemispheric infarction with edema, care must be taken to avoid intracranial hypertension that can complicate the intubation process as a result of hypoxia, hypercarbia, and direct tracheal stimulation (Table 4-1). IV lidocaine has been recommended to block the response to tracheal stimulation, but data supporting its use are lacking. Short-acting IV anesthetic agents such as etomidate or thiopental also block this response and additionally suppress brain metabolic rate, theoretically improving tolerance of a transient fall in cerebral perfusion pressure should it occur. Etomidate is generally preferred over thiopental because it is less likely to lower blood pressure.

The risk for respiratory impairment in association with large hemisphere stroke increases after a few days’ delay, as cerebral edema intensifies. With progressive brainstem dysfunction due to herniation, a complete loss of control of pharyngeal musculature and protective reflexes is present. (3) Respiratory

<table>
<thead>
<tr>
<th>TABLE 4-1 Sample Intubation Procedure for Patients With Ischemic Stroke at Risk for Elevated Intracranial Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoxygenation</strong></td>
</tr>
<tr>
<td>100% oxygen for approximately 5 minutes</td>
</tr>
<tr>
<td><strong>Induction</strong></td>
</tr>
<tr>
<td>Etomidate 0.1 mg/kg to 0.5 mg/kg or thiopental 1 mg/kg to 5 mg/kg</td>
</tr>
<tr>
<td><strong>Intubation</strong></td>
</tr>
<tr>
<td>Application of cricoid pressure (Sellick maneuver)</td>
</tr>
<tr>
<td>Laryngoscopy with intubation</td>
</tr>
<tr>
<td><strong>Confirmation of Placement With Auscultation, End-Tidal Carbon Dioxide, and Chest X-ray</strong></td>
</tr>
<tr>
<td><strong>Postintubation</strong></td>
</tr>
<tr>
<td>Full ventilatory support (assist control or intermittent mandatory ventilation)</td>
</tr>
<tr>
<td>Hyperventilation (increase minute ventilation to lower arterial PCO₂ to 25 mm Hg to 30 mm Hg) if acute neurologic deterioration or suspicion of increased intracranial pressure is present</td>
</tr>
<tr>
<td>Sedation with short-acting agents such as fentanyl, midazolam, or propofol, as needed</td>
</tr>
</tbody>
</table>
compromise may be caused by aspiration or systemic complications such as pneumonia, pulmonary embolism, or pulmonary edema. These complications should be considered any time a sudden change in respiratory status occurs in patients with acute ischemic stroke.

The mortality rate of patients with acute stroke who require intubation is high regardless of the reason for intubation, with only about 50% surviving 30 days and 30% surviving 1 year (Milhaud et al, 2004). Predictors of death include low Glasgow Coma Scale score at intubation and absent pupillary light reflexes. Patients who do survive may achieve good functional outcome, however, with more than two-thirds regaining normal activities of daily living with mild to moderate impairment (Santoli et al, 2001).

Intubated patients are at high risk of pneumonia via colonization of the oropharynx, sinuses, trachea, and gastrointestinal tract or contamination from hospital personnel or equipment. Appropriate measures should be taken to minimize this risk. Daily oral care and routine use of chlorhexidine gluconate help reduce this risk.

BLOOD PRESSURE MANAGEMENT

Hypertension occurs commonly after stroke. Even in patients without a history of hypertension, blood pressure is often elevated acutely and typically returns to baseline spontaneously over the first week. A U-shaped relationship between admission blood pressure and death has been found in some studies: both elevated and low blood pressures are associated with high rates of early and late death (Castillo et al, 2004). Theoretical reasons in favor of lowering elevated blood pressure acutely are to reduce the formation of edema and lessen the risk of hemorrhagic transformation. Additionally, allowing blood pressure to remain high risks acute myocardial infarction, pulmonary edema, and renal failure in a population already prone to cardiac and renal disease. However, the acute treatment of hypertension is controversial because of concerns that impaired autoregulation in the peri-infarct area will result in further reduction of cerebral blood flow (CBF) with lowering of blood pressure. In a recent report on hypertensive patients studied with PET within the first week after stroke, focally impaired autoregulation to a 15-mm Hg reduction in mean arterial pressure in the peri-infarct area was not seen. CBF did fall in some patients with lowering of blood pressure, but this was a global phenomenon likely related to an upward shift of the autoregulatory curve as a consequence of chronic hypertension (Powers et al, 2007). Larger blood pressure reductions have been associated with early neurologic worsening, larger infarct volumes, and higher rates of poor outcome and death (Castillo et al, 2004).

American Heart Association guidelines for the early management of ischemic stroke (Adams et al, 2007) recommend treating systolic blood pressures greater than 220 mm Hg or diastolic blood pressures greater than 120 mm Hg. But because of the risk of exceeding an upwardly shifted lower limit of autoregulation in the setting of poorly controlled chronic hypertension, it would be prudent to use any known information on prestroke blood pressure control in treatment decisions.

On the other end of the spectrum is the use of induced hypertension to increase CBF, a practice that is supported by experimental data. Preliminary studies suggest that the administration of vasopressors in carefully selected patients may improve neurologic and radiographic outcome (Hillis et al, 2003), but data from large clinical trials are not available, and the safety of induced hypertension in
acute ischemic stroke has not been established.

**Blood Pressure Management After Thrombolysis**

To reduce the risk of symptomatic hemorrhagic transformation after administration of recombinant tissue-type plasminogen activator (rt-PA), management of blood pressure in this setting follows stricter parameters. The guidelines for monitoring of blood pressure after treatment with rt-PA as used in the National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (t-PA) trial as well as suggested choice of agents (modified from those recommended in the NINDS t-PA trial) are listed in Table 4-2.

**GLUCOSE MANAGEMENT**

Hyperglycemia in the acute phase after ischemic stroke is common, occurring in most or all patients with a history of diabetes mellitus and in one-third to one-half of nondiabetic patients. Hyperglycemia is more common in severe strokes and in those involving the insular cortex, supporting at least some role for an underlying stress response that may involve autonomic dysregulation.

Early hyperglycemia is associated with larger infarct volume in experimental stroke models. In humans, hyperglycemia on admission is associated with increased cerebral edema volume, higher rates of hemorrhagic transformation, lower likelihood of recanalization and clinical benefit with thrombolytic therapy, and worse neurologic outcome. Although retrospective data suggested that early normalization of blood glucose reduced mortality nearly fivefold, the multicenter randomized UK Glucose Insulin in Stroke Trial (GIST-UK) failed to show improved 90-day outcome with IV glucose-potassium-insulin infusions for 24 hours after acute ischemic stroke (Gray et al, 2007). Because glucose-potassium-insulin therapy was associated with significantly lower blood pressure, the authors hypothesized that the blood pressure lowering may have counterbalanced any possible benefit of glucose lowering. Treatment achieved only modest reductions in mean plasma glucose concentration.

---

**TABLE 4-2** Management of Blood Pressure After Treatment With Recombinant Tissue-Type Plasminogen Activator

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monitor Blood Pressure</strong></td>
<td>Every 15 minutes during and for 2 hours after treatment</td>
</tr>
<tr>
<td></td>
<td>Then every 30 minutes for 6 hours</td>
</tr>
<tr>
<td></td>
<td>Then every hour for 16 hours</td>
</tr>
<tr>
<td><strong>Treat if Systolic Blood Pressure Is Greater Than or Equal to 180 mm Hg or Diastolic Blood Pressure Is Greater Than or Equal to 105 mm Hg</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Choice of Agents</strong></td>
<td>Labetalol 10 mg IV over 1 to 2 minutes, may repeat every 5 to 10 minutes</td>
</tr>
<tr>
<td></td>
<td>Nicardipine infusion, 5 mg/h, titrate up to desired effect by increasing 2.5 mg/h every 5 minutes to maximum of 15 mg/h</td>
</tr>
<tr>
<td></td>
<td>Hydralazine 10 mg to 20 mg IV, may repeat every 15 minutes</td>
</tr>
<tr>
<td></td>
<td>Enalapril 1.25 mg IV over 5 minutes, may repeat every 20 minutes to maximum of 5 mg in 6 hours</td>
</tr>
</tbody>
</table>


---

**KEY POINT**

- In the 24 hours after tissue plasminogen activator administration, blood pressure should be kept below 180/105 mm Hg to minimize the risk of hemorrhage.
(less than 18 mg/dL difference between the treatment and control groups); thus this trial did not address the potential benefit of more intensive insulin therapy. However, a recent meta-analysis of intensive glucose lowering in critically ill patients found that tight glucose control did not reduce hospital mortality compared with standard glucose management but was associated with a markedly increased risk of hypoglycemia (Wiener et al, 2008). Because hypoglycemia itself may lead to brain injury, this situation certainly should be avoided after stroke. Several other studies of glucose modulation in acute stroke are ongoing. Until more conclusive evidence becomes available, it seems prudent not to aggressively lower glucose but rather to target moderate glucose levels after acute ischemic stroke. The appropriate level of blood glucose that should prompt intervention is unknown, but a reasonable approach is to target control of glucose levels at 100 mg/dL to 150 mg/dL.

MANAGEMENT OF FEVER AND THERAPEUTIC HYPOTHERMIA

Fever
Fever is quite common in the early phase after ischemic stroke, occurring in more than half of patients (Hajat et al, 2000). The most common cause of fever after stroke is systemic infection, but in some patients the cause is not readily apparent, leading to the assumption of a central origin. A considerable body of evidence suggests a negative effect of fever on outcome in experimental stroke. Data have not been as consistent in humans, but a meta-analysis of nine studies totaling 3790 patients (in which the definition of fever ranged from greater than 37.0°C to greater than or equal to 38.0°C) found a 19% increase in mortality for febrile stroke patients (confidence interval, 0.99-1.43) (Hajat et al, 2000). Combining the probability values of the individual studies, fever was associated with significantly higher morbidity and mortality. Conversely, low body temperature on admission is an independent predictor of good short-term outcome. The mechanism(s) for a detrimental effect of fever on outcome are postulated to include increased metabolic demands, free radical production, and increased release of excitatory neurotransmitters.

American Heart Association guidelines recommend that sources of fever be treated and antipyretic medications be administered to febrile patients with stroke (Adams et al, 2007); however, the optimal treatment regimen is unknown, and the effectiveness of reducing fever in improving outcome has not been established. Several small clinical trials have reported modest success in achieving normothermia with aspirin, ibuprofen, acetaminophen, and intravascular or surface cooling. One trial evaluated the utility of acetaminophen in afebrile patients with stroke and found that, while treatment may result in a small reduction in body temperature, the effects were unlikely to have robust clinical impact (Kasner et al, 2002). The effect of prophylactic antibiotic administration to febrile patients with severe stroke has also been evaluated. A 4-day course of prophylactic mezlocillin plus sulbactam resulted in lower body temperature, reduced incidence of infections, and improved 90-day outcome in one study (Schwarz et al, 2008).

Therapeutic Hypothermia
Lowering body temperature via hypothermic therapy has been demonstrated to have a neuroprotective effect in experimental stroke models, and its early introduction has been shown to improve neurologic outcome after cardiac arrest. Hypothermia can be instituted via surface or intravascular cooling.
Surface cooling is typically achieved with a combination of cooling blankets, ice water, and alcohol packs. This method is uncomfortable, induces a vigorous shivering response, and may require elective intubation, neuromuscular paralysis, and sedation, thus reducing eligibility for treatment to a very small subset of patients with massive strokes. Newer devices designed to enhance contact with skin are more effective at lowering temperature; however, they still induce shivering. More localized cooling with a cooling helmet is being investigated. Alternatively, an IV heat exchange system can be used, which involves circulating warm or cool saline through a central venous catheter. This method is better tolerated than surface body cooling with potentially less of a shivering response and less need for intubation and paralysis.

Patients treated with hypothermia must be monitored in an intensive care setting where clinical status can be monitored and hemodynamic parameters controlled. Potential complications include arrhythmia, hypotension, infection, electrolyte abnormalities, thrombocytopenia, and coagulopathy and are seen more with profound levels of hypothermia (less than 30°C) than with mild to moderate hypothermia (32°C to 36°C). In addition, a rebound increase in intracranial pressure (ICP) may occur with rewarming after hypothermia, which can result in fatal herniation. Controlled slow rewarming (0.1°C to 0.5°C per hour) reduces this risk.

The optimal level of body temperature has not been determined. Several small pilot studies on the safety and feasibility of therapeutic hypothermia in acute ischemic stroke have recently been published, most of them targeting a temperature of 32°C to 33°C. This degree of temperature reduction requires aggressive sedation, which increases the risk of complications and reduces eligibility for the treatment. One study of surface cooling with the “forced air” method for a period of 6 hours in acute stroke showed that a more modest target of 35.5°C to 36.0°C allowed cooling without heavy sedation and was not associated with an increased frequency of complications or increased mortality (Kammersgaard et al, 2000). Two randomized controlled trials of mild to moderate hypothermia within 6 hours of stroke onset are ongoing.

**MANAGEMENT OF CARDIAC ISSUES**

Cardiac ischemia and arrhythmias are not only risk factors for ischemic stroke but are also potential complications after ischemic stroke. Coronary atherosclerosis and myocardial infarction are highly prevalent in patients with fatal ischemic stroke: among patients who died a median of 12 days after stroke, the percentage with coronary plaques, coronary stenosis, and myocardial infarction was 74%, 39%, and 44%, respectively (Gongora-Rivera et al, 2007). Two-thirds of the cases of myocardial infarction were clinically silent. Estimates of the risk of coronary events in the acute period after ischemic stroke primarily come from stroke treatment trials, where the risk of fatal myocardial infarction ranges from 2% to 5%. These rates could be an underestimate because healthier patients tend to be enrolled in such trials, but they may overestimate risk among patients without a history of heart disease.

Elevation of cardiac troponin levels on serial measurements can be found in approximately 10% of patients with acute ischemic stroke (Jensen et al, 2007) and is variably associated with an increased incidence of death. Increased troponin levels occur most frequently in older patients with other comorbidities (heart and/or renal failure) and more severe strokes. EKG
changes such as prolonged QT interval, inverted T waves, ST segment abnormalities, and abnormally prominent U waves are very common after ischemic stroke as are cardiac arrhythmias, particularly atrial fibrillation and premature atrial or ventricular contractions. Fortunately, malignant arrhythmias are rare, but sudden death may occur. A reasonable screen for cardiac ischemia in acute ischemic stroke is an EKG and two cardiac troponin levels obtained 8 to 12 hours apart, with continued measurement of any elevated troponin until it begins to decrease. Routine Holter monitoring will identify occult atrial fibrillation in about 5% of patients with acute ischemic stroke (Liao et al, 2007). Serial EKGS over the first few days may improve this detection rate.

The mechanisms underlying cardiac events in the setting of acute stroke are unknown but may involve disturbances in the autonomic system. This hypothesis is supported by the fact that patients with infarctions involving insular cortex (particularly on the right) have an increased risk of cardiac complications and sudden death, and the insula is the most important cortical area that controls cardiovascular regulation.

Atrial fibrillation with rapid ventricular response is typically managed with cardioselective beta-blockers or calcium channel blockers (Table 4-3). The antiarrhythmic drug amiodarone has atrioventricular node-blocking properties and can be used when other agents are contraindicated or ineffective. In a hemodynamically unstable patient, cardioversion is required (Case 4-2). There is no apparent benefit of acute heparin administration on the risk of early recurrent stroke since the increase in hemorrhagic stroke it produces entirely offsets the decrease in ischemic stroke. However, heparin is indicated if cardioversion is performed after more than 48 hours of atrial fibrillation.

Management strategies in acute myocardial infarction focus on achieving reperfusion, reducing blood pressure and heart rate to decrease myocardial oxygen demand, and limiting further thrombosis with antithrombotic therapy. Blood pressure goals in the setting

<table>
<thead>
<tr>
<th>Table 4-3: Management of Acute Atrial Fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assess for Hemodynamic Instability</strong></td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Heart rate greater than 100 beats per minute</td>
</tr>
<tr>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td><strong>If Hemodynamically Unstable</strong></td>
</tr>
<tr>
<td>Adenosine 6 mg to 12 mg IV bolus or</td>
</tr>
<tr>
<td>Direct-current cardioversion</td>
</tr>
<tr>
<td><strong>If Rapid Heart Rate Greater Than 100 Beats Per Minute</strong></td>
</tr>
<tr>
<td>Cardioselective beta-blocker</td>
</tr>
<tr>
<td>Metoprolol 5 mg to 15 mg IV bolus or</td>
</tr>
<tr>
<td>Esmolol 0.5 mg/kg IV over 1 minute, then 0.05 mg/kg/min to 0.1 mg/kg/min IV</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>Diltiazem 0.25 mg/kg IV bolus, then 10 mg/hour IV infusion or</td>
</tr>
<tr>
<td>Verapamil 2.5 mg to 5 mg IV bolus, then 0.05 mg/min to 0.2 mg/min IV infusion</td>
</tr>
<tr>
<td>Class III antiarrhythmic</td>
</tr>
<tr>
<td>Amiodarone 5 mg/kg IV over 30 to 60 minutes, then 1.2 g to 1.8 g IV over 24 hours</td>
</tr>
</tbody>
</table>

*Continuum Lifelong Learning Neurol 2009;15(3)*

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.
of acute myocardial infarction are often at odds with these goals in the setting of acute ischemic stroke, resulting in difficult management decisions. Consultation with a cardiologist is typically indicated to determine if an acute intervention, such as angioplasty, is indicated.

**Case 4-2**

A 75-year-old woman with a history of hypertension, diabetes, and coronary artery disease was admitted with left hemiparesis and hemianesthesia and right hemianopia. Blood pressure on presentation was 186/92 mm Hg. MRI revealed infarcts in the anterior superficial right MCA territory and the superficial left posterior cerebral artery territory. Later that day, she developed palpitations and dyspnea and was found on telemetry to have atrial fibrillation. EKG confirmed the atrial fibrillation with a ventricular rate of 120 beats per minute and demonstrated T wave inversions in the lateral leads. She was transferred to the ICU and treated with diltiazem. When rate control was not achieved, a loading dose of amiodarone was begun. During the bolus, blood pressure fell to 90/60 mm Hg and she became confused. The infusion was stopped but the blood pressure did not improve. Emergent direct-current synchronized cardioversion with 200 joules was performed, resulting in prompt reversion back to sinus rhythm with a rate of 80 beats per minute and blood pressure of 160/85 mm Hg. Neurologic status improved. Troponin I peaked at 4.0 ng/mL (reference: less than 0.24 ng/mL) 24 hours later.

**Comment.** This patient with multifocal cerebral infarcts was found to have an acute myocardial infarction and atrial fibrillation with rapid ventricular response shortly after admission. Rate control was attempted with diltiazem followed by amiodarone. Amiodarone is associated with a number of potential adverse effects, including hypotension, which occurred in this patient. Once she became hemodynamically unstable, direct-current cardioversion was indicated.

**KEY POINTS**

- Ischemic cerebral edema peaks 2 to 5 days after stroke onset and can lead to brain herniation and death. Routine intracranial pressure (ICP) monitoring is not helpful, however.
- Conservatively managed complete middle cerebral artery (MCA) territory infarction with massive brain edema (“malignant” MCA infarction) is associated with a high mortality rate.
Case 4-3
A 38-year-old man had a sudden onset of right-sided weakness and fell to the ground. On examination in the emergency department, blood pressure was 160/90 mm Hg, and he was alert with dysarthria and reduced speech output. He followed simple, but not two-step, commands. He had a forced left gaze and right visual field cut. Strength in the right arm and leg was antigravity only, and sensation was diminished on that side. Head CT showed a hyperdense left MCA sign. He received IV t-PA 150 minutes after symptom onset and was admitted to the ICU for monitoring. The examination remained unchanged over the subsequent 16 hours, but at that point blood pressure climbed to 190/100 mm Hg and he began to complain of headache, had episodes of emesis, and became progressively less alert. The right side became flaccid. Head CT showed a persistent hyperdense left MCA sign as well as hypodensity in the entire left MCA territory with 8 mm of midline shift, subfalcine herniation, and compression of the suprasellar cistern (Figure 4-1). Six hours later, he was noted to have a 7-mm unreactive left pupil.

Comment. The large size of this patient’s infarct was predicted by the extent of his deficits at onset. Just 16 hours after symptom onset, he already had signs of increased ICP due to cerebral edema. Given that edema typically reaches a maximum at 2 to 5 days, it is likely that he will continue to deteriorate for at least another 2 days. It should be remembered that younger patients may have earlier manifestations of developing edema because without the added space afforded by preexisting cerebral atrophy, herniation will occur sooner. Subfalcine and uncal herniation are most commonly seen with massive anterior circulation infarcts. As the expanding temporal lobe shifts the uncus and hippocampal gyrus over the lateral edge of the tentorium compressing the oculomotor nerve, an ipsilateral dilating pupil develops. Ipsilateral hemiparesis may follow as the opposite cerebral peduncle is compressed against the edge of the tentorium contralateral to the infarct.

As in Case 4-1, this patient requires airway management. With progressive decline in level of consciousness, loss of control of pharyngeal and tongue musculature and cough and gag reflexes occur. If intubation is performed, care should be taken to avoid further increases in ICP. Immediate reversal of herniation is indicated. Hyperventilation is a temporizing measure to reduce ICP until more definitive treatment can be instituted. Reducing arterial P_{CO_2} through hyperventilation constricts cerebral arterioles, decreasing cerebral blood volume and thus ICP; however, it does so at the expense of decreasing CBF, which risks worsening cerebral ischemia. In any case, despite a continued reduction in P_{CO_2} with sustained hyperventilation, the effect on the cerebral vasculature wanes after a period of about 4 hours (Raichle and Plum, 1972), and rapid weaning of sustained hyperventilation can cause a rebound increase in ICP.
within the first few hours often shows loss of gray/white matter distinction and sulcal effacement in the involved territory, and hyperdensity within the distal internal carotid artery (ICA) and/or proximal MCA, indicative of thrombus. The so-called carotid-T occlusion, in which acute occlusion extends from the suprACLoid portion of the ICA into the proximal segments of the middle and anterior cerebral arteries, has high specificity but low sensitivity to predict fatal brain edema. Clinical and radiographic predictors of fatal brain edema include high baseline NIH Stroke Scale (NIHSS) score, early nausea and vomiting, 12-hour systolic blood pressure greater than or equal to 180 mm Hg, early hypodensity of greater than 50% of the MCA territory on CT, diffusion lesion volume greater than 82 mL within 6 hours of onset, involvement of additional vascular territories, elevated white blood cell count, and history of hypertension or heart failure (Kasner et al, 2001). The typical pathologic pattern for the development of malignant MCA infarction is carotid occlusion with abnormal circle of Willis ipsilaterally. Patients with malignant MCA infarction tend to be younger, and there is a small but significant female predominance (Jaramillo et al, 2006).

Although frequently used in the past to treat stroke-induced cerebral edema, corticosteroids do not improve outcome and have fallen out of favor (Qizilbash et al, 2000).

**Hyperosmolar Therapy**

Osmotic agents such as mannitol and hypertonic saline lower elevated ICP and can reverse transtentorial herniation, effects that appear to be achieved primarily via extraction of water from the intracellular and interstitial spaces, resulting in temporary brain shrinkage. They may also improve cerebral perfusion through reduced viscosity or altered red blood cell rheology (Andrews et al, 1993). Despite their widespread use in treating stroke-induced cerebral edema, few investigations of hyperosmolar therapy in ischemic stroke have been done. In some experimental models of ischemic stroke, mannitol, primarily when administered within 6 hours after stroke onset, reduces infarct size, edema, and neurologic deficit (Karibe et al, 1995; Paczynski et al, 1997). Data from observational studies and retrospective reviews in patients with ischemic stroke suggest that, while mannitol may transiently reduce elevated ICP, it does not clearly improve outcome (Candelise et al, 1975; Santambrogio et al, 1978). Even fewer studies have addressed the use of hypertonic saline for the treatment of poststroke edema. While it may paradoxically increase brain water and infarct volume in experimental stroke (Toung et al, 2002), data from human ischemic stroke suggest that it can effectively treat “mannitol-resistant” stroke-induced intracranial hypertension (Suarez et al, 1998). The impact of hypertonic saline on outcome is unknown. While noting the lack of convincing evidence of efficacy, the American Heart Association guidelines (Adams et al, 2007) and others recommend the use of osmotic agents to treat poststroke edema.

The optimal dose and timing of treatment with osmotic agents in ischemic stroke are uncertain. Mannitol is typically administered as a bolus at a dose of 0.5 g/kg to 1.0 g/kg every 4 to 6 hours. Hypertonic saline is typically administered as a bolus (23.4% concentration) in roughly equi-osmolar doses to mannitol or as a continuous infusion (up to 8% concentration). No head-to-head comparisons have been done between the two agents or among different doses, however. Similarly, no studies have addressed the prophylactic use of these agents to treat stroke-associated intracranial hypertension and renal failure.

---

**KEY POINTS**

- Osmotic agents such as mannitol and hypertonic saline lower elevated ICP and can reverse transtentorial herniation. The optimal dosing regimen is uncertain.

- Clearing of mannitol between doses should be monitored with the osmolal gap, and urine output should be replaced with isotonic fluids to reduce risk of rebound intracranial hypertension and renal failure.
swelling and tissue shifts prior to the onset of intracranial hypertension. In addition to their osmotic effects, these agents produce hemodynamic effects that necessitate close monitoring of cardiac and fluid status. The most common complications are fluid and electrolyte imbalances and pulmonary edema. Although rebound intracranial hypertension and renal failure are often cited as major limitations to the use of mannitol, these effects appear to be an issue primarily if the drug is not completely cleared from the blood between administrations and urine output is not adequately replaced, leading to hypovolemia. Monitoring the clearance of mannitol between administrations is most effectively achieved with the osmolal gap (the difference between osmolality and osmolarity, calculated using the formula \(\frac{2 \times \text{sodium}}{\text{blood urea nitrogen}/3} + \frac{\text{glucose}}{18}\)) rather than simple osmolality since only the former correlates well with mannitol levels (Garcia-Morales et al, 2004).

**Decompressive Hemicraniectomy**

Decompressive surgery for large hemispheric infarction involves removing a large frontotemporal-parietal bone flap and opening the dura ipsilateral to the side of infarction to allow outward herniation of the brain, thus lowering ICP and alleviating or preventing downward herniation (Figure 4-2). Several nonrandomized studies have suggested that decompressive hemicraniectomy with duroplasty lowers mortality in patients with malignant MCA infarction without increasing the number of severely disabled survivors. A preplanned pooled analysis of three European randomized controlled trials of decompressive hemicraniectomy (Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarcts [DECIMAL], Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery [DESTINY], and Hemicraniectomy After MCA Infarction with Life-threatening Edema Trial [HAMLET]) compared with conservative treatment confirmed the beneficial effect of surgery suggested by earlier case series (Vahedi et al, 2007). Important eligibility criteria for the pooled analysis included age 18 to 60; NIHSS greater than 15; decrease in level of consciousness to a score of greater than or equal to 1 on item 1a of the NIHSS; CT hypodensity involving at least 50% of the MCA territory; absence of bilaterally fixed, dilated pupils; and inclusion within 45 hours of stroke onset. Surgery within 48 hours of stroke onset increased the chances of a favorable outcome (modified Rankin Scale score of 4 or less), but this includes a 10-fold greater risk of surviving with moderately severe disability.

*Figure 4-2*  CT scan obtained after decompressive hemicraniectomy of the patient in *Case 4-2* demonstrating herniation of brain through the skull defect and resultant lessening of midline shift and basilar cistern compression.
The North American-Hemicraniectomy and Durotomy for Deterioration From Infarction Relating Swelling Trial (HeaDDFIRST), which has only been published in abstract form (Frank, 2003), showed a benefit of surgery in improving survival at 21 days, but the survival benefit did not persist at 3 and 6 months, and there was no improvement in functional outcome at 6 months. Major differences in eligibility criteria for this trial compared with the European pooled analysis are that HeaDDFIRST permitted enrollment of older patients (up to age 75) as well as those who developed severe edema as late as 96 hours after stroke onset. This longer time window means that patients in HeaDDFIRST were more likely to have clinically deteriorated by the time surgery was performed.

The optimal timing of surgery remains unknown. Operating prior to the development of signs of herniation may result in the greatest chance at benefit but means that some patients will undergo surgery needlessly. At least one study reported lower mortality and improved functional outcome among those operated on within 24 hours compared with historical controls operated on after 24 hours of onset (Schwab et al, 1998). However, a systematic review of studies (Gupta et al, 2004) found that time to surgery did not predict outcome, and subgroup analysis from the pooled data cited above revealed no difference in outcome between patients assigned to early (less than 24 hours) versus later (24 to 48 hours) surgery. Nevertheless, early neurosurgical consultation (ie, prior to the development of signs of herniation) is warranted for any patient in whom decompressive hemicraniectomy is being considered.

Two categories of patients who deserve special mention are older adults and those with dominant hemisphere infarction. Age is nearly uniformly the strongest predictor of outcome after hemicraniectomy. Survival rates are clearly lower for those over age 60 compared with those under 60, and while surgery may improve survival in the older population, functional outcome remains poor (ie, no survivors over age 60 achieved a Barthel Index score greater than 60 or an mRS score of less than 4 in one series) (Yao et al, 2005). The age difference between patients in HeaDDFIRST and the European pooled analysis likely contributed to the discrepancy in results between the two patient groups.

Offering decompressive hemicraniectomy to patients with malignant infarction of the dominant hemisphere remains controversial because of a bias among clinicians that quality of life is heavily dependent on the ability to communicate; thus surgery for nondominant hemisphere infarction outpaces surgery for dominant hemisphere infarction fourfold. In fact, the available data do not suggest a worse functional outcome for patients who undergo decompression of the dominant hemisphere (Gupta et al, 2004), and a recent report documented significant recovery from aphasia after hemicraniectomy, especially in younger patients (Kastrau et al, 2005).

**Edema Associated With Cerebellar Infarct**

When cerebellar infarcts swell, life-threatening brainstem and fourth ventricular compression may occur. There may be upward herniation of the cerebellar vermis and hemispheres through the tentorial opening or downward tonsillar herniation through the foramen magnum. Radiographic signs of mass effect develop in up to 38% of cerebellar infarcts (Figure 4-3), and among these, about half are associated with neurologic deterioration (Koh et al, 2000), which may include cranial nerve dysfunction.
hemiplegia or quadriplegia, posturing, or depressed consciousness. In addition, it is critical to remember that the first sign of medullary compression with tonsillar herniation may be rapidly progressive bradycardia, respiratory arrest, and death. Thus, patients with large cerebellar infarcts, particularly those involving the full territory of the posterior inferior cerebellar artery or superior cerebellar artery, should be monitored closely in an ICU with consideration of early neurosurgical consultation.

In the setting of acute obstructive hydrocephalus, placement of an external ventricular drain can rapidly lower intracranial pressure. Suboccipital craniotomy can relieve both obstructive hydrocephalus and brainstem compression. Neither of these treatments has been compared with medical management (or with each other) in a randomized controlled trial.

REFERENCES


Frank JI. Hemicraniectomy and durotomy upon deterioration from infarction related to swelling trial (HeaDDFIRST) first public presentation of the primary study findings. Neurology 2003;60(suppl 1):A426.


