

Continuing Education for Pharmacists



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Hemorrhagic Stroke: Prevention and Treatment

Goals. The goal of this lesson is to discuss hemorrhagic stroke with focus on its clinical characteristics and treatment.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. recognize epidemiologic information and clinical characteristics relevant to hemorrhagic stroke;
2. identify symptomatology that characterizes hemorrhagic stroke and the principles that govern clinical confirmation and management; and
3. select from a list specific therapeutic measures that are reported to modify signs and symptoms of hemorrhagic stroke.

Background

Every year in the United States, 700,000 persons suffer from stroke, and 200,000 of these events are recurrent. Approximately 270,000 persons die each year in the United States because of stroke, ranking it third in mortality behind heart disease and cancer. Hemorrhagic stroke (intracranial hemorrhage) accounts for approximately 13 percent of all strokes. Hemorrhagic stroke not only has a high case fatality, but also limited treatment options and a poor, most often disabling, outcome. Stroke leads to more long-term disability than any other disease process, and

burdens the U.S. healthcare system by a reported \$57.9 billion each year.

Subarachnoid Hemorrhage Epidemiology.

Subarachnoid hemorrhage (SAH) accounts for 21,000 to 22,000 strokes each year in the United States, affecting young adults predominantly. The risk for women is 1.6 times that of men, and the risk for African-Americans is 2.1 times that of whites. The average mortality rate is 51 percent. Approximately one-third of survivors require lifelong care. Most deaths occur within two weeks after the event, with 10 percent occurring before the patient reaches a medical facility and 25 percent within 24 hours after the stroke. Overall, SAH accounts for 5 percent of deaths from stroke, but for 27 percent of all stroke-related years of potential life lost before age 65. One-half to two-thirds of survivors report a decrease in their quality of life.

A number of risk factors for SAH have been identified. Hypertension, a well established risk factor for ischemic stroke, is less well characterized as a risk factor in SAH.

Pathogenesis. Nontraumatic SAH is a neurologic emergency characterized by bleeding into spaces surrounding the brain that are normally filled with

cerebrospinal fluid (CSF). Recall that the brain and spinal cord are covered by three layers of connective tissue, termed the meninges, and encased in bone. The outer layer of the meninges is the dura mater, the middle layer the arachnoid, and the inner layer the pia mater. The arachnoid is a thin, delicate membrane. Separating the arachnoid from the pia mater is the sub-arachnoid space that contains CSF, which serves to cushion the brain and spinal cord. Bleeding into the subarachnoid space initiates a series of events that lead to spasms of the cerebral blood vessels. Spasm can significantly constrict these vessels, resulting in diminished cerebral blood flow. Blood flow is inversely proportional to the fourth power of the radius, so small changes in the vessel size can produce deleterious effects. If blood flow is reduced below the critical level needed to maintain membrane integrity, cerebral ischemia with edema formation and infarction may follow. Regional cerebral edema further compromises local blood flow causing further ischemia despite an overall normal intracranial pressure.

The principal causes of SAH are rupture of aneurysms and arteriovenous malformations (AV anomalies). Trauma can also cause subarachnoid bleeding. Ruptured aneurysms are the cause in 85 percent of patients.

Saccular Aneurysms. Saccular (“berry”) aneurysms are thin-walled outpouchings that protrude from arteries. They gradually enlarge and can ultimately rupture. Multiple aneurysms are found in about 15 percent of affected persons. Since the incidence of aneurysmal SAH is approximately one in 10,000, it is clear that most saccular aneurysms do not rupture. Surgical morbidity far exceeds these percentages. Following rupture, rebleeding is an early and devastating complication. Intracranial aneurysms, unless giant (greater than 1.5 cm in diameter), are usually asymptomatic. An estimated 5 to 15 percent of cases of stroke are related to ruptured intracranial aneurysms.

Clinical Characteristics and Confirmation. SAH should be suspected in persons complaining of a sudden onset of severe headache along with nausea and vomiting, neck pain or stiffness, photophobia and loss of consciousness. The classic symptom is a rapidly developing, severe headache. Patients typically describe it as the “worst headache of my life” or “like a hammer blow.” In three out of four patients, onset occurs within a few seconds. It is the only symptom in about a third of patients. Headache from SAH is usually diffuse. Prodromal (warning) headaches may precede the actual SAH by several weeks in over 40 percent of cases. It is however, not the severity, but the suddenness of onset, which is the characteristic feature of SAH, a feature that patients may fail to mention because it is the severity of pain for which they seek medical attention. SAH is believed to be misdiagnosed in up to half of persons being evaluated for the first time. The most common incorrect diagnoses are migraine and tension-type headache.

Arterial pressure is often elevated and body temperature increased, especially during the first few days after bleeding since sub-arachnoid blood products produce chemical meningitis. Nearly half of all victims experience transient changes in mental status.

A number of neurologic complications can occur if a patient does not die immediately after a SAH. Some result from blood in the subarachnoid space.

Other complications include rebleeding from the same aneurysm, cerebral vasospasm and its resulting ischemia leading to reduced blood supply, hydrocephalus (excessive accumulation of fluid in the cerebral area) from blockage of CSF outflow, and seizures. Non-neurologic complications include cardiac and electrolyte abnormalities.

Survivors of SAH may experience chronically disabling problems. More than half report problems with memory, mood or neuropsychological function. These deficits result in impairment of social roles, even in an absence of apparent physical disability. Up to two-thirds of survivors return to work by one year after a SAH.

Treatment. Patients with SAH should be evaluated and treated on an emergency basis. Following stabilization, they should ideally be transferred to a center with a dedicated neurologic critical care unit to optimize care. The primary goals of treatment are prevention of rebleeding, prevention and management of vasospasm, and treatment of accompanying medical and neurologic complications.

Medical management of a ruptured aneurysm is intended to reduce the risk of rebleeding and cerebral vasospasm and to prevent other medical complications before and after surgical intervention. The patient is provided general support including bed rest, gentle sedation as needed, analgesics for headache and stool softeners to minimize straining. Glucocorticoids may help reduce the headache and neck stiffness and/or pain caused by blood in the subarachnoid space. There is no solid evidence that they reduce cerebral edema, are neuroprotective or reduce vascular injury in SAH; their routine use is therefore not recommended. Hypertension, if present, should be treated but not aggressively since elevated blood pressure may be a normal compensatory mechanism, especially in a chronically hypertensive patient. At present, there is no conclusive evidence whether modifying blood pressure in acute SAH benefits the patient.

The calcium channel antagonist nimodipine (Nimotop) has an established role in decreasing vasospasm in all grades of SAH. A review concluded that calcium channel antagonists decrease the proportion of patients with poor outcome and ischemic neurological deficits after aneurysmal SAH. The results relating to poor outcome depend on one large trial, but against the background of the potentially devastating consequences of vaso-spasm, the use of nimodipine is indicated in all patients with non-traumatic SAH and should be started as soon as the diagnosis is made. A dose of 60 mg should be given every four hours orally or via a nasogastric tube. Nimotop carries a boxed warning to not administer the drug intravenously or by other parenteral routes because deaths and serious life threatening adverse events have occurred when the contents of the capsules have been injected parenterally. Blood pressure should be kept in the “high-normal” range in attempt to maintain cerebral perfusion pressure. If hypotension occurs, the dosage regimen may be changed to 30 mg every two hours.

Primary Intracerebral Hemorrhage

Nontraumatic intracerebral hemorrhage (ICH; within the brain substance) occurs mainly as a result of chronic, poorly controlled hypertension; spontaneous ICH refers to those cases that occur in the absence of trauma. A ruptured vascular malformation is responsible less often. Despite evidence that ICH is more than twice as deadly as SAH, clinical and laboratory research continues to focus primarily on SAH. Unlike the declining mortality with SAH due to improvements in surgical and critical care techniques, morbidity and mortality with ICH have remained relatively unchanged over the past several decades.

Epidemiology. Primary ICH is one of the most devastating forms of stroke, and is responsible for about 80 percent of all intracranial hemorrhages in the United States, affecting approximately 67,000 Americans each year. ICH has the distinction of having the highest mortality rate of all types of stroke.

Morbidity and mortality associated with ICH are dismal, with 30-day mortality ranging between 30 and 40 percent in hospital-based studies to as high as 52 percent in community-based studies. The annual mortality rate following 30-day survival was 8 percent per year for five years in one community-based study with almost half of all later deaths attributed to complications of the original hemorrhage. Only 21 to 28 percent of patients with ICH could live independently after six months.

The risk for primary ICH is estimated to be about twice as high in African-American, Hispanic and Japanese populations than in Caucasians. The reason for the large discrepancy among populations is unclear. Alcohol consumption and low serum cholesterol levels have been theorized to account for some differences in the Japanese population. There is a slight predominance of men with ICH versus women.

Pathogenesis. ICH is bleeding that occurs directly into the brain parenchyma (the functional tissue, as opposed to connective tissue). It is differentiated from intraventricular hemorrhage and SAH, which involve bleeding into the brain's ventricular system and subarachnoid space, respectively. ICH is classified as primary (unrelated to congenital or acquired lesions), secondary (directly related to congenital or acquired conditions), and/or spontaneous (not secondary to trauma or surgery). ICH typically consists of a large area of hemorrhaged blood that clots. Most hemorrhages occur at or near bifurcations of arteries (the point at which a vessel divides into two branches). The blood is slowly removed over the next several weeks by phagocytosis, and after several months, only a small collapsed cavity may remain. Large hemorrhages typically rupture into the ventricles with bleeding into the subarachnoid space.

It is believed that the initial hemorrhage encircles intact neural tissue, which causes neurologic deterioration attributed to the development of cerebral edema. This appears within hours secondary to the clot releasing plasma

proteins into the underlying white matter. Later, delayed thrombin formation may contribute to neural toxicity directly or through damage to the blood-brain-barrier indirectly with subsequent worsening of edema. Peak edema occurs three to seven days following the hemorrhage along with lysis of erythrocytes. Both hemoglobin and its degradation products have been implicated in neural toxicity. The importance of cerebral edema in ICH has been supported by evidence suggesting that patients with a larger amount of cerebral edema relative to the initial hemorrhage volume have a very poor prognosis. Evidence from serial contrast computed tomography (CT) scans show that hematomas can continue to expand over many hours and is the natural course of disease progression. Bleeding may cease when the lesion gets to a size sufficient to produce increased tissue compression (tamponade).

Hypertension is the most important risk factor for ICH especially in persons younger than 55 years of age. It is estimated that approximately 25 percent of ICH events would be prevented if all hypertensive patients received adequate antihypertensive therapy to maintain normal pressure. Smoking, excessive chronic alcohol consumption (more than two drinks/day), and cocaine use (especially in persons older than 45 years) also increases the risk. It is unknown why cholesterol levels less than 160 mg/dL increase the risk.

Warfarin anticoagulation remains a highly effective therapy for prevention of thromboembolic stroke in persons with atrial fibrillation. Anticoagulation to an International Normalized Ratio (INR) of 2.5 to 4.5 has been associated with risk of ICH of approximately 1 percent per year for stroke-prone patients. On the other hand, this rate is nearly 10 times greater than the risk of hemorrhage in a matched group of persons who have not undergone anticoagulation. When such hemorrhages occur, the fatality rate averages 60 percent. Predictors are advanced age, prior ischemic stroke, hypertension, and intensity of anticoagulation therapy.

ICH is the most feared complication of thrombolytic therapy used in acute myocardial infarction or stroke. When a recombinant tissue plasminogen activator (rt-PA) (e.g., alteplase/Activase) is administered within three hours after onset of ischemic stroke symptoms, the ICH rate is 6.5 percent, compared with 0.5 percent in placebo patients. Half of the individuals who sustain these hemorrhages die. The overall benefit of rt-PA therapy in appropriate patients with ischemic stroke is more than counterbalanced by the risk of hemorrhage.

Clinical Manifestations and Confirmation. Although not associated with exertion, ICH usually occurs when the patient is awake and sometimes when stressed. The classic presentation is sudden onset of a focal neurologic deficit that progresses over minutes to hours with accompanying headache, nausea and vomiting, elevated blood pressure and decreased consciousness. The neurologic abnormalities are similar to those caused by ischemic stroke since destruction of neural tissue is the root cause of the dysfunction that results from either entity. Specific signs and symptoms are determined by the location of the lesion. Since the site of ICH often differs from ischemic stroke, characteristic patterns of neurologic loss may be more frequently associated with ICH than with ischemic stroke. Hemorrhages may continue to enlarge over several hours as bleeding continues. Ischemic lesions, on the other hand, usually do not change in size following vascular occlusion. As a result, hemorrhages characteristically cause increasing loss of neurologic function with time until a plateau is reached, whereas ischemic strokes may remain static or fluctuate after the early phases of the stroke. About one-fourth of patients who initially are alert may show subsequent deterioration in their level of consciousness after an ICH. ICH in each of the four typical locations within the brain produces characteristic findings (Table 1).

ICH often cannot be confirmed based on clinical findings alone. The test of choice for assessing the type of stroke is CT.

Table 1
Clinical features of intracerebral hemorrhage

Symptom	Site of Hemorrhage			
	Putamen	Thalamus	Pons	Cerebellum
Unconsciousness	Later	Later	Early	Late
Sensory change	Yes	Yes	Yes	Late
Pupils				
Size	Normal	Small	Small	Normal
Reaction	Yes	Yes or No	Yes or No	Yes
Response to nutrition	Yes	Yes	No	Yes or No
Ocular bobbing	No	No	Sometimes	Sometimes
Gait lost	No	No	Yes	Yes
Vomiting	Occasional	Occasional	Often	Severe

Adapted from Zivin JA. Textbook of Medicine, 22 ed. Philadelphia:Saunders;2004:2298-2305.

Head CT provides substantial information including the size and location of the hemorrhage, and the presence of intraventricular, subarachnoid or subdural blood. It differentiates ICH from nonhemorrhagic cerebral infarctions and may reveal underlying structural abnormality. Magnetic resonance imaging (MRI) is sensitive for ICH; it is useful for dating hemorrhages and identifying small vascular lesions that may be missed with conventional CT. MRI is limited in early detection of ICH, time required to obtain imaging and by the limited ability to monitor patients while in the scanner. **Treatment.** No surgical or medical treatment has proved effective, although an estimated 7,000 surgeries to remove hemorrhaged blood are performed in the United States each year. Supportive treatment is the usual means to manage acute ICH, with early care given to maintenance of airway, oxygenation and nutrition, and treatment of secondary complications. Clinical trials of corticosteroids, glycerol and hemodilution (increasing plasma volume in relation to erythrocytes), have not demonstrated benefit. Corticosteroids, in fact, may increase the risk of infectious complications. There is no accepted means for management of increased intracranial pressure. Hyperventilation, neuromuscular paralysis and osmotherapy (treatment by the intravenous injection of hypertonic

solutions to produce dehydration) are without significant benefit. Fluid management should maintain a normal volume (euvoemia). Seizures should be treated despite a lack of data from randomized trials, since they can be particularly harmful for critically ill patients. Maintenance of normal body temperature is desirable and fever should be aggressively treated with acetaminophen or cooling blankets since fever may accelerate tissue destruction.

Prognosis. Most early deaths result from the direct neurologic consequences of the hemorrhage. The severity of bleeding (e.g., size, extension into ventricles) and level of neurologic function are the best predictors of poor outcomes. Long-term prognosis for various degrees of recovery is similar or better than that of cerebral infarctions of comparable severity. The risk of recurrent ICH has not been well studied, but the risk of at least one rebleed may be as high as 25 percent over the next several years. The risk of ICH can be reduced by appropriate treatment although there is no specific therapy. Control of mild to moderate hypertension decreases the risk of hemorrhagic stroke by one-third to one-half.

Summary and Conclusions

All patients with suspected stroke require rapid assessment and intervention. Assessment aims to establish the diagnosis of stroke and its etiological subtypes, and to estimate the prognosis for complications, recurrent events, survival and handicap. Intervention strives to reverse any ongoing brain hemorrhage or ischemia, lessen the risk of complications and recurrent stroke, and optimize physiological homeostasis and rehabilitation.

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1. Most deaths from subarachnoid hemorrhage (SAH) occur within:

- a. two minutes.
- b. two hours.
- c. two days.
- d. two weeks.

2. The arachnoid is the thin, delicate membrane that constitutes which of the following layers of the meninges?

- a. Inner
- b. Middle
- c. Outer

3. The principal causes of SAH are arteriovenous malformations and rupture of:

- a. aneurysms.
- b. plaque.
- c. arterioles.
- d. granulomas.

4. The classic symptom of SAH is severe:

- a. cramping.
- b. depression.
- c. headache.
- d. syncope.

5. General support for patients experiencing an SAH include all of the following EXCEPT:

- a. antiemetics.
- b. analgesics.
- c. sedatives.
- d. stool softeners

6. Spontaneous intracerebral hemorrhage (ICH) refers to those cases that occur in the absence of:

- a. syncope.
- b. symptoms.
- c. thromboembolism.
- d. trauma.

7. The bleeding associated with ICH occurs directly into the brain parenchyma which is:

- a. connective tissue.
- b. functional tissue.
- c. interstitial tissue.
- d. mesenteric tissue.

8. The most important risk factor for ICH, especially in persons younger than 55 years of age, is:

- a. hyperkalemia.
- b. hyperlipidemia.
- c. hypertension.
- d. hyperthrombosis.

9. The root cause of the dysfunction that results from either ICH or ischemic stroke is:

- a. destruction of neural tissue.
- b. initiation of arterial fibrillation.
- c. precipitation of ventricular tachycardia.
- d. rupture of atherosclerotic plaque.

10. Which of the following has been proven to be effective in treating ICH?

- a. Medical treatment only
- b. Surgical treatment only
- c. Both medical and surgical treatment
- d. Neither medical nor surgical treatment



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