Management of Aneurysmal Subarachnoid Hemorrhage

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Aneurysmal subarachnoid hemorrhage (SAH) accounts for approximately 6–8% of all strokes. Unlike other forms of cerebrovascular disease, the incidence of SAH has not declined during the last 2 decades.1 Based on the US population and available data on the incidence of SAH (11/100,000), the calculated number of SAH cases per year is approximately 26,000. SAH is a serious disorder with a potential for high mortality.2 Approximately 10% of persons with aneurysmal SAH will die rapidly because of the consequences of SAH.

The outcome in patients with aneurysmal SAH begs for improvement. Currently, about half of the patients die within 3 months, half of the survivors have a major disability, and about two thirds of those who have successful aneurysm obliteration never regain their prehemorrhage quality of life.3 The leading causes of morbidity and mortality are the neurological and medical sequelae of the initial hemorrhage, recurrent aneurysmal rupture, and ischemic deficits resulting from cerebral arterial vasospasm. Early recognition and prompt management of SAH is of critical importance, but unfortunately, pitfalls in diagnosis remain common.4,5 Computed tomography (CT), cerebrospinal fluid (CSF) analysis in CT-negative cases, and four-vessel cerebral angiography remain the standard methods of diagnosis. Several scales (Table 1) have been developed to forecast prognosis and assist in examining response to treatment, but they are subject to interobserver variability.6,7 One currently used scale is that of the World Federation of Neurological Surgeons.

General Principles of Management

All patients with SAH should be admitted to the hospital for emergency evaluation and treatment. The optimal care of these patients is provided by a team consisting of neurosurgeons, neurologists, neuroradiologists, neuroanesthesiologists, and intensive care specialists in a stroke or intensive care unit where close nursing and medical observation are possible. Cardiac monitoring is recommended. A massive sympathetic discharge, which often accompanies SAH, is frequently associated with life-threatening cardiac arrhythmias, electrocardiographic abnormalities, and morphological changes in the heart.8 These changes may be preventable by early treatment with propranolol.9 If the patient is comatose when first seen, management of the airway and maintenance of adequate ventilation and oxygenation should be accomplished immediately.

Patients are placed at absolute bed rest in a quiet and darkened room. The head of the bed is elevated no more than 30° to promote venous drainage and reduce the potential for cerebral edema. Stimulation is minimized, and visitors are restricted. The skin pressure areas are regularly examined for early signs of breakdown. Maintenance of adequate respiratory toilet is essential. Prevention of venous thrombosis is attempted with pneumatic compression stockings. Nutritional requirements are best met with a high-fiber, soft oral diet. Patients are not allowed to feed themselves. A tube-feeding formula may be required in those unable to maintain adequate caloric intake by mouth. Stool softeners may be necessary to avoid straining. We use dioctyl sodium sulfosuccinate, 50–200 mg orally, or psyllium, 3.7–11 g orally, given daily. After the first week patients can be helped to a bedside commode. Incontinent or comatose patients should be catheterized, preferably with a condom catheter in men or a closed Foley catheter in women.

The alert patient will have headache and neck pain. Analgesia is provided with codeine phosphate or meperidine hydrochloride given intramuscularly or orally at regular intervals. In general, a dose of 30 mg of codeine every 4–6 hours or 50–100 mg of Demerol every 2–4 hours is given. Patients who are nauseated or vomiting may receive trimethobenzamide hydrochloride or hydroxyzine hydrochloride. Because of the possible occurrence of gastric mucosal ulceration and gastrointestinal hemorrhage in SAH patients, the histamine H2 blocking agent ranitidine can be used. Agitated or restless patients should be sedated. Phenobarbital, 30–60 mg every 6 hours, is preferred for both its sedative and anticonvulsant properties. Diazepam or hydroxyzine may also be useful. Approximately 10–26% of patients with aneurysmal SAH will experience seizure-like...
TABLE 1. Commonly Used Clinical Grading Scales in Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical description</th>
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<tbody>
<tr>
<td><strong>Hunt-Hess Scale</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Asymptomatic or mild headache</td>
</tr>
<tr>
<td>II</td>
<td>Moderate to severe headache, nuchal rigidity, can have oculomotor palsy</td>
</tr>
<tr>
<td>III</td>
<td>Confusion, drowsiness, or mild focal signs</td>
</tr>
<tr>
<td>IV</td>
<td>Stupor or hemiparesis</td>
</tr>
<tr>
<td>V</td>
<td>Coma, moribund, and/or extensor posturing</td>
</tr>
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**Cooperative Aneurysm Study Scale**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical description</th>
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<tbody>
<tr>
<td>I</td>
<td>Free of symptoms</td>
</tr>
<tr>
<td>II</td>
<td>Mildly ill, alert and responsive, headache present</td>
</tr>
<tr>
<td>III</td>
<td>Moderately ill</td>
</tr>
<tr>
<td>a</td>
<td>Lethargic, headache, no focal signs</td>
</tr>
<tr>
<td>b</td>
<td>Alert, focal signs present</td>
</tr>
<tr>
<td>IV</td>
<td>Severely ill</td>
</tr>
<tr>
<td>a</td>
<td>Stuporous, no focal signs</td>
</tr>
<tr>
<td>b</td>
<td>Drowsy, major focal signs present</td>
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</table>

**World Federation of Neurological Surgeons Scale**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical description</th>
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<tbody>
<tr>
<td>I</td>
<td>Glasgow Coma Scale Score 15: no headache or focal signs</td>
</tr>
<tr>
<td>II</td>
<td>Glasgow Coma Scale Score 15: headache, nuchal rigidity, no focal signs</td>
</tr>
<tr>
<td>III</td>
<td>Glasgow Coma Scale Score 13-14: can have headache, nuchal rigidity, no focal signs</td>
</tr>
<tr>
<td>IV</td>
<td>a Glasgow Coma Scale Score 13-14: can have headache, nuchal rigidity, or focal signs</td>
</tr>
<tr>
<td></td>
<td>b Glasgow Coma Scale Score 9-12: can have headache, nuchal rigidity, or focal signs</td>
</tr>
<tr>
<td>V</td>
<td>Glasgow Coma Scale Score 8 or less: can have headache, nuchal rigidity, or focal signs</td>
</tr>
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The use of prophylactic anticonvulsant therapy in patients with aneurysmal SAH is controversial. Since seizure prevention is desirable in a patient with a ruptured aneurysm in whom a sudden increase in blood pressure associated with seizure activity can have ominous consequences, we regularly use either phenobarbital or phenytoin.

Hyponatremia can occur in SAH as the result of inappropriate secretion of antidiuretic hormone (SIADH) or a central salt-wasting syndrome. If hyponatremia occurs as a consequence of true SIADH, patients have an expanded blood volume requiring fluid restriction. Patients with central salt wasting have hyponatremia and hypernatremia but decreased blood volumes. Infusions of normal saline, packed red cells, and colloids are required. Daily intake of fluids should be approximately 2,000-3,000 ml. Avoidance of either dehydration or overhydration is important. Daily determination of fluid intake and output is necessary. An intravenous access line is placed, using normal saline or half-normal saline. Hypo-osmolar fluids such as dextrose in water may raise intracranial pressure and should be avoided.

The blood pressure should be measured frequently or monitored continuously during the first 48-72 hours after SAH because transient arterial hypertension often develops. One possible consequence of hypertension is rebleeding. Blood pressure frequently returns to normal after the patient is sedated, headache subsides, and raised intracranial pressure is lowered. Arterial hypotension poses the risk of exacerbating neurological deficits from cerebral vasospasm. Some antihypertensives may increase intracranial pressure by causing cerebral vasodilatation. Hence, normotension must be judiciously obtained. Only when the systolic blood pressure becomes considerably elevated, i.e., >180 mm Hg, is it imperative to treat. If the patient is incapable of oral intake, several parenteral regimens may be used. Apresoline, propranolol, nifedipine, labetalol, or sodium nitroprusside are the most commonly used agents. Methyldopa is avoided because it may cause depression of the central nervous system. The doses of hydralazine and propranolol may be repeated every 6 hours. For rapid control of severely elevated blood pressure, nitroprusside remains the preferred therapy.

Increased intracranial pressure results from extensive SAH, a large parenchymal hematoma, cerebral vasospasm, brain edema, or hydrocephalus. If there are signs of increased intracranial pressure and herniation, the use of intubation, hyperventilation, and mannitol is indicated.

Mannitol (20–25% solution for infusion) is given initially in a dose of 1 g/kg body wt over 20–30 minutes, followed by a dose of 0.25 g/kg body wt every 4 hours depending on clinical findings, serum osmolality, and intracranial pressure values. Dexamethasone is sometimes given to patients with raised intracranial pressure and cerebral edema after SAH although the use of steroids is...
controversial. Furosemide is often used in conjunction with mannitol. Ventricular drainage and surgical removal of intraparenchymal hemorrhage may be needed in cases of life-threatening hematoma or obstructive hydrocephalus.

Prevention of Rebleeding

Much of the general treatment of patients with recent SAH is aimed at preventing rebleeding. Rebleeding is maximum on the day of the initial hemorrhage, when the incidence reaches 3.8%. A smaller peak of recurrent hemorrhage occurs at 1 week after SAH. Rebleeding happens within 1 month in one third of cases, and in the first 6 months at least half of unoperated patients will rebleed. Approximately one half to two thirds of the patients who have acute rebleeding die. Winn et al reported a 10-year follow-up study of 213 nonsurgically treated patients who had survived at least 6 months after the initial bleed from either a single posterior communicating or anterior communicating artery aneurysm. The rebleeding rate was at least 3%/yr with a mortality rate associated with late rebleeding of 2%/yr.

Rebleeding is attributed to lysis of the clot that plugs the aneurysmal tear after the original rupture. A plug of platelets and fibrin tamponades the leaking dome of the aneurysm and is responsible for cessation of the hemorrhage. Raised levels of fibrinogen degradation products can be found in the CSF following SAH. Focal parenchymal damage may also increase fibrinolysis within the CSF and plasma. The perianeurysmal clot may be dissolved by this increased fibrinolytic activity.

Bed rest only do not prevent rebleeding. Two strategies have been proposed to reduce rebleeding: early surgery and antifibrinolytic therapy. Surgical obliteration of the aneurysm is the optimal method to prevent rebleeding. The aim of antifibrinolytic therapy is preservation of the perianeurysmal clot, thereby reducing the risk of recurrent hemorrhage while waiting for surgery.

There has been considerable debate about the use of antifibrinolytic drugs following SAH. A survey of physicians indicated that many use them routinely, while others do not. Antifibrinolytics do reduce the risk of rebleeding but do not reduce early mortality. Anti-fibrinolytics retard clot lysis by inhibiting the formation of the proteolytic enzyme plasmin from plasminogen and reduce fibrinogen degradation products in the CSF.

The two drugs most commonly prescribed are e-aminocaproic acid (EACA) and tranexamic acid, which is most popular in Europe, is around 6 g (4–12 g).

Recent studies suggest that the reduction in mortality from rebleeding among patients given antifibrinolytics is offset by deaths from cerebral infarction. Furthermore, although antifibrinolytic treatment reduces the risk of recurrent hemorrhage during the first 2 weeks after SAH, it does not prevent rebleeding during the first few days. This failure has been attributed to inadequate initial blood levels of antifibrinolytics when a loading dose has not been administered.

Given these limitations, we use EACA in patients scheduled for late surgery but not in patients operated on early. EACA is given from the day of admission to the day of surgery but no longer than 21 days. Continuous intravenous infusion is preferable to maintain a therapeutic plasma concentration; oral administration is avoided. Our current practice is to give EACA as an intravenous bolus of 5 g, followed by a continuous infusion of 1–1.5 g/hr in patients in whom late surgery is planned. During this time patients are kept well hydrated. If signs of cerebral ischemia develop, EACA is discontinued. The potential benefit of antifibrinolytic therapy, combined with the calcium ion entry blocker nicardipine, has been recently reported.

Surgery

Surgery is the only accepted means to prevent long-term aneurysmal rupture. The optimal timing of surgical intervention for ruptured intracranial aneurysms remains controversial. The decision of when to operate requires careful judgment based on individual patient status and, most importantly, on the experience of the operating surgeon. Early surgery removes the threat of rebleeding, facilitates the use of hypertensive therapy and volume expansion to treat cerebral vasospasm, and allows cisternal lavage with removal of the maximal amount of clot. However, brain swelling is more often present during early surgery, subarachnoid blood may obscure the normal anatomy, and intraoperative aneurysmal rupture is more common than with delayed surgery. Late intervention entails a lower perioperative morbidity and mortality; however, fewer patients survive to undergo surgery.

In an attempt to resolve the dilemma of when to operate, the International Cooperative Study on the Timing of Aneurysm Surgery was organized. This study failed to demonstrate a clear mandate for early (within 3 days of SAH) versus late surgery (7–14 days after SAH). While early surgery effectively reduced the complication of rebleeding, this benefit was offset by a higher frequency of cerebral ischemia (N.F. Kassell, J.C. Torner, J.A. Jane, unpublished study).

One approach to the problem is to operate early on clinical grade I and II patients, provided the CT shows no cerebral edema or mass effect and angiography demonstrates an aneurysm in a favorable
anatomical site without vasospasm. Operative treatment is delayed in poorer grade patients, those with aneurysms in more difficult locations, and those with angiographic or clinical vasospasm. EACA is given only to patients operated on late. Timing in those with vasospasm is based on clinical improvement and angiographic resolution.

**Prevention and Management of Cerebral Vasospasm**

Delayed focal or diffuse ischemic neurological deficits associated with cerebral arterial vasospasm are a leading cause of death and long-term disability after SAH. Cerebral arterial vasospasm may be focal, segmental, or diffuse and symptomatic or asymptomatic. Symptomatic or clinical vasospasm refers to the delayed ischemic deficits associated with cerebral arterial narrowing. The usual symptoms of vasospasm develop gradually and are characterized by increasing headaches, drowsiness, increased meningismus, low-grade fever, and focal neurological signs. Approximately 70% of patients who suffer aneurysmal SAH will have angiographic evidence of arterial narrowing; about 30% will develop clinical deterioration from ischemic symptoms. If clinical deterioration occurs, a CT is obtained to evaluate ventricular size, the possibility of rebleeding, or the presence of cerebral infarction. Angiography is done to confirm the existence of vasospasm. Transcranial Doppler sonography is also useful to assess the time course and severity of cerebral arterial vasospasm after SAH.

Cerebral vasospasm may begin by Day 3, peaks around Days 6–10, and usually subsides in 3 weeks after aneurysmal SAH. Some patients are at high risk for developing vasospasm: seriously ill patients with poor clinical grade, those with prominent meningeal signs, patients with focal, thick collections of blood or a diffuse subarachnoid layer of blood on CT, and patients with early cortical enhancement on CT. Early intracranial surgery or the use of antifibrinolytic agents may also increase the risk of cerebral ischemia following aneurysmal rupture.

It is unclear whether vasospasm represents contraction or failure of relaxation of arterial smooth muscle cells or whether it is at least in part a proliferative vasculopathy. The extravasation of a wide variety of vasoactive substances into the subarachnoid blood is the most likely mechanism for vasospasm.

Effective therapy to prevent or treat symptomatic vasospasm remains elusive. Wilkins reviewed the wide variety of experimental and clinical approaches to treatment or prevention of cerebral vasospasm. The current emphasis is on calcium ion entry blocking agents. This class of drugs reduces myoplasmic calcium by blocking the "slow channel" influx of extracellular calcium, which is essential for contraction of smooth and cardiac muscle but not skeletal muscle. Calcium ion entry blocking drugs produce dilation of collateral vessels, improve red blood cell deformability, and interfere with platelet aggregation. In addition, calcium channel blockers may have a beneficial effect on parenchymal cells during ischemia.

There are currently three calcium blocking drugs available in the United States: verapamil, diltiazem, and nifedipine. Unfortunately, none of these agents is helpful in the prevention of cerebral arterial vasospasm after SAH. The agents that have received most attention are the experimental dihydropyridine drugs nimodipine and nicardipine.

In a prospective trial of oral nimodipine versus placebo, Allen et al randomized 121 patients in good condition. Nimodipine or placebo was given within 96 hours of aneurysmal SAH and was administered for 21 days. At the end of 21 days, the incidence of cerebral arterial vasospasm was not reduced, nor was the rebleeding rate influenced by nimodipine. At the end of 21 days, the number of patients who had completely recovered from ischemic neurological deficits was similar in both groups. However, severe neurological deficits from cerebral arterial vasospasm were significantly more common in the placebo group. Auer et al also documented a favorable response to nimodipine in an uncontrolled multicenter study involving 120 good-condition SAH patients. Nimodipine was applied topically during operation and was given intravenously for 7–14 days after SAH, followed by oral administration for another week. Ljunggren et al reported similar favorable results with the use of intravenous nimodipine.

The University of Iowa and New York University Medical Center have recently completed a dose-escalation study of 60 patients to determine the highest nontoxic and potentially optimal dose of nicardipine for the prevention of cerebral vasospasm after aneurysmal SAH. Patients received a continuous intravenous infusion of nicardipine for up to 14 days after SAH. Seven dose levels progressing from 0.01 mg/kg/hr to 0.15 mg/kg/hr were administered. Seriously ill patients, who are at high risk for cerebral vasospasm, were treated. Only three patients had permanent neurological deficits secondary to cerebral vasospasm. The results of this study form the basis of a new, multicenter, randomized, placebo-controlled trial currently in progress.

Patients with ischemic neurological deficits associated with cerebral vasospasm have lost cerebral autoregulation. Therefore, cerebral blood flow responds passively to changes in systemic blood pressure and cardiac output. Currently, the most commonly accepted therapy for symptomatic vasospasm is to increase the cerebral perfusion pressure with plasma volume expansion and, if required, vasopressor agents. All patients receiving hypervolemic and hypertensive therapy should have an arterial line placed for continuous monitoring of arterial pressure and a central venous catheter or a pulmonary artery catheter to measure the central venous or pulmonary capillary wedge pressure.
Different protocols have been used. By using intra-vascular volume expansion in combination with vasopressor agents, Kassell et al. obtained improvement of neurological deficits in 74% of 58 patients treated. A number of risks are associated with hypervolemic/hypertensive therapy. Increased systemic arterial pressure may aggravate cerebral edema and may also promote aneurysmal rebleeding and hemorrhagic infarction. Other risks include myocardial infarction, pulmonary edema, cardiac arrhythmias, hemotherax, and hyponatremia. We generally begin therapy with plasma volume expansion using plasmapheresis or hetastarch to elevate the central venous filling pressure to approximately 10 mm Hg or the pulmonary capillary wedge pressure to about 14–18 mm Hg. The hematocrit is maintained at approximately 40%. If no response is obtained with these measures, hypertension is induced with dopamine or dobutamine to elevate the mean arterial blood pressure by 20–40 mm Hg from pretreatment levels. With a favorable response this therapy is maintained for 48–72 hours and then gradually reduced depending on neurological function.

References


