Aneurysmal Subarachnoid Hemorrhage: Strategies for Preventing Vasospasm in the Intensive Care Unit

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Abstract

This article addresses the intensive care unit (ICU) management of patients with aneurysmal subarachnoid hemorrhage (SAH), with an emphasis on the prevention of cerebral vasospasm and delayed cerebral ischemia (DCI), which are major contributors to morbidity and mortality. Interventions addressing various steps in the development of vasospasm have been attempted, with variable success. Enteral nimodipine remains the only approved measure to potentially prevent DCI. Since oral and intravenous administrations are limited by hypotension, direct administration via sustained-release pellets and intraventricular administration of sustained-release microparticles are being investigated. Studies of other calcium channel blockers have been disappointing. Efforts to remove blood from the subarachnoid space via cisternal irrigation, cisternal or ventricular thrombolysis, and lumbar cerebrospinal fluid drainage have met with limited and variable success, and they remain an area of active investigation. Several interventions that had early promise have failed to show benefit when studied in large trials; these include tirilazad, magnesium, statins, clazosentan, transluminal angioplasty, and hypervolemia.

Keywords
- subarachnoid hemorrhage
- aneurysm
- vasospasm
- hypertension
- treatment

Subarachnoid hemorrhage (SAH) refers to bleeding that occurs primarily within the subarachnoid space. The most common cause of SAH is trauma, but among cases of spontaneous SAH, rupture of an intracranial saccular aneurysm accounts for approximately 85%.[1] Other causes of spontaneous SAH include bleeding from arteriovenous malformations, moyamoya syndrome, bleeding disorders, cocaine and stimulant abuse, and extension of intracerebral hematomas. In up to one-fifth of cases, no source of bleeding is identified.[2]

Acute aneurysmal SAH results from the sudden extrusion of blood from a defect in the wall of an arterial aneurysm. The duration of the bleeding event determines the impact of the primary injury, and ranges from a severe headache to syncope to sudden death in about a quarter of patients.[3] The amount of blood in the subarachnoid space sets the stage for secondary injury from hydrocephalus,[4] vasospasm, and delayed cerebral ischemia (DCI).[5,6] The focus of treatment is anticipating, preventing, and managing these secondary complications.

In addition to the neurologic consequences of SAH, intense activation of the sympathetic nervous system occurs, which can produce a variety of extracranial consequences including hypertension, stunned myocardium,[7] neurogenic pulmonary edema,[8] abnormal renal function, and systemic inflammatory response syndrome (SIRS).[9]

Risk Factors

Several risk factors for SAH have been identified, although it is not clear whether these factors identify risk of developing an aneurysm or risk of rupture of an aneurysm that already exists. Modifiable risk factors include hypertension, cigarette

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smoking,[10] and heavy alcohol consumption.[11] Genetic factors also play an important role in SAH.[12] The odds ratio of SAH for individuals with one affected first-degree relative is 2; this increases to 51 for individuals with two affected first-degree relatives.[13] Aneurysm development is more common in patients with connective tissue disease and polycystic kidney disease, and identifying other genetic markers is an active area of investigation.[14–17]

Pathophysiology

Most aneurysms are located near the circle of Willis at the base of the brain and near arterial bifurcations (aneurysms secondary to bacterial endocarditis [mycotic aneurysms] tend to form more distally). About 85% of aneurysms occur in the carotid circulation, with the most common sites being the origin of the posterior communicating artery from the internal carotid artery (41%), anterior communicating artery/anterior cerebral artery complex (34%), and middle cerebral artery (20%).[1] Up to 20% of patients have multiple aneurysms.[18]

Presentation

The typical presentation of acute SAH is the sudden onset of a severe headache, nausea, vomiting, and syncope. Presenting with focal neurologic deficits is very unusual, but may be seen due to mass effect from a giant aneurysm, parenchymal hemorrhage, subdural hematoma, or a large localized subarachnoid clot. In addition, third cranial nerve palsies (dilated pupil, ptosis, and limited eye movements) may be present due to aneurysmal compression of the nerve, particularly with posterior communicating artery aneurysms. Seizures at onset may be reported by family, but it is not clear how many of these episodes represent true epileptic events versus abnormal posturing.[19]

Initial Management

The initial steps in managing a patient who is suspected of having a SAH focus on airway evaluation, early computed tomographic (CT) imaging, blood pressure control, serial assessment of neurological function, and stabilization to undergo additional diagnostic studies (CT angiography, catheter angiography). Clinical status is usually described using the method proposed by Hunt and Hess[20] and World Federation of Neurological Surgeons (WFNS) Scales[21] (►**Table 1** and **2**).

Diagnosis

A noncontrast CT scan remains the diagnostic test of choice to detect SAH. Current CT scanners have a sensitivity of 98.7% when performed within 6 hours of onset in patients presenting with thunderclap headache and a normal neurological examination.[22] Blood appears as a hyperdense signal in the cisterns surrounding the brainstem. CT may be falsely negative if the volume of blood is very small, if the hemorrhage occurred several days prior, if the blood is primarily located in the posterior fossa, or if the hematocrit is extremely low. Traditional teaching has been that if the CT is normal and suspicion of SAH remains strong, a lumbar puncture (LP) should be performed. More recent studies suggest that the yield of LP in this setting is quite low.[23]

Conventional catheter angiography is the gold standard for the detection of intracranial aneurysms. CT angiography has recently improved to the point where some centers perform it routinely.[24,25] Magnetic resonance angiography techniques are rapidly advancing, but there can be some limitations of its use in the acute care setting.

In 15 to 20% of cases, angiography fails to demonstrate the cause of SAH.[26] If a high-quality complete angiography does not identify a source of bleeding, patients have a very low incidence of rebleeding, especially if the blood is limited to the perimesencephalic and ambient cisterns.[27]

If the patient is lethargic or agitated, consideration should be given to elective intubation to facilitate performing safe and rapid angiography.

Table 1 Hunt–Hess scale

Grade	Symptoms
1	Asymptomatic or mild headache
2	Moderate to severe headache, nuchal rigidity, with or without cranial nerve deficits
3	Confusion, lethargy, or mild focal symptoms
4	Stupor and/or hemiparesis
5	Deep coma, decerebrate rigidity

Table 2 World Federation of Neurologic Surgeons

Grade	Glasgow Coma Scale	Motor deficits
I	15	Absent
II	13–14	Absent
III	13–14	Present
IV	7–12	Present or absent
V	3–6	Present or absent

Medical Complications

Blood pressure is typically elevated following SAH due to pain and anxiety and sympathetic activation. Left untreated, hypertension is thought to increase the risk of aneurysmal rerupture; however, few data exist to support this notion.[28] Still, most recommend normalization of blood pressure.[29] Analgesics alone may be effective; otherwise, rapidly acting antihypertensive agents are employed. Preferred agents include labetalol, hydralazine, and nicardipine.[30,31] An important exception to treatment of hypertension is when hydrocephalus is present. In that situation, blood pressure should be addressed only after the hydrocephalus is treated.

Cardiovascular abnormalities are common in SAH. Electrocardiographic changes include sinus arrhythmia, tall

peaked "cerebral" T-waves, ST segment depression, and prolonged QT segments.[32] Cardiac enzymes are often mildly elevated. Arrhythmias occur frequently, but are most commonly benign unless associated with electrolyte abnormalities; however, some patients may have more serious arrhythmias, sometimes leading to cardiac arrest.

In rare cases, patients may present with severe cardiac dysfunction. Myocardial contractility is markedly impaired, leading to a fall in cardiac output and blood pressure as well as pulmonary edema.[33,34] This condition has been referred to as "stunned myocardium," and may also include an element of neurogenic pulmonary edema.[8,35] The typical pattern on echocardiography is that of Takotsubo cardiomyopathy,[36] and management is similar to other causes of acute pump failure with inotropic agents, diuretics, high concentrations of oxygen, and PEEP.[8,36] The condition is remarkably transient and completely resolves in a few days.[37,38] The severity of the SAH is the most important predictor of cardiac dysfunction.

Initial ICU Management

Patients may be admitted to the intensive care unit (ICU) directly from the emergency department or following surgical or endovascular repair of the aneurysm. Routine monitoring includes serial neurological examinations; continuous electrocardiographic monitoring; and frequent determinations of blood pressure, electrolytes, body weight, fluid balance, and, in many centers, transcranial Doppler (TCD) measurement of cerebral blood flow velocities and continuous electroencephalography.

Prevention of Rebleeding

The risk of rebleeding is highest immediately following SAH, occurring in 8 to 10% within the first 24 hours, and declining over the next few days. Rates are highest in women and those with a poor clinical grade, in poor medical condition, and with elevated systolic blood pressure. More than half of the patients who rebleed die.

Prior to aneurysm repair, factors associated with rebleeding (e.g., cough, Valsalva) should be minimized. Excessive stimulation should be avoided. Agitated patients should be sedated with short-acting agents, but should remain responsive enough for assessment of neurologic status. Over-sedation should be avoided, as it may mask clinical deterioration. Definitive prevention of rebleeding is by repair of the aneurysm, either by surgical or endovascular means. This should be completed within 24 hours of presentation.

Vasospasm and Delayed Cerebral Ischemia

While in general the term "vasospasm" implies vasoconstriction leading to a reduction in the caliber of a vessel, it has many other meanings when used in the context of SAH. For the purposes of this discussion, "vasospasm" will be used to refer to the blood vessel changes that occur and are seen on cerebral angiography. Delayed neurologic deficits with or without vasospasm will be referred to as delayed neurologic ischemia (DCI).

The relationship between SAH and arterial narrowing seen on cerebral angiography was first described by Ecker and Riemenschneider in 1951.[39] Previously, Robertson ascribed ischemic brain lesions identified on autopsy to probable spasm of arteries.[40] Fisher and colleagues published a sentinel paper in 1977 in which they associated neurologic deficits with vasospasm.[41] From that point until very recently, arterial vasospasm was considered the proximate cause of delayed neurologic deterioration, ischemia, and infarction.[42] Over the past decade, several observations have weakened that association and opened up many new areas of investigation.[43,44]

Histologically, following SAH there are structural alterations in endothelial and smooth muscle cells of the arterial wall.[45] The release of oxyhemoglobin into the subarachnoid space seems to instigate these changes.[46] Oxyhemoglobin stimulates the secretion of endothelin (ET)-1, a potent vasoconstrictor;[47] inhibits the vasodilatory effects of nitric oxide (NO); and produces oxygen-free radicals,[48] which may play a role in lipid peroxidation, possibly mediating the structural changes in the vessel wall.

The role of inflammation in the development of vasospasm is an active area of investigation. The incidence of vasospasm is increased in the presence of SIRS,[9] and cerebrospinal fluid (CSF) levels of cytokines are elevated in patients who develop vasospasm.[49,50] Endothelial NO synthase (eNOS) gene polymorphisms are associated with vasospasm.[51]

Vasospasm has been clearly linked to neurologic deficits, reduced cerebral blood flow, and ischemia and infarction; yet, all of these can occur in its absence.[52,53] Large trials of an endothelin antagonist demonstrated a reduction in the incidence of vasospasm, but had no effect on clinical outcome.[54,55] Regions of reduced cerebral blood flow and cerebral infarction are frequently seen independent of vasospasm.[56,57] Several alternative hypotheses to explain this discrepancy have been proposed and are under investigation; however, no insights to date have provided a clear direction for clinical intervention.

Reducing the Impact of Vasospasm/DCI

Due to their delayed onset, vasospasm and DCI are very attractive targets for preventive therapies. By targeting various steps, their development may be entirely averted or their impact reduced. Since the volume of subarachnoid blood is a strong predictor of vasospasm and DCI, reduction of SAH volume was a focus of early interventions.

Cisternal Thrombolysis and Lumbar CSF Drainage

Cisternal irrigation with saline is routinely performed at the time of surgery to clear subarachnoid blood. Its efficacy has never been directly tested, however. Since the rates of vasospasm and DCI appear to be the same whether the aneurysm is repaired by surgical or endovascular means, the effectiveness of this practice is in doubt. Attempts have been made to enhance clearance by instilling tissue

plasminogen activator (t-PA) into the cisterns and ventricles, and meta-analyses suggest some potential benefit.[58,59] In a large randomized trial, there was no overall effect on vasospasm, but in patients with thick subarachnoid clots, there was a 56% relative risk reduction of severe vasospasm in the t-PA-treated group.[60] An alternative approach is to instill t-PA into a ventricular drain,[61] which may accelerate the clearance of both ventricular and subarachnoid blood, especially when administered early.[62]

Attempts have been made to apply this approach to patients undergoing coil embolization of aneurysms. In those patients, a microcatheter was inserted in the lumbar region and navigated up to the cisterns where urokinase was instilled; the treatment appeared to reduce symptomatic vasospasm.[63]

Another approach to clearing blood from the subarachnoid space is through lumbar CSF drainage. In a non-randomized controlled-cohort study, CSF drainage reduced the incidence of clinical vasospasm, the use of angioplasty, and vasospasm-related infarction.[64] A subsequent single-center, prospective, randomized controlled trial found reduced prevalence of DCI and improved early outcome, but no improvement in outcome at 6 months.[65] Additional studies are underway.

Calcium Channel Blockers

Enteral

Nimodipine is the only drug approved by the U.S. Food and Drug Administration for use in the treatment of vasospasm. A dihydropyridine, it blocks calcium influx through the L-type calcium channels in blood vessels and neurons. It reduces the risk of poor outcome and secondary ischemia after aneurysmal SAH.[66–68]

How nimodipine exerts its beneficial effects is incompletely understood. It may involve neuronal as well as vascular effects, acting as a neuroprotective and vasodilatory agent.[69] It does not appear to reverse angiographic vasospasm, but this has not been well studied. Nimodipine is routinely administered to all aneurysmal SAH patients beginning from the time of presentation through 21 days. The approved dose is 60 mg orally every 4 hours, the dose being limited by hypotension. Some patients do not tolerate the recommended dose, especially when being treated with induced hypertension for DCI. This appears to be exacerbated by hypovolemia. Dose adjustment to 30 mg every 2 hours may limit hypotension, but in some patients, nimodipine is discontinued due to refractory hypotension. This has its downside, however; high compliance with scheduled nimodipine is associated with better outcome.[70]

In a large randomized trial, oral nicardipine decreased the incidence of DCI, reduced the use of rescue therapy for refractory DCI, and reduced angiographic vasospasm; yet, it did not improve overall outcome at 3 months.[71] While, based on this trial, the use of nicardipine was largely abandoned in the United States, some argue that the lack of benefit seen in the trial was due to increased use of rescue therapies in the control group. Phase I and II safety studies of diltiazem in SAH demonstrated safety but no effect on vasospasm.[72]

Intravenous

While intravenous calcium channel blockers are often used for blood pressure control in SAH patients,[30,73] they have also been administered in an attempt to reduce vasospasm and DCI. In Europe, nimodipine is also used as a continuous intravenous infusion, although this is often associated with hypotension requiring dose adjustment.[74,75]

Intrathecal

Nimodipine and nicardipine cross the blood–brain barrier, but they do so in very low concentrations. As doses are limited by hypotension, attempts have been made to administer the drugs directly into the subarachnoid space. This approach is challenging as it must be available for days, requiring repeated administration or use of a sustained-release formulation.

One approach has been the use of prolonged-release implants placed at the time of aneurysm clipping.[76] In a small phase II study, use of implants reduced the incidence of cerebral vasospasm and DCI and improved clinical outcome.[77] Early studies of intrathecal nicardipine have shown encouraging results.[78] The main limitation to the use of implants is that they must be surgically implanted. The growth of endovascular methods to repair aneurysms makes this option unavailable to many SAH patients.

An alternative approach that could be used in both surgical and endovascular patients is to administer the drug directly into the ventricular system via an external ventricular drain. The feasibility of this approach has been greatly enhanced by the development of sustained-release microparticles.[79] They have the advantages of requiring only a single administration, instilling the drug directly into the site of action, and not requiring a craniotomy. In a recently completed phase I/IIa study, intraventricular nimodipine sustained-release microparticles were compared with standard dose oral nimodipine. The microparticles were safe and well tolerated without hypotension. They were associated with reduced DCI and needed for rescue therapy, as well as improved clinical outcome.[80]

Prophylactic Hypervolemia

It is widely accepted that SAH patients can spontaneously develop hypovolemia and that hypovolemia can impair cerebral perfusion and increase risk of DCI. Thus, it was proposed that prophylactic hypervolemia may reduce DCI and improve outcome in SAH patients. However, in prospective controlled studies, it failed to reduce the incidence of DCI and vasospasm, did not improve cerebral blood flow, and had no effect on outcome.[81–84] In addition, costs and complications were higher in the group treated with prophylactic hypervolemia.[83] To date, prophylactic hypervolemic therapy has not been shown to effectively raise cerebral blood flow or improve neurological outcome. In addition, there is evidence for harm using overly aggressive hydration; however, careful monitoring of volume status is recommended to avoid hypovolemia.[85]

Prophylactic Transluminal Balloon Angioplasty

Based on success in a dog model of SAH, a pilot study of prophylactic transluminal balloon angioplasty in patients

with Fisher grade 3 SAH was performed, which had promising results.[86] In a larger trial, fewer patients developed DCI after treatment with transluminal balloon angioplasty and there was a reduced need for therapeutic angioplasty.[87] While the procedure appeared to be beneficial, this was offset by a high rate of procedural complications resulting in three deaths, and the approach was abandoned. Since that time, advances in angioplasty balloon design have renewed interest in the approach.

Tirilazad

Following promising results in primate vasospasm models, tirilazad, a non-glucocorticoid 21 amino-steroid free radical scavenger, was studied in SAH. The effect on outcome was variable, in part related to gender differences in drug metabolism and an interaction with phenytoin.[88–91]

Magnesium

Magnesium is a noncompetitive calcium antagonist and has potentially neuroprotective vascular effects. It can lead to vasodilatation by blocking the voltage-dependent calcium channel and decreasing entry of calcium into the cell. In addition, magnesium attenuates the effect of various potent vasoconstrictors, such as endothelin 1, and blocks the formation of reactive oxygen species. Several small trials of aggressive intravenous magnesium administration suggested benefit.[92] In a phase II trial enrolling 283 patients, magnesium treatment reduced the risk of DCI by 34% and poor outcome by 23%.[93] However, a follow-up phase III study of 1,204 patients failed to show any benefit.[94]

More recently, attempts have been made to administer magnesium directly into the CSF via continuous cisternal irrigation. In a preliminary trial of 73 patients, a reduction in vasospasm was noted, but there was neither a reduced incidence of DCI nor improved outcome.[95]

Statins

Statins appear to have neuroprotective properties independent of cholesterol reduction due to their ability to upregulate endothelial nitric oxide synthase. Early small randomized trials found improved outcome in patients treated with simvastatin and pravastatin.[96–98] In an international, multicenter, randomized, double-blind trial, 803 patients were randomly assigned to receive either simvastatin 40 mg or placebo for 21 days. The trial did not find any benefit for short- or long-term outcome.[99]

Clazosentan

Endothelin is a potent vasoconstrictor and is thought to play a key role in the development of arterial vasospasm. Clazosentan is an endothelin receptor antagonist designed to inhibit endothelin-mediated cerebral vasospasm. Two early trials demonstrated the ability of the drug to reduce angiographic vasospasm.[100,101] They were followed by two large trials powered to detect an effect on clinical outcome.[54,55] Both of these studies demonstrated a clear reduction in angiographic vasospasm, but while the higher dose reduced short-term vasospasm-related morbidity and all-cause mortality in one study, neither study demonstrated improved 3-month clinical outcome.

Summary

Vasospasm and DCI following aneurysmal SAH are major contributors to morbidity and mortality. The delayed nature of their onset has made them an attractive target for preventive therapies. Interventions addressing various steps in the development of vasospasm have been attempted with variable success.

Enteral nimodipine remains the only approved measure to prevent DCI. Since oral and intravenous administration is limited by hypotension, direct administration via sustained-release pellets placed during surgery or intraventricular administration of sustained-release microparticles has been investigated. These approaches show promise of being even more effective, and confirmatory trials are underway.

Efforts to remove blood from the subarachnoid space via cisternal irrigation, cisternal or ventricular thrombolysis, and lumbar CSF drainage have met with limited and variable success, and they remain an active area of investigation.

Several interventions that had early promise have failed to show benefit when studied in large trials, including tirilazad, magnesium, statins, clazosentan, transluminal angioplasty, and hypervolemia.

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