



# Subarachnoid Hemorrhage and Cerebral Vasospasm

Cerebral vasospasm increases morbidity and mortality in persons with subarachnoid hemorrhage.

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Subarachnoid hemorrhage (SAH) is a severe subtype of stroke associated with significant morbidity and mortality. In 85% of people who experience nontraumatic SAH, a ruptured intracranial aneurysm is the underlying cause. Cerebral vasospasm is the narrowing of intracranial arteries, which can lead to hypoperfusion, delayed ischemic deficits, and stroke. Vasospasm continues to be a major complication of SAH and a source of morbidity owing to poorly understood mechanisms and limited treatment options. Survival after aneurysmal subarachnoid hemorrhage (aSAH) has increased in the last few decades, mostly due to early aneurysm repair, vasospasm-prevention treatments, and advances in diagnostic and treatment strategies. Nevertheless, survivors commonly have cognitive impairment that affects their quality of life and functional capacity.

## Aneurysmal Subarachnoid Hemorrhage Epidemiology

Aneurysmal subarachnoid stroke (aSAH) is associated with high mortality, morbidity, and disease burden on health care.<sup>1</sup> Accounting for 5% of strokes, aSAH has a peak incidence during the 6th and 7th decades of life. In a large prospective registry, incidence in women was 60% greater than in men (rate ratio: 1.6, 95% CI: 1.3-2).<sup>2</sup> Intracranial saccular aneurysms are relatively common, occurring in 1% to 2% of the population.<sup>3</sup> A large observational study in Europe and China reported a 28-day case fatality rate of 42%.<sup>4</sup> The risk for permanent disability is high, with disability and dependency occurring in close to 50% of survivors. Outcomes correlate with the person's level of consciousness at presentation, age, blood distribution on images, and the presence of vasospasm or cardiopulmonary complications. Early aggressive treatment and optimal medical and surgical management for complications in experienced centers is paramount to improve outcomes.<sup>5</sup>

## Clinical Presentation

The classic initial symptom with aSAH is a severe thunderclap headache that is maximal at onset and dissimilar to previous headaches but can be preceded by a warning "sentinel headache" in up to 40% of individuals with aSAH.<sup>6</sup> Associated factors include physical or psychologic stress; however, aSAH occurs more commonly during activities of daily living with a higher incidence during daily routines that include the Valsalva maneuver (eg, sneezing, defecation).<sup>7</sup> A study showed that 50% of aSAH occurred during sleep or rest, but 19% occurred during or within 2 hours of moderate-to-heavy exercise (odds ratio [OR]: 2.7, 95% CI: 1.6-4.6).<sup>8</sup> Other symptoms include nausea and/or vomiting, photophobia, and focal neurologic deficits. Severely affected persons can present with profound coma, and the degree of encephalopathy at presentation is a major determinant of the prognosis.<sup>9</sup>

## Diagnosis

Tools for diagnosing aSAH include MR angiography (MRA), CT angiography (CTA), and digital subtraction angiography (DSA). Noncontrast head CT head has sensitivity approaching 100% that drops with time and is approximately 98% at 6 hours if the scan is evaluated by an experienced physician.<sup>10</sup> Historically, if head CT results are negative, a lumbar puncture has been performed to rule out SAH in the emergency setting. Meta-analysis of 7 studies of 813 individuals with normal neurologic examination findings, thunderclap headache, normal head CT, and negative results from cerebrospinal fluid (CSF) analysis found no cases of SAH in at least 3 months of follow-up.<sup>11</sup>

## Delayed Cerebral Ischemia and Cerebral Vasospasm

Delayed cerebral ischemia (DCI) is the subsequent deterioration that occurs after aSAH and is multifactorial in etiology, including combined effects of cerebral and microvascu-



lar spasm, thrombosis, cortical spreading depolarization, and cerebral autoregulation failure.<sup>12,13</sup> Although cerebral vasospasm and DCI may complicate traumatic SAH or ruptured vascular malformations, the most common occurrence is in conjunction with aSAH.<sup>14</sup>

### Pathophysiology and Biomarkers

Along with impaired cerebral autoregulation, vasospasm contributes to decreased cerebral blood flow and delayed ischemia that typically occurs 4 to 14 days after aSAH, with a peak incidence between 6 and 10 days. Angiographic vasospasm occurs in approximately 60% to 70% of people who experience aSAH, and although only 40% of these people develop clinical symptoms, up to 20% will die or have severe deficits.<sup>15</sup>

Recent research implicates different pathogenic mechanisms including inflammatory pathways, alternations in CSF metal ion concentrations, cholesterol levels, and nitric oxide synthase (NOS) activity. Red blood cell lysis in the subarachnoid spaces releases hemoglobin that causes an immune response triggered by inflammatory cells including neutrophils and macrophages that enter the subarachnoid space. Within 2 to 4 days, this causes endothelin and oxygen free radical release that also plays a role in inflammation and cerebral vasoconstriction.<sup>16</sup>

Although arterial narrowing has been considered a main mechanism of DCI, treatments to restore luminal patency alone have not resulted in improved clinical outcomes and in a study, 27% of individuals with DCI did not have arterial narrowing.<sup>17-19</sup>

### Risk Factors and Prediction of Vasospasm

Clot volume after SAH is among the most important risk factors to predict vasospasm. The modified Fisher scale grades the degree and extent of SAH on noncontrast head CT at initial presentation and predicts strongly the likelihood of developing vasospasm.<sup>20</sup> Advanced age, smoking, alcohol intake, diabetes mellitus or hyperglycemia, preexisting hypertension, and poor neurologic grade at initial presentation also correlate with development of vasospasm.<sup>21,22</sup>

### Medical Treatment

**Triple-H Therapy.** The use of hypertension, hypervolemia, and hemodilution was first introduced in the 1970s and remains widely used with the intent of increasing cerebral perfusion pressure, blood volume, and cardiac output while optimizing blood viscosity. Although triple-H therapy can be effective in reversing vasospasm, it carries risks including cardiac failure, electrolyte abnormalities, cerebral edema and bleeding diathesis from dilution of clotting factors, and benefit as a prophylactic therapy is questionable.<sup>15</sup> In a retrospective study of 45 people,

during 55 periods of moderate hypertension, an observable increment in brain oxygenation was seen in 90% of hypertension intervals; and 3 individuals had complications (8%). More aggressive hypervolemic blood pressure augmentation increased the brain oxygenation during 6 of the intervals (60%), with complications in 5 people (50%).<sup>23</sup> In a randomized prospective study of 82 participants assigned to receive isotonic crystalloid or 5% albumin solution every 2 hours to maintain normal or elevated cardiac filling pressures (normovolemic vs hypervolemic), there was no difference in mean global cerebral blood flow (CBF) or minimum regional CBF between the 2 treatment groups. Symptomatic vasospasm occurred in 20% of the people in each group.<sup>24</sup> Current American Heart Association (AHA)/American Stroke Association (ASA) guidelines recommend maintaining euvolemia and normal circulating blood volume to prevent DCI (Class I; Level of Evidence B).<sup>25</sup>

**Calcium Channel Blockers.** Nimodipine is a dihydropyridine calcium channel blocker. In a prospective randomized study with placebo ( $n = 276$ ) or nimodipine 60 mg ( $n = 278$ ) given orally every 4 hours for 21 days, the incidence of cerebral infarction was 22% (61/278) for those treated with nimodipine compared with 33% of those given placebo (92/276), with a relative reduction of 34% (95% CI: 13-50;  $P = .003$ ). Nimodipine significantly reduced the incidence of poor outcomes (death, vegetative state, severe disability) by 40% ( $P < .001$ ).<sup>26</sup> The AHA/ASA guideline recommends nimodipine treatment for all persons who experienced an aSAH. (Class I; Level of Evidence A).<sup>25</sup>

**Other Medications.** Because endothelial injury and inflammation may play a role in development of DCI, steroids have been considered, and a randomized controlled trial of methylprednisolone in 97 participants with a diagnosis of aSAH did not reduce the incidence of symptomatic vasospasm but did improve functional outcome at 1 year.<sup>27</sup>

Meta-analysis of 6 randomized trials showed a lower incidence of DCI and mortality in those participants who were also treated with statins, but randomized clinical trials have not shown any benefit of statin treatment (40 or 80 mg for 21 days) on decreasing incidence of DCI or on short- or long-term outcomes of people with DCI.<sup>28-30</sup> Similarly, although magnesium is known to be a well-tolerated neuroprotectant, no benefit on outcomes with magnesium treatment has been seen.<sup>31-33</sup> A meta-analysis demonstrated that prophylactic intravenous magnesium sulfate decreased incidence of DCI but did not increase the probability of good neurologic outcome for persons with aSAH.<sup>34</sup>

### Endovascular Treatments for Cerebral Vasospasm

**Balloon Angioplasty.** A mechanical means of re-expanding an intracranial vessel, balloon angioplasty is thought to



inflict a paralytic injury on smooth muscle cells that prevents subsequent vasoconstriction.<sup>35</sup> Although it is highly successful at restoring luminal diameter, there are several limitations. First, balloon angioplasty can only be done on larger, more proximal vessels and so does not address micro-circulatory processes thought to be the primary pathology associated with DCI. Balloon angioplasty is also the most invasive treatment with the highest risk, and complications include vessel perforation, arterial dissection, ischemic stroke, and hemorrhagic transformation of infarcted tissue.<sup>36</sup> In a study comparing the effectiveness of balloon angioplasty to intra-arterial nimodipine for refractory vasospasm, both therapies were effective for achieving radiographic resolution of vasospasm.<sup>37</sup> An evaluation of prophylactic balloon angioplasty in 85 people with Fisher grade 3 SAH significantly decreased the need for urgent rescue therapy for symptomatic vasospasm (12 vs 26%,  $P = .03$ ) but no statistical difference in the rate of cerebral infarction or poor outcome at 3 months.<sup>38</sup>

**Intra-arterial Vasodilators.** Calcium channel blockers (nimodipine, nicardipine, verapamil) and phosphodiesterase inhibitors (papaverine, milrinone) are among the intra-arterial vasodilators used for endovascular treatment of vasospasm. These treatments are generally low risk; however, complications can occur including intra-cranial hypertension, systemic hypotension, and seizures.

A recent comprehensive meta-analysis included 55 studies (1,571 participants) to evaluate the effect of intra-arterial vasodilators in vasospasm treatment showed a robust immediate angiographic response (almost 90%) with post-procedure neurologic improvement of just less than 60%. Of the studies that provided information on clinical outcome in 1,111 people, 66% had overall a good clinical outcome. When those who were selected for intra-arterial vasodilation based on findings of transcranial Doppler ultrasound (TCD), the rate of a good outcome increased to 72% and the adjusted mortality estimate was 5%. Intra-arterial fasudil showed the highest rates of angiographic response at 99% with good clinical outcome and lowest mortality.<sup>39</sup> In another meta-analysis of 1,154 individuals, nicardipine infusion reduced the risk of poor outcome and mortality after aSAH.<sup>40</sup> Another study enrolled 29 participants; intra-arterial nimodipine led to vasodilation in angiography and improvement in clinical symptoms.<sup>41</sup>

### Investigational Treatments

Intrathecal drug administration for treatment of vasospasm may be effective because it delivers a higher drug concentration with minimal side effects. Calcium channel blockers (eg, nicardipine) via an external ventricular drain have had positive results in both preventing and treating vasospasm, but further studies are warranted.<sup>42,43</sup> In another

study, stent retriever use resulted in cerebral vasodilation and reversal of focal neurologic deficits with a longer lasting effect.<sup>44</sup> Continuous low-dose unfractionated heparin infusion is being studied in the ASTROH<sup>a</sup> trial.

### Conclusion

Despite advances in aneurysm treatments, cerebral vasospasm remains a contributor to morbidity and mortality in aSAH. The pathogenesis of vasospasm and DCI is likely multifactorial and includes angiographic vasospasm, cortical spreading depression, microthrombosis, and microcirculatory restrictions. Although a number of pharmacologic treatments and endovascular interventions are available, nimodipine remains the only adjunctive treatment demonstrated to improve clinical outcomes in randomized controlled trials. ■

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a. Aneurysmal subarachnoid hemorrhage trial randomizing heparin (NCT02501434).



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