A review of current and future medical therapies for cerebral vasospasm following aneurysmal subarachnoid hemorrhage

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In an effort to help clarify the current state of medical therapy for cerebral vasospasm, the authors reviewed the relevant literature on the established medical therapies used for cerebral vasospasm following aneurysmal subarachnoid hemorrhage (SAH), and they discuss burgeoning areas of investigation. Despite advances in the treatment of aneurysmal SAH, cerebral vasospasm remains a common complication and has been correlated with a 1.5- to threefold increase in death during the first 2 weeks after hemorrhage. A number of medical, pharmacological, and surgical therapies are currently in use or being investigated in an attempt to reverse cerebral vasospasm, but only a few have proven to be useful. Although much has been elucidated regarding its pathophysiology, the treatment of cerebral vasospasm remains a dilemma. Although a poor understanding of SAH-induced cerebral vasospasm pathophysiology has, to date, hampered the development of therapeutic interventions, current research efforts promise the eventual production of new medical therapies.

KEY WORDS • cerebral vasospasm • aneurysmal subarachnoid hemorrhage • medical therapy

Established Medical Therapy

Hypervolemia, Hypertension, and Hemodilution

At present, the mainstay of medical treatment of cerebral vasospasm, alongside calcium channel blockers, is hyperdynamic or triple-H therapy, referring to hypervolemia, hypertension, and hemodilution. The rationale behind this treatment is that maintenance of high circulating blood volume, increased perfusion pressures, and decreased blood viscosity will enhance CBF in the setting of vasoconstriction. The fluids used to achieve volume expansion vary, but the principle remains the same: an increasing volume status increases cardiac output, which increases blood pressure, thereby increasing CBF in ischemic areas. The use of a pulmonary artery catheter is suggested given the complications that can arise from such vigorous fluid therapy. Hypertension is sometimes achieved simply with volume expansion, but vasoactive drugs, namely dopamine or phenylephrine, may be used to attain a desired level of hypertension. Hemodilution to a hematocrit of 30 to 35% is believed to be a reasonable compromise between oxygen-carrying capacity and viscosity. Hemodilution is the most controversial component of hyperdynamic therapy. Triple-H therapy is not

UBARACHNOID hemorrhage secondary to ruptured saccular aneurysms contributes to approximately 5 to 15% of cases of stroke. Overall mortality rates for this condition range from 30 to 70%, and 10 to 20% of survivors experience severe neurological disability. Twelve percent of patients die before medical treatment can be given, 25% die within 24 hours, and an additional 40 to 60% die within 30 days. Outcome following aneurysmal SAH is dependent on several factors, including initial event severity, perioperative medical management, intraoperative variables, and incidence of complications.

Cerebral vasospasm contributes to poor outcome in approximately 10 to 40% of patients with SAH and continues to be a major cause of morbidity. The diagnosis of cerebral vasospasm may be suspected based on clinical examination and results of transcranial Doppler ultrasonography studies, and is later confirmed on cerebral angiography. Symptoms are specific to the area of the brain in which ischemia occurs and, if the vasospasm is severe enough, cerebral infarction may ensue.

A number of medical, pharmacological, and surgical therapies are currently in use or being investigated in an attempt to reverse cerebral vasospasm, but only a few have proven to be significantly useful. Although much has been elucidated regarding its pathophysiology, the treatment of cerebral vasospasm remains a dilemma. Therefore, to help clarify the current state of medical therapy for cerebral vasospasm we review the relevant literature on the established medical therapies used in treating this condition following aneurysmal SAH and discuss burgeoning areas of investigation.

Abbreviations used in this paper: CAM = cell adhesion molecule; CBF = cerebral blood flow; eNOS = endothelial nitric oxide synthase; ET = endothelin; NXY-059 = disodium 2,4-disulfophenyl-N-tert-butyl nitrone; SAH = subarachnoid hemorrhage.
without medical complications including pulmonary edema, myocardial ischemia, and hyponatremia, which may offset its overall benefits.\(^\text{63}\)

Although the efficacy of triple-H therapy in ameliorating cerebral vasospasm and improving clinical outcome has been established,\(^\text{30,75}\) the ability of this treatment to prevent the occurrence of cerebral vasospasm during the postoperative period has come into question. Despite widespread use of triple-H therapy to prevent cerebral vasospasm following SAH, few prospective comparative trials focus on the question of its efficacy and harm. In one such study, Solomon and colleagues\(^\text{84}\) randomized 82 patients on postoperative Day 1 to maintain hypervolemia or normovolemia until Day 14. No significant difference in mean global CBF was demonstrated during the treatment period, leading the authors to conclude that prophylactic triple-H therapy is unlikely to confer additional benefits over maintenance of euvolemia. A recent systematic review of the literature on this subject revealed that there are insufficient “evidence-based medicine” data to make recommendations for the use and optimal regimen of triple-H as a prophylactic treatment.\(^\text{92}\) The authors emphasize the need for a well-designed, randomized controlled trial, which would be sufficiently powered to investigate the efficacy of triple-H prevention.

**Calcium Antagonists**

In addition to triple-H therapy, calcium channel antagonists have been evaluated in multiple clinical trials, with varied degrees of success and have become a mainstay in the treatment of cerebral vasospasm. Nimodipine is the most widely administered calcium channel blocker based on its relative selectivity for dilation of the cerebral arteries. Although nimodipine does not appear to decrease the incidence of angiographic vasospasm, analysis of multiple trials has shown it to improve outcomes.\(^\text{96,87}\) Results of the British aneurysm nimodipine trial demonstrated a reduction from 33 to 22% in the occurrence of cerebral infarction in patients treated with nimodipine, and a 40% reduction in poor outcomes.\(^\text{80,66}\) In a metaanalysis of nimodipine treatment after SAH, Barker and Ogilvy\(^\text{6}\) demonstrated that the prophylactic use of this drug is effective in increasing the odds of a good outcome after SAH. This efficacy was both statistically and clinically significant. In addition, in a retrospective analysis comparing cost of treatment with increase in life expectancy it was shown that nimodipine is extremely cost-effective and is associated with minimal adverse effects.\(^\text{38}\) Therefore, nimodipine may be considered the standard of care following aneurysmal SAH, as it is both safe and effective for the treatment of symptomatic vasospasm.\(^\text{93}\)

Nicardipine is another dihydropyridine calcium antagonist that displays regional selectivity on vascular smooth muscle. Unlike nimodipine, however, nicardipine may be administered parenterally. It has been demonstrated in initial dose-escalation studies that intravenous nicardipine administration results in improvement in symptoms and angiographic findings in patients with cerebral vasospasm.\(^\text{96}\) However, authors of subsequent prospective randomized studies found that although nicardipine significantly lowers the incidence of documented vasospasm, it confers no benefit to neurological outcome.\(^\text{24-26}\)

Rinkel and colleagues\(^\text{74}\) examined the efficacy of calcium antagonists from 12 different trials in a systematic review. The end points of their study included clinical outcome, secondary ischemia, death, rebleeding, and adverse effects. The use of calcium antagonists was associated with improved outcomes, with nicardipine having the greatest effect and magnesium having the least. Although calcium channel blockers significantly diminished the rate of secondary ischemia after aneurysmal SAH (from 40 to 27%), their use did not reduce the high mortality rate associated with rupture.

**Burgeoning Therapies**

Although a number of factors have been implicated in the development and progression of cerebral vasospasm, the precise pathophysiology of this condition has yet to be fully elucidated. Many hypotheses have been tested through pharmaceutical and physical manipulation in animal models, but cross-over to the clinical arena remains a task for future research.

**Magnesium Therapy**

Calcium has been implicated as an important mediator of cerebral vasospasm and is thought to be the most important second messenger in the regulation of smooth-muscle contraction. Magnesium has long been used to treat eclamptic vasospasm and exerts inhibitory activity on calcium influx. A number of recent studies have examined the potential use of magnesium as an antivasospastic agent for treating cerebral vasospasm.\(^\text{103}\) Unfortunately, in an experimental primate model of SAH, Macdonald and coworkers\(^\text{48}\) found that MgSO\(_4\) did not prevent vasospasm, even when given at therapeutic serum concentrations. Although interspecies differences in response to cerebral ischemia must be taken into account, subsequent studies in humans have failed to demonstrate neuroprotective benefits with magnesium.

Veyna and associates\(^\text{99}\) compared the incidence of cerebral vasospasm following aneurysmal SAH in patients who were receiving magnesium during the postoperative period with those who were not, and they failed to demonstrate a difference between the two groups (30% compared with 31%, respectively). It is possible that magnesium’s calcium antagonist effects are redundant and of little additional benefit to patients already receiving nimodipine. It is important to note that although magnesium is currently not implemented for the prevention of cerebral vasospasm, in a recent randomized trial van den Bergh, et al.\(^\text{97}\) suggested that magnesium reduces delayed cerebral ischemia and improves outcomes. In addition, in a randomized trial Prevedello and colleagues\(^\text{96}\) recently reported on decreased morbidity and duration of hospital stay after administration of magnesium sulfate. More definitive conclusions regarding the clinical usefulness of magnesium in patients with aneurysmal SAH will necessitate a Phase III trial.

**Inflammatory Mediators**

There is now evidence that supports the role of inflammation as an important player in the pathology of vasospasm. Authors of recent studies have demonstrated that...
leukocyte–endothelial cell interactions appear to play a major role in mediating cerebral vasospasm following aneurysmal SAH. 12,13,50,57,58,82 A number of specific CAMs have been identified, including LFA-1 (CD11/CD18) and intercellular CAM that are present on endothelium and neutrophils/macrophages, respectively. 7,12,13,50,57,58 Uregulation of CAMs on endothelial cells following aneurysmal SAH leads to diapedesis of neutrophils into the subarachnoid space. Increased levels of intercellular CAM, vascular CAM, and E-selectin have been demonstrated in patients with aneurysmal SAH, but the results of these studies are inconclusive as to whether the levels correlate with the incidence of cerebral vasospasm. 40,58,78 These neutrophils are capable of contributing to vasospasm in three ways: production of ETs, production of reactive oxygen species, and depletion of NO. 13,71,82

To this end, antiinflammatory agents that modulate the early extravasation of leukocytes into the subarachnoid space may be an adjunct in the treatment of cerebral vasospasm; blocking leukocyte–endothelial cell interactions with antibodies has been shown to prevent post-SAH vasospasm in a number of animal models. 7,12,13,67,71,77 Using a rabbit model of SAH, Frazier, et al., 20 showed that treatment with a controlled-release polymer of ibuprofen delivered into the cisterna magna at either 30 minutes or 6 hours following SAH significantly inhibited vasospasm. In a similar model, Pradilla, et al., 71 demonstrated a significant increase in lumen patency following systemic administration of an anti-CD11/CD18 monoclonal antibody. Finally, Lin and colleagues, 46 in a murine model of SAH, demonstrated that the pharmacological blockade of E-selectin could partially prevent SAH-induced vasospasm. 46 These findings further support the hypothesis that E-selectin may contribute to the pathophysiology of cerebral vasospasm.

In addition, cell-mediated immune response has also been implicated in the pathogenesis of cerebral vasospasm. Steroids have been evaluated as protective agents against vasospasm, but results have been disappointing. In a retrospective case–control study, high-dose methylprednisolone seemed to reduce delayed ischemic deficits. 11 However, due to their adverse systemic effects, corticosteroids are not recommended in this setting. 1 Cyclosporin was evaluated in a pilot study of nine patients with Fisher Grade 3 SAH and was found to be ineffective in preventing cerebral vasospasm. 31 These results perhaps are not surprising given that the predominant effect of these agents is on lymphocytes. 72

Nitric Oxide

An imbalance between endothelin-mediated vasoconstriction and NO-mediated vasodilation has been implicated in the pathogenesis of cerebral vasospasm. Nitric oxide is a ubiquitous, endothelium-derived, relaxation factor with extensive roles in neurotransmission, inflammation, and vascular autoregulation. 3 Because release of NO from the endothelium is necessary for autoregulation of cerebral vascular tone, 18 it has been postulated that a reduction in the local availability of NO after SAH may be pivotal in the pathogenesis of cerebral vasospasm. 21 The NO levels are decreased after SAH for the following reasons: 1) endogenous inhibition of endothelial NOS; 92 2) toxicity of oxyhemoglobin to neurons containing neuronal NOS; 93 and 3) scavenging of NO by oxyhemoglobin released from the subarachnoid clots. 12,6 It has been shown that inactivation of NO by exogenous inhibitors after induction of SAH leads to delayed vasospasm. 86 Furthermore, a significant decrease in neuronal NOS activity occurred after SAH in a primate model of cerebral vasospasm, whereas the administration of NO donors or NOS substrates has been shown to ameliorate cerebral vasospasm in experimental and clinical settings. 29,68,69,88–90 The clinical utility of NO, however, is limited by its short half-life, side effects, and potential toxicity. 2,15,29,49,69

To address these issues, investigators have attempted to treat experimental cerebral vasospasm by using intravascular, intrathecal, and periadventitial administration of NO or NO donor compounds. 2,28,30,68,88–91 Using an intracranial controlled-release polymer in a rabbit model, Gabikian, et al., 27 demonstrated a significant increase in basilar artery lumen patency in treated animals compared with untreated animals (93.0 ± 4.9 and 71.4 ± 11.9%, respectively; p = 0.035). In an attempt to more closely reflect a true clinical scenario, Pradilla, et al., 70 studied the effects of delayed administration of an NO controlled-release polymer. They found that treatment with the polymer 24 and 48 hours after SAH resulted in a significant increase of basilar artery patency. 70

Results of studies in humans in which NO donors were used, however, have been less convincing. In addition, the clinical application of these agents has been limited by side effects, including severe hypotension, 17,41 CBF “steal syndrome,” 4,34,65 and increased intracranial pressure. 37 Thomas and Rosenwasser 89 reported the use of sodium nitroprusside in three patients with cerebral vasospasm, and their initial results prompted them to expand their cohort to 21 patients with aneurysmal SAH. 86 In symptomatic patients, amelioration of vasospasm was confirmed angiographically in five of six of the individuals in their study. Moreover, among patients treated prophylactically, none later suffered neurological deficits. 75,86 Results of studies by Raabe, 73 Vajkoczy, 75 and their colleagues, however, have suggested high variability in both the duration and efficacy of sodium nitroprusside.

Recent data provide evidence for nitrite as a potent vasodilator. Nitrite reacts with deoxyhemoglobin, present in significant concentrations following SAH, to produce NO. 14,67 Pluta, et al., 67 demonstrated that a continuous intravenous infusion of nitrite for 14 days prevented vasospasm after SAH in a primate model. The selectivity and safety of nitrite highlight a potential avenue for overcoming the serious adverse effects of current NO donor therapy.

Endothelin Antagonists

There is growing evidence for a central role of the polypeptide ET-1 in the pathophysiological cascade leading to cerebral vasospasm. As discussed earlier, the interplay between ET and NO is critical to the maintenance of cerebral vascular dilation. Endothelin-1 is an extremely potent vasoconstrictor, and investigators have demonstrated a close correlation between cerebral vasospasm and increasing levels of ET-1 in CSF and plasma. 22,36,79,85

Human cerebral arteries express two types of ET-1 recep-
tors, ETα, and ETγ. Activation of the smooth-muscle ETα receptor induces vasoconstriction, whereas a release of NO resulting in vasodilation is mediated by the ETγ receptor located on the endothelium. Clazosentan is a selective ETα receptor antagonist that has proved to be effective in the treatment of cerebral vasospasm in both a rabbit and canine model of SAH, and has since been tested in a Phase IIA multicenter trial by Vajkoczy and colleagues. These authors demonstrated a statistically significant benefit of clazosentan in the prevention and treatment of cerebral vasospasm, thereby supporting the role of ETα in the pathogenesis of cerebral vasospasm.

**Statin Therapy**

As discussed earlier, NO depletion is associated with histopathological damage to cerebrovascular endothelium. Treatment with 3-hydroxy-3-methylgluteryl coenzyme A reductase inhibitors (statins) improves endothelial function and directly upregulates eNOS expression. McGirt, et al., demonstrated the beneficial effects of statin administration in a murine model of SAH. Thirty-four mice were pretreated with simvastatin and 36 mice with placebo. The main effect was an improvement in vascular diameter 72 hours after SAH, with a 50% reduction in placebo-treated mice compared with 27% in simvastatin-treated mice (p = 0.003). In addition, neurological scores were significantly improved in simvastatin-treated mice. Although the exact mechanism is unknown, pre-treatment with simvastatin increased cerebral eNOS expression two- to threefold in both the sham-treated and SAH groups. Furthermore, a posttreatment study yielded similar but less substantial results, and the results did not show an increase in eNOS expression. In a recent match-controlled cohort study by Parra, et al., statin use demonstrated lower transcranial Doppler ultrasonography values and improved 14-day functional outcomes, further supporting the potential benefits of statin use in the treatment and prevention of vasospasm following aneurysmal SAH.

In a well-designed and powered Phase II randomized placebo-controlled trial, Tseng, et al., demonstrated that acute treatment with pravastatin after aneurysmal SAH is safe, ameliorates cerebral vasospasm, and reduces vasospasm-related delayed ischemic neurological deficits. In the primary end point of that study, the incidence of vasospasm was reduced 62.5% and 42.5% in the placebo and statin groups, respectively (p < 0.006), and the incidence of impaired autoregulation was reduced by 2.4 days in the treatment group. In addition, the secondary end points of delayed ischemic neurological deficits and all cause mortality were reduced 83 and 75%, respectively, in the treatment group. Although the study was not powered to detect a clinical improvement, multivariate analysis highlighted statin administration as the only independent predictor of improved outcome at discharge from the hospital. After a 40-mg daily dose of pravastatin was administered, drug tolerance was very high, and only two patients withdrew early from the study. In a similar study published shortly after, Lynch, et al., demonstrated that treatment with 80 mg simvastatin daily reduced the overall rate of vasospasm by 43% (p < 0.05). In that study of 39 patients the authors also examined plasma levels of von Willebrand factor (a marker of endothelial injury) and protein S100B (a marker of astrocyte activation), which have both been correlated with prognosis and occurrence of vasospasm after SAH. The plasma concentrations of these two markers were significantly reduced in patients treated with simvastatin, consistent with the hypothesis that simvastatin exerts its therapeutic effect by endothelial-protective and antiinflammatory properties. Although precise mechanisms remain to be worked out, the data from these two trials are promising and suggest that statins may come to play an integral part in the acute management of aneurysmal SAH.

**Antioxidants and Free-Radical Scavengers**

Various free-radical scavengers have been studied in experimental models and Phase II and III trials. Nicaravirin, a hydroxyl radical scavenger, was used in a prospective, placebo-controlled, double-blind trial and seemed to improve outcomes at 1 month but not at 3 months. Trilizad mesylate, a synthetic nonglucocorticoid aminosteroid agent that inhibits the activation of lipid peroxidation, has been shown to prevent SAH-induced cerebral vasospasm in a rabbit model. Furthermore, results of a multicenter European–Australian study showed that patients treated with trilizad had better neurological outcomes than control volunteers. A subsequent North American study, however, failed to confirm the beneficial effects of this therapy.

A nitrone radical trapping agent, NXY-059 has been shown to improve neurological function and reduce infarct volume in a primate model of permanent focal ischemia. Most importantly, this compound is well tolerated by humans and can be administered to produce plasma concentrations exceeding those effective in animal models. Results from recent trials suggest that administration of NXY-059 within 6 hours after the onset of acute ischemic stroke significantly reduce disability at 90 days. The efficacy of NXY-059 in preventing or reversing cerebral vasospasm has yet to be studied.

**Serine Protease Inhibitors**

Serine proteases activate the complement pathway and lead to a plasma–protein mediated inflammatory cascade. Nafamostat mesilate (FUT-175), a serine protease inhibitor, inhibits complementary factors thrombin and plasmin, and suppresses the protease-based inflammation. Outcomes in a retrospective case–control study in which FUT-175 was evaluated were excellent or good in 35% of the control group and in 65% of the treated group. The occurrence of delayed cerebral ischemia was also reduced from 55 to 13%.

**Conclusions**

Despite advances in the treatment of aneurysmal SAH, cerebral vasospasm remains a common post-SAH complication and has been correlated with a 1.5- to threefold increase in death within the first 2 weeks after SAH. At present, cerebral vasospasm fails to respond consistently to maximal medical management, thereby indicating a need for further research into the underlying mechanisms of SAH-induced cerebrovascular dysfunction. Although a
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poor understanding of SAH-induced cerebral vasospasm pathophysiology has, to date, hampered the development of therapeutic interventions, current research efforts promise the eventual production of new medical therapies.

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