

Evaluation and Management of Cerebral Vasospasm after Subarachnoid Hemorrhage, Review Article

Abstract:

Constriction of the large and medium-sized cerebral arteries following an aneurysmal subarachnoid haemorrhage (aSAH) is a well-known condition that primarily affects the anterior circulation supplied by the internal carotid arteries. SAH is a rare but potentially fatal type of stroke. Across the literature, authors have defined vasospasm using terms such as "symptomatic vasospasm," "delayed cerebral ischemia" (DCI), "transcranial Doppler vasospasm," and "angiographic vasospasm." Because posthemorrhagic vasospasm causes significant neurologic morbidity and death, there has been a great deal of interest and research into its physiologic basis and developing effective preventative and treatment strategies. The triple-H therapy hemodynamic augmentation technique, which includes hypertension, hemodilution, and hypervolemia, has been an important part of the treatment. In this article, we'll look at cerebral vasospasm following subarachnoid haemorrhage, including its causes, epidemiology, evaluation, and, most importantly, management.

Introduction:

The constriction of the big and medium-sized cerebral arteries following an aneurysmal subarachnoid haemorrhage (aSAH) is a well-described condition that most commonly affects the anterior circulation supplied by the internal carotid arteries. In instances of aSAH, cerebral vasospasm leading to delayed cerebral ischemia (DCI) remains a prominent consequence and cause of morbidity. [1,2,3] Authors have used words like "symptomatic vasospasm," "delayed cerebral ischemia" (DCI), "transcranial Doppler vasospasm," and "angiographic vasospasm" to define vasospasm across the literature. Each definition has its own set of advantages and disadvantages. Symptomatic vasospasm affects 20% to 40% of SAH patients, and it usually refers to clinical worsening after other plausible

reasons for deterioration have been ruled out. This is a subjective diagnosis that might be limited to low-grade instances with small or unnoticeable differences in the examination. A DCI is defined as a symptomatic vasospasm, a vasospasm-related infarction, or both. [4,5-9]

Because posthemorrhagic vasospasm causes significant neurologic morbidity and death, there has been a great deal of interest and research into understanding its physiologic basis and developing effective preventative and treatment strategies. The cause of cerebral vasospasm, on the other hand, is unknown. Although a variety of treatment techniques have been proven to have variable degrees of value in avoiding vasospasm and its subsequent neurologic sequelae, no one therapy approach has been proven to be universally helpful in preventing vasospasm and its subsequent neurologic sequelae. [1]

In poor-grade instances, DCI allows for the identification of clinically relevant vasospasm with minimum neurological exams; nonetheless, infarcts caused by spasm must be separated from those caused by surgery, angiography, or other reasons. Furthermore, because DCI is a post-mortem diagnosis made after an infarct has been discovered, the number of therapeutic actions to prevent this result is restricted. Angiographic vasospasm can occur in up to 70% of patients, although the link between angiographic spasm and clinical symptoms can be shaky, and it's unknown how widespread or severe angiographic spasm must be to be clinically meaningful. [4]

The triple-H therapy hemodynamic augmentation technique, which comprises hypertension, hemodilution, and hypervolemia, has been a key component of treatment. Increases in mean arterial pressure (MAP) have been found to be helpful on their own and can be induced with a variety of drugs. Calcium-channel antagonists have been extensively studied for the prevention of vasospasm in aSAH, with nimodipine being recommended as the first-line pharmacological therapy for post-aSAH cerebral vasospasm prevention. Intra-arterial vasodilator medication and balloon angioplasty are two more invasive treatments for vasospasm that rely on the use of cerebral angiography. According to the guidelines, these techniques have been approved as appropriate for the treatment of symptomatic individuals who are not responding to hypertensive medication. [1]

Etiology and Epidemiology:

Aneurysmal SAH is an uncommon yet life-threatening kind of stroke. Despite the fact that SAH accounts for just around 3% of all strokes and 5% of all stroke fatalities, the young age of those affected implies that this event is responsible for a quarter of all years of life lost as a result of stroke. In the nearly 80 years since the first cases of SAH were detected in living people, advances have been made in our understanding of the pathogenesis of the disease, and the prognosis has vastly improved. According to a systematic review of 12 SAH epidemiological studies, case-fatality rates fell by 0.9 percent per year between 1960 and 1992, when adjusted for age and gender. [10]

In a retrospective analysis of 1200 consecutive SAH patients, in-hospital mortality was 18 percent, with Hunt-Hess grade 4 or 5 patients having the greatest rates (24 percent and 71 percent, respectively). Hemorrhage, aneurysmal re-rupture, and medical problems were the main reasons for the removal of life support. In around 80% of instances, a burst cerebral aneurysm causes non-traumatic SAH, which accounts for 5 to 10% of all strokes in the United States. Furthermore, data suggests that high-volume centers had better mortality outcomes than low-volume centers, which could be attributed to improved resource access (e.g., neuro-intensivists, surgical treatments, and so on). As a result, resource allocation and management are anticipated to be critical for improving outcomes for patients suffering from SAH and its consequences (e.g., vasospasm). [11-16]

The patient's initial neurological status is the strongest predictor of prognosis following an aneurysmal SAH, although it's unclear how this contributes to delayed neurological deterioration. Initial global ischemia induced by aneurysm rupture, increased intracranial pressure (ICP), and reduced perfusion pressure are all factors in immediate brain damage after SAH. Lowered blood flow can occur without increasing ICP or after ICP has been reduced, and there is a drop in cerebral metabolism that accounts for at least some of the reduction in cerebral blood flow. Blood flow reductions assessed after SAH in rats were not enough to produce frank ischemia right away, but they were enough to sensitize tissue to later assaults. [10]

Evaluation:

Depending on the severity of the disorder and which cerebral arteries are most impacted, a physical examination may reveal a constellation of signs and symptoms of continuing vasospasm. Lethargy, disorientation, meningism, and a new or worsening headache are examples of non-localizing symptoms.

The specific vascular implicated in focal neurologic impairments is as follows: [1]

- Disinhibition, confusion, mutism; lethargy, delayed sensitivity, abulia; leg loss of strength; with involvement of the recurrent artery of Heubner (a large ACA perforator), contralateral faciobrachial numbness without cortical findings; with participation of the recurrent artery of Heubner (a large ACA perforator), contralateral faciobrachial weakness without cortical results
- Hemiparesis, faciobrachial weakness, monoparesis, aphasia, apractagnosia, neglect, middle cerebral artery (MCA) distribution
- Visual disturbance, hemianopsia in the distribution of the posterior cerebral artery (PCA).

Vasospasm can be diagnosed by a variety of methods, including cerebral angiography, ultrasonography, and symptomatic assessment. Traditional cerebral angiography has a high specificity since the arteries may be immediately viewed, and it often demonstrates constriction and spasm of the cerebral arteries. The passage period of contrast through the vessels is usually slowed or increased. Although this is considered the gold standard for diagnosis, it is invasive, not always available, and comes with its own set of dangers. There is also evidence that computed tomography (CT) angiography and perfusion have a high sensitivity (75%) and specificity (93%) and can be used to diagnose vasospasm. Transcranial Doppler (TCD) is an essential method for identifying vasospasm because it employs ultrasonography to determine velocity across the middle cerebral artery. [11]

The Hunt-Hess scale can be used to assess the neurological condition of patients at the time of admission. Clinically significant arrhythmia (defined as any cardiac arrhythmia other than sinus tachycardia, bradycardia, or sinus rhythm with premature atrial or ventricular complexes) should be recorded, as well as pulmonary edema (diagnosed by clinical examination and chest X-ray), myocardial

infarction (diagnosed by ECG, troponin values, and echocardiography), cardiac arrest, cerebral edema (diagnosed by CT), fever, and The length of stay in the hospital and critical care unit also should be recorded [4]

Management:

Nimodipine is a dihydropyridine drug that inhibits voltage-gated calcium channels and causes arterial smooth muscle to dilate. With a half-life of around 9 hours, it is the only FDA-approved medication for vasospasm. Its anti-CVS benefits are most likely due to its neuroprotective qualities as compared to arterial smooth muscle cell relaxation. Nimodipine has a low complication risk and may have excellent angiographic response and clinical outcomes. Furthermore, nimodipine may lower the incidence of subsequent cerebral ischemia following aneurysmal haemorrhage. The safety and efficacy of nimodipine were recently demonstrated in a meta-analysis done in 2011, in which treatment of nimodipine was linked to a substantial reduction in CVS following aneurysm rupture. [17]

Haptoglobin in CSF: Haptoglobin is the most abundant hemoglobin-binding protein in plasma. Toxic byproducts such as reactive oxygen species can be produced when free haemoglobin is liberated from red blood cells. Haptoglobin, on the other hand, attaches to free haemoglobin quickly and prevents the harmful biochemical processes. Humans have two haptoglobin alpha chain alleles, each of which may form three different kinds of haptoglobin dimers (alpha1-alpha1, alpha1-alpha2, and alpha2-alpha2). Although alpha1 and alpha2 have identical haemoglobin binding affinities, alpha1 can more effectively prevent the harmful oxidative processes caused by free haemoglobin. As a result, it's been claimed that people with alpha2 are more prone to inflammation, oxidative damage, and even vasospasm. [11]

The hemodynamic augmentation method, known as triple-H treatment, which comprises hypertension, hemodilution, and hypervolemia, has been an essential component of the current therapeutic alternatives. This method was supposed to increase brain perfusion by raising mean arterial pressure (MAP) and lowering blood viscosity. Patients with vasospasm have been proven to benefit from increases in MAP alone, and a variety of medicines have been researched and used to achieve this aim. The chief pressors used in this situation are phenylephrine, norepinephrine, and dopamine. Most of the data appears to support the use of phenylephrine; multiple trials have demonstrated that it is

useful in individuals with maintained left ventricular function. Other drugs, such as vasopressin, may be used as a supplement to help with treatment. [1,18–23]

The CCB verapamil, like nimodipine, inhibits voltage-gated calcium input into arterial smooth muscle cells. According to the literature, verapamil has been used to treat cardiac vasospasm for a long time. Its usage in the treatment of refractory coronary spasm is both safe and efficacious, as well as convenient and affordable. Alana et al. prospectively evaluated participants with vasospasm who were scheduled for cerebral angiography with likely IA verapamil injection, and their findings contradicted previous publications that claimed IA verapamil had no systemic hemodynamic effects. With satisfactory clinical results, Mikeladze et al. described a female patient who received selective IA verapamil for the treatment of CVS following a severe subarachnoid parenchymal haemorrhage caused by an internal carotid artery bifurcation aneurysm. [17,24–27]

Retrievable stent angioplasty: For severe or refractory vasospasm, endovascular treatment such as balloon angioplasty has been demonstrated to be effective. Early and frequent endovascular therapy has been shown to lower the likelihood of delayed cerebral ischemia and, as a result, improve functional outcomes. Prophylactic balloon angioplasty can dramatically reduce the requirement for urgent rescue treatment for symptomatic vasospasm, according to a randomized study with 175 patients. On the other hand, the dangers and disadvantages of balloon angioplasty should be considered. The endothelial wall is mechanically stretched and the extracellular matrix is disrupted during balloon angioplasty, resulting in enhanced cerebral blood flow. [11]

Magnesium: Magnesium sulphate was originally used to suppress uterine smooth muscle contractions in pre-eclamptic pregnant women. It's a noncompetitive calcium antagonist with a number of essential vascular and neuroprotective properties. By inhibiting the voltage-dependent calcium channel and reducing glutamate release as well as calcium entry into the cell, magnesium causes vasodilation. Magnesium also inhibits the generation of reactive oxygen species and attenuates the action of certain powerful vasoconstrictors, such as endothelin 1. [17]

Multimodality monitoring: MMM (multimodality monitoring) is one of the most recent advances in neurosurgical critical care treatment for patients with neurological illnesses. Intracranial pressure (ICP) has traditionally been used for

invasive monitoring. ICP, on the other hand, has limits since it does not depict the entire cerebral environment. ICP and cerebral perfusion pressure (CPP) have been shown in a number of clinical investigations to not always identify brain hypoxia and ischemia. According to clinical trials employing jugular venous catheters or a brain oxygen tension (PbtO₂) monitor, cerebral ischemia can develop in the context of normal ICP and CPP. [11]

There are several methods for treating vasospasm. One of which is for seizure prevention. All patients can be given nimodipine every 4 hours and phenytoin perioperatively. All patients can be given 0.9 percent normal saline at a rate of 1 mL/kg per hour, with an additional 5 percent albumin solution, to keep central venous pressure above 5 mm Hg. All patients on admission, as well as between SAH days 4 and 8 in patients with poor-grade status (Hunt-Hess grade 3–5), or as needed to evaluate neurological deterioration or new infarction on CT, or for accelerated TCD values in patients with good-grade status. Every day, all of the patients can have standardised serial neurological exams done without sedation. Head CT scans can be done on an as-needed basis for clinical reasons only. [4]

Why did clazosentan's reduction in angiographic vasospasm not translate into a similar reduction in delayed neurological deterioration or improved outcome? One theory is that the treatment's favourable benefits are counterbalanced by medication toxicity. Although there was no indication of significant hypotension or other adverse effects in the first analysis, more evaluation of the trial data is needed to evaluate the toxic consequences. Another possibility is that the contribution of angiographic vasospasm to poor results is too small or that the outcome measurements are too insensitive to show an effect in a CONSCIOUS-1-sized trial (about 400 patients). However, given that infarction is strongly connected to bad results, and trials with nimodipine demonstrate that a reduction in infarcts is associated with improved outcomes, this hypothesis does not appear to be plausible. [10]

Patients with symptomatic vasospasm or DCI can be given vasopressors (usually phenylephrine or norepinephrine) to keep their systolic blood pressure between 180 and 220 mm Hg, adjusted to clinical response, or inotropes to keep their cardiac index > 4.0 L/min per metre squared with milrinone or dobutamine as needed. To keep a positive fluid balance and a central venous pressure of > 8 mm Hg, normal saline and 5% albumin solutions can be given, and blood transfusions

are given to keep a goal haemoglobin of > 10 mg/dL. In patients who have symptomatic spasms or DCI, angiography can be regularly conducted. Angioplasty or intra-arterial chemical vasodilation with papaverine or verapamil can be used as endovascular treatments for vasospasm. [4]

Advances in diagnosis and therapy, most notably the use of nimodipine, intensive care management, hemodynamic adjustments, and endovascular neuroradiology operations, have improved the prospects for these patients, although the results are still unsatisfactory. The endothelin receptor antagonist clazosentan has been shown to significantly reduce vasospasm in recent clinical studies, although patient outcomes have not improved. [28]

Conclusion:

Despite the fact that it is a rare case, the high mortality attracts the majority of the attention. A variety of management techniques are available. Notably, Nimodipine is the sole FDA-approved medication for vasospasm. Moreover, the triple-H therapy hemodynamic augmentation technique, which comprises hypertension, hemodilution, and hypervolemia, is a key component of the treatment. We hope in the future, more research is done on multiple management techniques that are available.

References:

1. William W Ashley, Brian H Kopell, et al. Cerebral Vasospasm After Subarachnoid Hemorrhage. Medscape.
<https://emedicine.medscape.com/article/2500045-overview>
2. Sobey CG, Faraci FM. Subarachnoid haemorrhage: what happens to the cerebral arteries?. Clin Exp Pharmacol Physiol. 1998 Nov. 25 (11):867-76.
3. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijndicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke. 2010 Oct. 41 (10):2391-5.
4. Jennifer A. Frontera, Andres Fernandez, J. Michael Schmidt, Jan Claassen, Katja E. Wartenberg, Neeraj Badjatia, E. Sander Connolly, and Stephan A. Mayer Defining Vasospasm After Subarachnoid Hemorrhage. Originally published Apr 2009
<https://doi.org/10.1161/STROKEAHA.108.544700>Stroke. 2009;40:1963–1968.
5. Dorsch NW. Therapeutic approaches to vasospasm in subarachnoid hemorrhage. Curr Opin Crit Care. 2002; 8: 128–133.
6. Kassell NF, Torner JC, Jane JA, Haley EC Jr, Adams HP. The international cooperative study on the timing of aneurysm surgery. Part 2: Surgical results. J Neurosurg. 1990; 73: 37–47.
7. Ohta H, Ito Z. Cerebral infraction due to vasospasm, revealed by computed tomography (author's translation). Neurol Med Chir (Tokyo). 1981; 21: 365–372.
8. Roos YB, de Haan RJ, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M. Complications and outcome in patients with aneurysmal subarachnoid

- haemorrhage: A prospective hospital based cohort study in the netherlands. *J Neurol Neurosurg Psychiatry*. 2000; 68: 337–341.
9. Schmidt JM, Fernandez A, Rincon F, Claassen J, Ostapkovich ND, Badjatia N, Parra A, Connolly ES, Mayer SA. Frequency and clinical impact of asymptomatic cerebral infarction due to vasospasm after subarachnoid hemorrhage.
 10. Macdonald, R., Pluta, R. & Zhang, J. Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution. *Nat Rev Neurol* 3, 256–263 (2007).
<https://doi.org/10.1038/ncpneuro0490>
 11. Alvin Y. Chan, Elliot H. Choi, Ichiro Yuki, Shuichi Suzuki, Kiarash Golshani, Jefferson W. Chen, Frank P.K. Hsu, Cerebral vasospasm after subarachnoid hemorrhage: Developing treatments, *Brain Hemorrhages*, Volume 2, Issue 1, 2021, Pages 15-23, ISSN 2589-238X,
<https://doi.org/10.1016/j.heest.2020.08.003>.
 12. H. Lantigua, S. Ortega-Gutierrez, J.M. Schmidt, et al. Subarachnoid hemorrhage: Who dies, and why? *Crit Care*, 19 (2015), p. 309.
 13. A.S. Pandey, J.J. Gemmete, T.J. Wilson, et al. High subarachnoid hemorrhage patient volume associated with lower mortality and better outcomes *Neurosurgery*, 77 (2015), pp. 462-470.
 14. F. Rincon, R.H. Rossenwasser, A. Dumont The epidemiology of admissions of nontraumatic subarachnoid hemorrhage in the United States *Neurosurgery*, 73 (2013), pp. 217-222.
 15. M.T. Lawton, G.E. Vates Subarachnoid hemorrhage *N Engl J Med*, 377 (2017), pp. 257-266.
 16. R.L. Macdonald, T.A. Schweizer Spontaneous subarachnoid haemorrhage *Lancet*, 389 (2017), pp. 655-666.
 17. Liu, Yf., Qiu, HC., Su, J. et al. Drug treatment of cerebral vasospasm after subarachnoid hemorrhage following aneurysms. *Chin Neurosurg JI* 2, 4 (2016). <https://doi.org/10.1186/s41016-016-0023-x>
 18. Reynolds MR, Buckley RT, Indrakanti SS, Turkmani AH, Oh G, Crobeddu E, et al. The safety of vasopressor-induced hypertension in subarachnoid hemorrhage patients with coexisting unruptured, unprotected intracranial aneurysms. *J Neurosurg*. 2015 Oct. 123 (4):862-71.

19. Darby JM, Yonas H, Marks EC, Durham S, Snyder RW, Nemoto EM. Acute cerebral blood flow response to dopamine-induced hypertension after subarachnoid hemorrhage. *J Neurosurg.* 1994 May. 80 (5):857-64.
20. Meyer R, Deem S, Yanez ND, Souter M, Lam A, Treggiari MM. Current practices of triple-H prophylaxis and therapy in patients with subarachnoid hemorrhage. *Neurocrit Care.* 2011 Feb. 14 (1):24-36.
21. Miller JA, Dacey RG Jr, Diringer MN. Safety of hypertensive hypervolemic therapy with phenylephrine in the treatment of delayed ischemic deficits after subarachnoid hemorrhage. *Stroke.* 1995 Dec. 26 (12):2260-6.
22. Komotar RJ, Schmidt JM, Starke RM, Claassen J, Wartenberg KE, Lee K, et al. Resuscitation and critical care of poor-grade subarachnoid hemorrhage. *Neurosurgery.* 2009 Mar. 64 (3):397-410; discussion 410-1
23. Muehlschlegel S, Dunser MW, Gabrielli A, Wenzel V, Layon AJ. Arginine vasopressin as a supplementary vasopressor in refractory hypertensive, hypervolemic, hemodilutional therapy in subarachnoid hemorrhage. *Neurocrit Care.* 2007. 6 (1):3-10.
24. Jun P, Ko NU, English JD, Dowd CF, Halbach VV, Higashida RT, et al. Endovascular treatment of medically refractory cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *AJNR Am J Neuroradiol.* 2010;31:1911–6.
25. Stuart RM, Helbok R, Kurtz P, Schmidt M, Fernandez L, Lee K, et al. High-dose intra-arterial verapamil for the treatment of cerebral vasospasm after subarachnoid hemorrhage: Prolonged effects on hemodynamic parameters and brain metabolism. *Neurosurgery.* 2011;68:337–45. 345.
26. Flexman AM, Ryerson CJ, Talke PO. Hemodynamic stability after intraarterial injection of verapamil for cerebral vasospasm. *Anesth Analg.* 2012;114:1292–6.
27. OD, Lubnin A, Tabasaranskii TF, Iakovlev SB. Intra-arterial injection of verapamil in treatment of cerebral vasospasm in a patient with acute subarachnoid hemorrhage from an aneurysm: Case report. *Zh Vopr Neurokhir Im N N Burdenko.* 2013;77:57–60. 60.
28. Macdonald RL, Pluta RM, Zhang JH. Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution. *Nat Clin Pract Neurol.* 2007 May;3(5):256-63. doi: 10.1038/ncpneuro0490. PMID: 17479073.

UNDER PEER REVIEW