

Vasospasm management: a meta-synthesis of current modalities used by different medical societies

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ABSTRACT

Background: Cerebral vasospasm is a life-threatening complication of an aneurysmal subarachnoid hemorrhage (aSAH), with approximately 6 to 10 cases per 100,000 patients yearly. Despite the publication of numerous guidelines from various medical societies, there is a lack of standardized consensus on what the optimal management strategies for this severe complication truly are. This meta-synthesis aims to synthesize these endorsed recommendations to ultimately identify standardized care guidelines and improve patient outcomes after aSAH.

Methods: A comprehensive database search of existing guidelines published by major medical societies in the past 10 years was performed.

Results: The analysis included 28 relevant documents from 7 major medical societies. Key findings included: 1) Unanimous endorsement for oral nimodipine administration for 21 days post-aSAH. 2) Varying recommendations for alternative calcium channel blockers and hemodynamic management methods. 3) Targeted hypermagnesemia and routine statin therapy were not universally recommended due to insufficient evidence. 4) Use of antifibrinolytics was considered on a case-by-case basis. 5) Endovascular interventions were recommended for refractory cases, specifically.

Conclusion: This meta-synthesis reveals consistencies and divergences in vasospasm management recommendations across medical societies, highlighting the need for more robust clinical trials, regular guideline updates, and increased medical society collaboration.

Keywords: Vasospasm, cerebral vasospasm, aSAH, management, guidelines, meta-synthesis

INTRODUCTION

1.1 VASOSPASM AND ANEURYSMAL SUBARACHNOID HEMORRHAGE

Vasospasm, a complex pathophysiological phenomenon, involves abnormal and/or prolonged constriction of blood vessels (typically arteries) across different vascular beds within the body. The resulting reduction in artery diameter can cause a simultaneous reduction in perfusion of brain tissues, ultimately leading to complications, such as ischemia, infarction, and neurological deficits. The severity and duration of

vasospasm is not uniform in all patients and can vary widely, with more severe and prolonged cases leading to poorer clinical outcomes.¹ Cerebral vasospasm following an aneurysmal subarachnoid hemorrhage (aSAH) is the most clinically significant and extensively studied form of vasospasm.

1.2 CEREBRAL VASOSPASM

Cerebral vasospasm involving the narrowing of major cerebral arteries is estimated to occur in up to 70% of all aSAH patients. It remains a major cause of morbidity and mortality due to its potential life-threatening complications, including a reduction of cerebral perfusion and ischemia.¹ This constriction typically occurs 3–14 days following the ictal event and reaches its maximum on the 5th–7th postictal days, with

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a potential for significant cerebral blood flow reduction.² The exact mechanisms underlying vasospasm and cerebral vasospasm specifically are multifaceted and not yet fully understood but involve a combination of mechanical, biochemical, and cellular processes believed to be related to the posthemorrhagic depletion of nitric oxide, a potent vasodilator.³

1.3 VASOSPASM THERAPEUTIC MANAGEMENT

Various medical societies have published numerous guidelines for the prevention and treatment of vasospasm, recommending modalities such as hemodynamic therapy, calcium channel blockers, statins, magnesium, endothelins, and endovascular interventions.¹ However, there is currently no consensus about the optimal management strategy due to the complex nature of this condition.

1.4 PURPOSE

Cerebral vasospasm is estimated to occur in up to 70% of all aSAH patients and has had numerous recent advances in its pharmacological management. Yet, it is apparent that vasospasm-associated morbidity and mortality rates are significant and need more investigation.⁴ This study aims to conduct a meta-synthesis of various clinical studies on different vasospasm management modalities endorsed by major neurosurgical and neurological medical societies. The goal is to synthesize high-quality evidence to identify optimal vasospasm management guidelines and standardize care across different institutions and medical societies to improve patient outcomes after aSAH.

METHODS

2.1 SEARCH STRATEGY

A comprehensive database review of guidelines, position statements, and consensus documents published by major neurological, neurosurgical, and critical care societies evaluating pharmacological and endovascular interventions for vasospasm management after aSAH published within the past 10 years was conducted. The websites of medical societies

were also manually searched for additional documents. Keywords included “vasospasm”, “cerebral vasospasm”, “management”, “vasospasm treatment”, “guidelines”, “aSAH”, and the names of major medical societies (e.g., American Society of Anesthesiologists, American Heart Association, etc.).

2.2 INCLUSION CRITERIA

Inclusion criteria for this search included guidelines, consensus statements, or position papers from recognized medical societies, published in English between January 2010 and June 2024, and focused on adult patients and cerebral vasospasm management.

2.3 EXCLUSION CRITERIA

Excluded documents were those not published or endorsed by official medical societies, publications focusing solely on pediatric populations, and guidelines established earlier than 2010.

2.4 DATA EXTRACTION

Information from each study was extracted using a standardized collection approach. Extracted information included the publishing medical society, year of publication, recommended modalities for vasospasm management, and specific dosing or procedural details (when available).

2.5 DATA SYNTHESIS

The numerous management modalities were categorized into medical, endovascular, surgical, and novel/investigational approaches. Recommendations were compared across societies, noting both areas of agreement and differences.

RESULTS

3.1 SEARCH RESULTS

After removing duplicate studies, the electronic database search yielded 28 relevant documents from

Table 1. Summary of Vasospasm Management Recommendations by Modality

Management Modality	Treatment	Recommendations
Pharmacological	Calcium channel blockers	Oral nimodipine unanimously recommended for 21 days post aSAH ⁵⁻¹¹ IV administration if oral not possible ⁵⁻¹¹ Mixed views on other CCBs (nicardipine, verapamil) ^{7-9,11}
	Magnesium sulfate	Not recommended (lack of benefit) ⁵⁻⁸
	Statins	Not routinely recommended ^{5-7,11} Potential benefits under study
	Antifibrinolytics	Short-term use (<72 hours) may be considered ⁵⁻⁷ Long-term use not recommended ⁵⁻⁷
	Endothelin receptor antagonists	Generally, not recommended (conflicting results, increased risks) ^{7,8}
Medical	Hemodynamic management	Maintain euvolemia ^{5,7-8,10} Induced hypertension for DCI (endorsed by some societies) ¹¹ ESO against induced hypertension/hypervolemia ⁶
	Prophylactic therapies	Generally, not recommended (lack of evidence, potential complications) ^{5-6,9,11}
	Other factors	Monitor fever and glucose levels ^{6,10} Pain management with mild analgesics ^{6,10} Anti-epileptic drugs for clinical seizures ^{6,10} Mixed views on anti-inflammatory treatments ^{6,8,11}
Endovascular	Intra-arterial vasodilators	Recommended for refractory vasospasm ^{7,9} Specific agents vary by society ^{5,8-11}
	Balloon angioplasty	Generally recommended for accessible vessels with severe vasospasm ^{5-6,9-11}
	Other interventions	ESO: cilostazol as potential treatment, do not exclude elderly patients from interventional therapies ⁶ SNIS: consider interventional therapies when medical therapies is contraindicated/unfeasible ⁹

CCB-calcium channel blockers; DCI-delayed cerebral ischemia; ESO-European Stroke Organization; SAH-subarachnoid hemorrhage; SNIS-Society of Neurointerventional surgery

the following 7 medical societies: the American Heart Association/American Stroke Association (AHA/ASA), the European Stroke Organization (ESO), the Neurocritical Care Society (NCS), the Society for Neuroscience in Anesthesiology and Critical Care (SNACC), the Society of Neurointerventional Surgery (SNIS), the American Association of Neurological Surgeons (AANS), and the Congress of Neurological Surgeons (CNS). Twelve comprehensive guidelines, 9 consensus statements, and 7 position papers were thoroughly reviewed, compared, and cross-referenced. The identified modalities

for vasospasm management can be broadly categorized into medical management and endovascular intervention approaches. The recommendations gathered from the seven different medical societies varied in terms of preferred modalities, sequences in which these therapies should be employed, and the strength of the evidence supporting their use. Some societies provided comprehensive guidelines covering multiple modalities, while others focused on specific interventions and/or demographics. Table 1 summarizes each medical society's guidelines and recommendations.

3.2 PHARMACOLOGICAL MANAGEMENT

3.2.1 CALCIUM CHANNEL BLOCKERS

All medical societies unanimously recommend oral nimodipine administration for the 21 days following aSAH to improve neurological outcomes and prevent delayed cerebral ischemia (DCI).⁵⁻¹¹ If oral administration is not possible and/or contraindicated, intravenous administration is recommended as the next preferred method of pharmacological management but should be considered only if oral administration is not possible. The ESO and SNACC specifically recommend administering a dose of 60 mg PO q4h as a standard of care, while the remaining 5 medical societies do not identify a specific dosage.^{6,8} The SNIS states that pulsed dose intra-arterial calcium channel blocker infusions may be beneficial and may be considered for symptomatic cerebral vasospasm refractory to maximal medical therapy.⁹ Nuances exist among medical societies regarding the recommendation of calcium channel blockers (CCBs) beyond nimodipine, such as nicardipine and verapamil. While the SNACC, SNIS, and CNS all state that nicardipine and verapamil may be beneficial as second line treatments in the management of aSAH patients with cerebral vasospasm, the NCS is against intravenous nicardipine for DCI prevention and states there is insufficient evidence against the administration of CCBs other than nimodipine by intravenous or intraventricular routes.^{7-9,11} Further, the ESO recommends against applying calcium antagonists into the subarachnoid space following surgical occlusion of an aneurysm due to its unproven benefit.⁶

3.2.2 MAGNESIUM SULFATE

Recommendations regarding magnesium sulfate are universal among the medical societies that clearly defined their stance on its use in treatment; targeted hypermagnesemia is not currently recommended by the AHA/ASA, ESO, NCS, and SNACC due to a lack of benefit in outcomes.⁵⁻⁸

3.2.3 STATINS

Statin therapy in the treatment of cerebral vasospasm does not have an extensive literature citing its benefits, a fact recognized by 4 of the 7 studied medical

societies. The AHA/ASA, ESO, NCS, and CNS all recognize that while some statins have demonstrated potential benefit, current research does not demonstrate benefits strong enough to recommend its routine use.^{5-7,11}

3.2.4 ANTIFIBRINOLYTICS

Limited statements on fibrinolytic use were offered by the studied medical societies, but a universal consensus exists among these societies. The AHA/ASA, ESO, and NCS all recommend against the long-term use of antifibrinolytic therapy due to a lack of demonstrated benefit but state that short-term use (<72 hours) may be considered in certain cases to reduce the risk of early rebleeding, especially in cases of unavoidable treatment delays.⁵⁻⁷

3.2.5 ENDOTHELIN RECEPTOR ANTAGONISTS

The NCS is against endothelin receptor antagonist administration due to a lack of benefit on mortality and functional outcomes and increased risk of adverse events.⁷ The SNACC recommends clazosentan as a potential treatment option but explicitly states that it is an “experimental and less efficacious medical therapy” with conflicting results and increased risk of pulmonary edema, anemia, and hypotension.⁸

3.3 MEDICAL MANAGEMENT

3.3.1 HEMODYNAMIC MANAGEMENT

There is variability in the recommendations provided for hemodynamic management of cerebral vasospasm, typically recognized as “triple-H therapy.” Regarding fluid and blood pressure management, the AHA/ASA, AANS, SNACC, and NCS suggest maintaining euvolemia (via targeted fluid administration to reduce pulmonary edema risk) and induced hypertension for patients with DCI.^{5,7-8,10} The AHA/ASA specifically stresses the importance of tailoring management to individual patients based on their risk factors and clinical status.⁵ The CNS supports avoiding hypovolemia through fluid management similar to the other societies but recommends that induced hypertension be considered for patients

with DCI particularly if they are not responding to initial management.¹¹ Similarly, the SNIS supports the maintenance of a euvolemic state and the use of induced hypertension in conjunction with endovascular treatments.⁹ Last, the ESO recommends against induced hypertension or hypervolemia to improve outcomes in patients with delayed ischemic deficit due to “increased risks of cerebral edema, hemorrhagic transformation in areas of infarction, reversible leukoencephalopathy, myocardial infarction, and congestive heart failure.”⁶

3.3.2 PROPHYLACTIC THERAPIES

The AHA/ASA and CNS guidelines reflect a shift away from aggressive prophylactic measures by not recommending prophylactic hemodynamic augmentation as a standard approach to treatment due to potential complications and lack of improvement in patient outcomes.^{5,11} The SNIS does not support prophylactic invasive interventional therapies for post-hemorrhagic cerebral vasospasm, and the ESO outlines a lack of evidence supporting prophylactic use of antiepileptic drugs, advocating against their routine use.^{6,9}

3.3.3 OTHER FACTORS

In addition to the outlined guidelines, some societies provide recommendations on the medical management of other factors, such as pain, glucose levels, temperature, and more. The ESO and AANS recommend consistent monitoring of fever and glucose levels to ensure proper treatment of hyperglycemia and fever as needed.^{6,10} Regarding pain and seizure management, mild analgesics and antiepileptic drugs for clinically apparent seizures, respectively, are defined as potential methods of treatment, while salicylates and prophylactic antiepileptic drugs are recommended against.^{6,10} Distinctions in approaches to anti-inflammatory treatments are also made by several medical societies. The SNACC recommends nafamostat (synthetic protease inhibitor) and methylprednisolone (glucocorticoid) as specific treatments; the ESO and NCS claim insufficient evidence supporting routine use of steroid/mineralocorticoid administration for anti-inflammatory effects and maintenance of normal sodium concentrations/fluid balance.^{6,8,11}

Tirilazad, nicaraven, and ebselen (free radical scavengers) and ozagrel (thromboxane inhibitors) are indicated for treatment if necessary by the SNACC as well.⁸

3.4 ENDOVASCULAR INTERVENTION

3.4.1 INTRA-ARTERIAL VASODILATORS

All societies acknowledge the use of intra-arterial vasodilators with varying levels of recommendation. The SNIS and NCS strongly recommend their use in refractory vasospasm, with SNIS specifying that may be beneficial in treatment of symptomatic post-hemorrhagic cerebral vasospasm refractory to maximal medical therapy.^{7,9} The SNIS states that the efficacy of intra-arterial papaverine is not well established, while the SNACC suggests papaverine and verapamil as potential intra-arterial medical therapies to consider on an individualized treatment basis.^{8,9} The AHA/ASA, AANS, and CNS all recommend case-by-case consideration of intra-arterial vasodilators for refractory vasospasm and/or in patients with vasospasm refractory to medical management.^{5,10–11} The AHA/ASA additionally specifies milrinone as an emerging therapy with promising results for DCI prevention, but this drug requires more study to determine its beneficial and adverse effects.⁵

3.4.2 BALLOON ANGIOPLASTY

There is general agreement on the use of balloon angioplasty for accessible vessels with severe vasospasm. The SNIS, AANS, and CNS strongly recommend its use in appropriate cases, and the AHA/ASA and ESO mention it as a treatment option but carries risks and requires further study into its functionality.^{5–6,9–11} The SNIS also highlights patients with unsecured ruptured aneurysms in whom aggressive medical therapy carries a high risk of rebleeding from the index lesion as a particular demographic that could benefit from transluminal balloon angioplasty through the local treatment of remote vascular territories.⁹

3.4.3 OTHER INTERVENTIONS

Some medical societies mention additional considerations and circumstances in which endovascular

intervention is appropriately recommended. The ESO mentions cilostazol as a potential treatment, while other societies do not include it in their recommendations.⁶ The ESO also notes that elderly patients (>70 years) should not be excluded from interventional therapy considerations; decisions regarding whether to treat the patient should depend on the clinical and physical condition of each individual patient and the presence of aneurysm-specific factors favoring, or even requiring, endovascular intervention.⁶ The SNIS also highlights that interventional therapies should be considered when medical therapy is contraindicated or beneficial to the patient but cannot be sustained due to cardiopulmonary, intestinal, or other serious treatment-related complications.⁹ Invasive interventional management strategies should be considered in aSAH patients with new neurological deficits suspected to be the result of posthemorrhagic cerebral vasospasm when the deficits are not reversed or incompletely reversed by medical therapy. If a satisfactory response to medical therapy is not realized within 1 hour of initiation, the decision for interventional management should not be further delayed.

DISCUSSION

This meta-synthesis reveals both consistencies and variations in the recommendations for vasospasm management across different medical societies. While there is strong agreement on the core principles of vasospasm management, such as the use of nimodipine, significant differences exist in certain specific recommendations provided by different medical societies, such as the approach to hemodynamic management and the use of emerging therapies. In addition, the role of novel and investigational techniques, such as cilostazol, remains an area of ongoing research with currently limited guidance from medical societies.

Variations in the recommendations made by these different medical societies can be attributed to several factors, including varying interpretations of available evidence, regional differences in resources and practices, timing of guideline updates, the ever-evolving nature of vasospasm management research, different patient populations, and even cultural and historical factors.

These variations can promote ongoing research, foster innovation, and allow for individualized and tailored treatment approaches on a case-by-case basis. However, disadvantages include the potential for confusion and inconsistent care. Ultimately, this meta-synthesis highlights the need for more robust, large-scale clinical trials of emerging treatment approaches to provide high-quality evidence, regular updates to society guidelines incorporating emerging and supported evidence, increased collaboration between medical societies to harmonize recommendations for standardized care, and personalized approaches to vasospasm management based on institutional capabilities and patient-specific factors.

Further studies are warranted to investigate the ever-changing nature of this field, focusing on addressing the existing gaps in knowledge and providing more definitive evidence for emerging therapies as they arise. Case studies, imaging and biomarker studies, and long-term outcome studies are all potential areas warranting future investigation into the approaches defined by this current study. Future research should also focus on more robust, large-scale comparative effectiveness studies, exploring potential synergistic effects of different modalities, and evaluating the impact of personalized treatment approaches based on individual patient/demographic risk factors and characteristics.

CONCLUSION

The findings of this meta-synthesis highlight both consistencies and heterogeneity across different medical societies and the need for further research and collaboration to establish evidence-based, standardized guidelines for vasospasm management by medical societies and other professional organizations. Critical reviews by these societies to establish uniform recommendations and promote standardized approaches to vasospasm management could lead to improved patient outcomes, streamlined clinical decision-making, enhanced patient safety, efficient resource use, reduced overall treatment costs, and improved communication. The observed variations underscore the importance of considering regional resources, patient populations, and healthcare system capabilities when developing and following established guidelines. Increased

collaboration among medical societies coupled with ongoing research efforts will be pivotal in refining and standardizing vasospasm management protocols to optimize patient outcomes.

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