High-Grade Subarachnoid Hemorrhage - Beyond Guidelines

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KEYWORDS

• Subarachnoid hemorrhage • ARDS • Intracranial hypertension • Vasospasm
• Delayed cerebral ischemia • Practice guidance

KEY POINTS

- Despite higher risk for complications and delayed cerebral ischemia (DCI), outcomes in high-grade subarachnnoid hemorrhage (SAH) patients can be favorable.
- Acute respiratory distress syndrome (ARDS) are common in high-grade SAH. ARDS management using higher positive end-expiratory pressure, lower tidal volume ventilation and prone positioning may affect intracranial pressure and cerebral perfusion pressure and require close monitoring.
- Angiographic vasospasm alone does not correlate well with cerebral infarction, DCI, or SAH outcome, and prophylactic treatment of asymptomatic vasospasm is not recommended.
- Prophylactic hemodynamic augmentation leads to complications without improving outcome and is not recommended.
- Symptom-driven treatment approaches for DCI commonly include hemodynamic augmentation and endovascular rescue therapies.

INTRODUCTION

Spontaneous subarachnoid hemorrhage (SAH), commonly caused by the rupture of an intracerebral aneurysm (85% of all cases of SAH), remains a life-threatening condition with high mortality and long-term morbidity. SAH patients present in a spectrum of clinical severity, commonly measured using the Hunt and Hess (HH) or the World Federation of Neurologic Societies (WFNS) score.[1] High-grade SAH is commonly defined as SAH patients who present with HH or WFNS scores of 4 or 5. These patients have significantly higher mortality and are at higher risk for SAH-associated complications, including delayed cerebral ischemia (DCI).

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Although no novel therapeutics have improved SAH outcomes in clinical trials since the original nimodipine study in 1983, overall SAH survival and outcome are steadily improving over time. In-hospital mortality has decreased from 22.6% during 1985 - 1994 to 16.7% in 2005 - 2014, and the proportion of patients with good functional outcome at 6 months has increased from 64.8% to 78.8%.[2] Despite higher risk for morbidity and mortality, outcomes in high-grade SAH patients can be favorable.[3,4] This marks the critical nature in clinical decision making and critical care support of high-grade SAH patients, who experience many more severe complications. This article specifically examines the critical clinical scenarios commonly faced by high-grade SAH patients, including respiratory failure/acute respiratory distress syndrome (ARDS), severe DCI and cerebral vasospasm, and long-term outcomes beyond the modified Rankin score (mRS).

RESPIRATORY FAILURE AND ACUTE RESPIRATORY DISTRESS SYNDROME

Up to 38.5% of SAH patients experience acute respiratory failure requiring mechanical ventilation,[5,6] particularly high-grade SAH patients with reduced arousal. For SAH patients requiring mechanical ventilation, the 2023 American Heart and American Stroke Association (AHA/ASA) guideline recommends the use of the standardized ICU care bundle, which includes low tidal-volume ventilation, moderate positive end-expiratory pressure (PEEP), early enteral nutrition, standardized antibiotic therapy for hospital-acquired pneumonia, and a systematic approach to extubation.[5]

Common complications associated with acute respiratory failure include ventilator-associated pneumonia (VAP), and, in severe cases, acute respiratory distress syndrome (ARDS). A recent large randomized clinical trial (RCT) PROPHY-VAP examined brain-injured patients, including those with SAH, with Glasgow coma score (GCS) less than 12 and anticipated mechanical ventilation duration of more than 48 hours. In this population, 1 dose of prophylactic ceftriaxone reduced the incidence of VAP, mechanical ventilation duration, ICU length of stay, and mortality.[7]

ARDS occurs in up to 30% of SAH patients, with an incidence of up to 3.6% in the first 7 days after aneurysmal SAH,[8] with high-grade SAH patients are particularly at risk.[9] Developing ARDS with SAH is associated with worse functional outcomes and higher mortality.[9–13] Despite its high incidence and clinical impact, no RCT has specifically investigated optimal ARDS management in SAH.

Current evidence and recommendations from the American Thoracic Society guidelines support general management strategies for ARDS including using higher PEEP, limited tidal volume ventilation with permissive hypercapnia, prone positioning, neuromuscular blockade, glucocorticoids, and veno-venous extracorporeal membrane oxygenation (VV-ECMO).[5,14] There are limited data on the risk and benefit of these maneuvers in high-grade SAH patients who have concomitant high risk conditions such as cerebral edema and intracranial hypertension, which could be exacerbated by these maneuvers.[15] **Table 1** summarizes potential neurologic considerations of common ARDS management strategies in high-grade SAH patients.

Prone Positioning and Alveolar Recruitment Maneuvers

Prone positioning use in severe ARDS with hypoxemia can improve ventilation-perfusion matching and reduce lung compression, and is associated with improved survival in severe ARDS with arterial partial pressure of oxygen (Pa_{O_2}) to fraction of inspired oxygen (Fi_{O_2}) ratio less than 150 mm Hg.[16] However, prone positioning can

Table 1
Acute respiratory distress syndrome management strategies and potential neurologic impacts in high-grade subarachnnoid hemorrhage

ARDS Treatment Strategies per the 2024 American Thoracic Society (ATS) guidelines[14]	Potential Considerations in High-Grade SAH Patients
Higher PEEP without lung recruitment maneuvers	PEEP may increase ICP, particularly at higher levels recommend for ARDS therapy
Limit tidal volume (4–8 mL/kg predicted bodyweight) and inspiratory pressures (plateau pressure, 30 cm H_2O) and permissive hypercapnia	Hypercapnia may increase ICP
Prone positioning for 12 h per day in severe ARDS	• Prone positioning may increase ICP • Sedation needs may limit neurologic examination.[19]
Glucocorticoid use	Increased adverse events without clinical benefit in SAH
Neuromuscular blockers use with early severe ARDS	Neuromuscular blockade limits neurologic examination
VV-ECMO use in severe ARDS	• Systemic anticoagulation may be high risk in severe SAH, especially in patients with external ventricular drain (EVD) track hemorrhage or large areas of infarction • ECMO cannulation of internal jugular vein may reduce cerebral venous drainage and increase ICP

induce hemodynamic changes that impact cerebral blood flow (CBF). In patients with severe brain injury and cerebral edema at risk for intracranial hypertension, the cerebrovascular impact of prone positioning requires special consideration. Prone positioning can increase intrabdominal pressure. Data regarding the impact of increased intra-abdominal pressure on venous return and cardiac output is mixed, and the relationship may depend on factors such as intravascular volume status and preload responsiveness.[17–20] However, increased abdominal pressure can reduce cerebral venous outflow leading to intracranial pressure (ICP) increase, while simultaneously decreasing central venous return and lowering cardiac output, which in turn lowers the mean arterial pressure (MAP) and further reduces cerebral perfusion pressure (CPP). Head positioning associated with prone positioning may further impact cerebrovascular physiology and ICP by compressing neck veins, leading to decreased cerebral venous drainage and CBF.[21,22] Finally, body position and sedation required to achieve prone position can limit neurologic examination.[19]

Small RCTs and clinical case series provide data on prone positioning, ICP, CPP, cerebral oxygenation and cerebral perfusion in SAH patients (**Table 2**). While prone positioning clearly exerts physiologic effects on ICP and CPP, the changes may not be clinically significant and may not occur in every patient. The impact on CPP varies and may depend on adjuvant therapies to decrease ICP and increase MAP. A recent cohort study demonstrated that CPP and cerebral blood flow (measured by transcranial doppler) can be maintained even with increases in ICP during proning.[23] In exchange, prone positioning generally improves Pa_{O_2} and brain tissue oxygen (PbO2). Given the potential for ICP and CPP changes with prone positioning, monitoring of these parameters before and during prone positioning should be considered to ensure safety.

Table 2
Impact of prone positioning in subarachnnoid hemorrhage and severe brain injury

	Patient Population	Prone Duration	Neuro-Monitoring	ICP/CPP Treatment	Effects of Prone Positioning
Reinprecht et al[57] 2003	SAH (n = 16) with ARDS	$\geq$ 14 h	ICP & brain tissue oxygenation (IP probe)	EVD whenever possible; Mannitol, THAM, or hypertonic saline infusions administered for ICP >20 mm Hg	• Increased Pao_2 and PbO2 • Increase in ICP and decrease in CPP, not clinically significant • 2 patients turned to the supine position after 6 and 8 h because of ICP >25 mm Hg
Thelandersson et al,[58] 2006	SAH (n = 3), ICH (n = 2), and TBI (n = 6) with mechanical ventilation and $Fio_2 \geq 0.4$	$\leq$ 3 h	ICP (EVD)	EVD closed during procedure and not used for drainage	• Increase in Pao_2 and SaO2 • No significant changes in ICP or CPP • Prone position immediately for ICP > 20 mm Hg and CPP <60 mm Hg in 1 patient
Nekludov et al,[59] 2006	SAH(n = 2), ICH (n = 1), and TBI (n = 6) on mechanical ventilation	1 h	ICP (EVD)	Norepinephrine infusion to maintain CPP $\geq$ 60 mm Hg	• Increase in Pao_2 • Increase in ICP not clinically significant • Increase in CPP
Roth et al,[60] 2014	SAH (n = 15), ICH (n = 5), ischemic stroke (n = 1) and TBI (n = 8) patients with prone positioning because of respiratory failure	$\leq$ 8 h	ICP (EVD)	EVD as needed	• Increase in Pao_2/Fio_2 ratio • Increase in ICP not clinically significant • No significant decrease in CPP • Prone positioning replaced by continuous lateral rotational therapy because of elevated ICP in 3 patients

Bernon et al,[61] 2021	SAH (n = 11), ICH (n = 7), and TBI (n = 10) with ARDS	≤ 16 h	ICP and brain tissue oxygenation monitoring in 4 patients (method not specified)	EVD, craniectomy, hypothermia, osmotherapy, thiopental as needed	• Increase in Pao_2/Fio_2 ratio • Increase in ICP, sometimes clinically significant • Prone positioning discontinued because of sustained ICP elevation in 5 patients
Elmaleh et al[23] 2024	SAH (n = 4), ICH (n = 6), and other (n = 2) with ARDS	16 h	ICP & brain tissue oxygenation (intraparenchymal [IP] probe), CBF (estimated by TCD)	Vasopressor as needed to maintain CPP	• Increase in PbO2 and Pao_2/Fio_2 ratio • Increase in ICP • No significant decrease in CPP • No significant reduction of CBF

Abbreviations: ARDS, acute respiratory distress syndrome; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; EVD, external ventricular drain; Fio_2, fractional inspired oxygen; ICH, intracerebral hemorrhage; ICP, intracranial pressure; IP, intra-parenchymal; Pao_2, arterial partial pressure of oxygen; PbO2, brain tissue oxygen partial pressure; SaO2, arterial oxygen saturation; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; TCD, transcranial doppler; THAM, tris-hydroxymethyl aminomethane.

Higher Positive End-Expiratory Pressure Without Lung Recruitment Maneuvers

The latest evidence suggests higher PEEP use without prolonged lung recruitment maneuvers (LRMs) in patients with moderate-to-severe ARDS is associated with impact on CBF, ICP, and CPP. Although data on the impact of PEEP on ICP are variable, there is concern that higher PEEP may be transmitted through the pleural space, elevate central and jugular venous pressure, and thereby increase ICP while simultaneously decreasing central venous return and reducing cardiac output, thus leading to reduced MAP, which may further lower CPP.[24,25] In brain-injured patients, elevated ICP may actually limit the transmission of PEEP to the intracranial compartment by compressing the cerebral venous system.[26] Additionally, reduced lung compliance in ARDS may minimize airway pressure transmission, thus reducing the possible impact of PEEP on MAP and ICP.[27] A recent study on PEEP changes in acute brain injury patients showed that PEEP changes did not result in clinically significant changes in ICP.[28]

Critical care support of SAH patients with ARDS demands a delicate balance to improve oxygenation while maintaining ICP control and cerebral perfusion. Some clinical studies in SAH suggest that PEEP of 20 mm Hg or greater may increase ICP and reduce MAP and CBF; however, vasopressors can restore MAP and normalize CBF despite sustained high PEEP (**Table 3**).[27,29] Of note, all studies of higher PEEP in SAH used concomitant ICP and CPP monitoring, which is prudent in this clinical scenario. There are limited data on the application of prolonged LRMs (eg, PEEP $\geq$ 35 cm H_20 for >60s) in SAH patients, and their use is no longer recommended.[14,30]

Corticosteroids

Corticosteroids are recommended in ARDS but not for the treatment of SAH-related inflammation, as metanalyses of observation and controlled clinical studies have shown increased adverse events such as hypokalemia, hyperglycemia, gastrointestinal bleeding, blood pressure changes, pulmonary embolus, and heart failure without significant changes in neurologic outcomes.[31,32] Given the benefit of corticosteroids in ARDS, corticosteroids should be considered in SAH patients with ARDS where mortality reduction may supersede the potential impact of adverse events.

Neuromuscular Blockade

Neuromuscular blockade use is recommended in severe ARDS, but it can impede serial neurologic examination in SAH patients. This should not preclude the use of neuromuscular blockage when indicated. In such instances, the addition of other neuromonitoring modalities to assess changes in neurologic status may be helpful.[15]

Venovenous Extracorporeal Membrane Oxygenation

ECMO is a potential rescue therapy in ARDS but presents unique challenges in patients with acute brain injury, such as SAH. The need for systemic anticoagulation with VV-ECMO should raise concern for recurrent intracranial bleeding, particularly in patients with craniotomy, intraparenchymal hemorrhage, large cerebral infarcts, or if the bleeding aneurysm has not been secured. Fluctuations in partial pressure of carbon dioxide ($Paco_2$) with VV-ECMO may directly impact CBF and ICP. Large cannulas in the internal jugular vein may obstruct cerebral venous outflow and raise ICP. Data on VV-ECMO in SAH patients with ARDS are limited to case reports but serve to address potential risks through protocol alterations such as avoiding continuous therapeutic anticoagulation and placing the ECMO return cannula in the left subclavian instead of the internal jugular vein.[33,34]

Table 3
Impact of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure in severe brain injury and acute respiratory distress syndrome

	Patient Population	PEEP Levels	Neuro- Monitoring	Findings
Muench et al,[29] 2005	SAH (n = 10) requiring mechanical ventilation	PEEP up to 20 cm H_20 on days 1,3, and 7 after SAH with measurements of cerebral and hemodynamic markers 10 min after each incremental PEEP change	Thermal diffusion regional CBF probe Brain tissue oxygen probe	Only PEEP $\geq$20 cm H_2O resulted in a significant decrease in mean arterial pressure (MAP) and CBF, and higher ICP After MAP was restored with norepinephrine, CBF normalized despite the continued higher PEEP
Caricato et al,[27] 2005	aSAH (n = 11), severe TBI (n = 10) requiring mechanical ventilation	PEEP up to 12 cm H_2O, with measurements of cerebral and hemodynamic markers 15 min after each PEEP change Divided into patients with normal (>45 mL/cm H_2O) vs low lung compliance (<45 mL/cm H_2O)	ICP by EVD	No changes in ICP because of PEEP regardless of lung compliance group PEEP reduced MAP and CPP only in the normal lung compliance group

Acute respiratory distress syndrome impact on neurologic outcomes

ARDS in SAH patients is associated with increased duration of mechanical ventilation, longer ICU and hospital length of stay, higher mortality,[9–13] and worse functional outcomes as measured by the Glasgow Outcome Score (GOS) or mRS. There are currently no data on the impact of ARDS on cognitive function, quality of life, and other important patient-centered outcomes in SAH survivors.

Cerebral vasospasm and delayed cerebral ischemia

In addition to initial SAH severity and age, DCI is a leading cause of disability and unfavorable outcome in SAH, and one that is potentially reversible. This second phase of clinical deterioration may occur 3 to 10 days after the initial aneurysm rupture, and it may be associated with abnormal angiographic findings and/or new infarcts on computed tomography (CT) or MRI brain scan. The traditional hypothesis is that narrowing of cerebral arteries secondary to pathophysiologic mechanisms associated with SAH leads to reduced blood flow and decreased cerebral perfusion, and may result in ischemic infarction of the tissue distal to the arterial segments affected by vasospasm. Growing clinical evidence supports this being an overly simplistic concept. The association between angiographic findings, cerebral infarction, and clinical symptomatology is limited. In fact, up to one-third of patients with cerebral infarctions following SAH do not have corresponding angiographic findings in parent vessels.[35] Multiple large RCTs showed therapeutics that reduced or prevented angiographic cerebral vasospasm but did not improve patient outcomes.[1,36] Emerging science now suggests that ischemia from vasospasm is only one of multiple independent pathophysiologic mechanisms that contribute to secondary brain injury following SAH.[37]

Overlapping Terminologies

A myriad of variable and overlapping terminologies used interchangeably through the medical literature has added to the imprecision in the diagnoses of this second phase of brain injury after SAH:

- Angiographic cerebral vasospasm refers to constriction of cerebral arteries following SAH visible on digital subtraction cerebral angiography (DSA), cerebral CT angiography (CTA), brain MR angiography (MRA), or detected using transcranial Doppler ultrasound (TCDs) criteria. Anatomic studies, such as DSA, CTA, and MRA enable visualization of all major cerebral arteries and branches with variable resolution or more distal vessels. TCD detection of vasospasm is sensitive and specific for proximal vessels in the Circle of Willis such as the first segment of the middle cerebral artery (MCA), but less reliable in the posterior circulation, and does not visualize the anterior cerebral artery beyond the A1 segment.[38]In large SAH RCTs, vasospasm is often defined as reduction of cerebral artery diameter by more than two-thirds of its original caliber.[39] This terminology has also been applied to findings on cerebral CTA, although DSA remains the gold standard for vasospasm diagnosis. Patients with findings of angiographic cerebral vasospasm may or may not have clinically detectable neurologic symptoms.[40]
- Symptomatic cerebral vasospasm refers to new neurologic deterioration or persistent neurologic dysfunction attributable to ischemia in the vascular territory with angiographic cerebral vasospasm. In high-grade SAH, patients with altered levels of consciousness and/or requiring sedation for respiratory failure and ARDS, clinical detection of new neurologic deficits may be limited.

- Delayed ischemic neurologic deficit (DIND) is defined as at least a 2-point decrease on the modified GCS or an increase of at least 2 points on the abbreviated National Institute of Health stroke scale (NIHSS) lasting at least 2 hours.[39] This is an endpoint often used in SAH RCTs. To date, the most widely accepted definitions for DCI were published in 2010[41] and subsequently adopted through large consensus effort as common data elements (CDEs) in SAH in 2019.
- Clinical deterioration caused by DCI: focal neurologic impairment (such as hemiparesis, aphasia, apraxia, hemianopia or neglect) or a decrease of at least 2 points on the GCS lasting at least 1 hour, not immediately apparent after aneurysm occlusion, and cannot be attributed to other causes by clinical, radiographic, or laboratory investigations.
- Cerebral infarction caused by DCI: cerebral infarction on CT or MRI of the brain within 6 weeks of SAH or proven at autopsy, not present on CT or MRI between 24 and 48 hours after aneurysm occlusion.

Therapeutic Options for Vasospasm and Delayed Cerebral Ischemia

There is a large body of literature documenting a multitude of approaches and efforts to prevent and treat cerebral vasospasm and DCI. They can largely be separated into prophylactic treatments used before clinical deterioration or the diagnosis of DCI, versus symptoms-driven approaches.

Prophylactic treatments

Nimodipine. Enteral nimodipine use for 21 days following SAH is a high-level recommendation in the latest AHA/ASA and the Neurocritical Care Society (NCS) SAH guidelines (**Table 4**).[5,42] Nimodipine is often thought to work through prevention or treatment of vasospasm, which was not demonstrated in the original or subsequent studies. This assumption has at times erroneously led providers to discontinue nimodipine early and not complete the 21-day course established in the original RCT. Nimodipine can lead to hypotension, raising concern for CPP in vulnerable SAH patients with severe vasospasm and/or DCI, and nimodipine is often dose-reduced or stopped in these clinical scenarios. Although there are insufficient clinical data to determine the impact of total nimodipine dose on SAH outcomes, emerging pharmacogenomic studies suggest individual genetic variabilities in nimodipine metabolism significantly impact serum nimodipine levels, suggesting a future personalized medicine approach may be needed.[43]

Prophylactic agents previously tested in large phase III randomized controlled trials. Multiple potential therapeutic agents aimed at preventing or reducing cerebral vasospasm have been evaluated in large, multicenter phase III RCTs over several decades. These therapeutic agents include intravenous nicardipine (calcium channel antagonist), tirilazad mesylate (free radical scavenger), clazosentan (endothelin receptor antagonist), high-dose intravenous magnesium, oral simvastatin, and intraventricular extended-release nimodipine.[1] Although there was no increase in adverse events, none of these therapeutics met their primary end point of improving 90-day functional outcome compared with placebo. Of note, the clazosentan RCTs demonstrated that the drug reduced angiographic appearance of vasospasm but did not improve overall outcomes, further highlighting the potential discordance between angiographic vasospasm and SAH-related brain injury and outcomes.[44,45]

Targeting clinical deterioration caused by vasospasm/ delayed cerebral ischemia

Symptomatic vasospasm/DCI is common in high grade SAH patients. However, there are currently no high-level data to guide clinical management other than what not to

Table 4
Delayed cerebral ischemia prevention and treatment options: comparison of guidelines

DCI Treatment Option	AHA[5] Rec/Level of Evidence	NCC[42] Rec/Level of Evidence	Benefit	Caution
Nimodipine	Early initiation of enteral nimodipine (level 1A)	Recommend (strong; moderate quality)	Prevention of DCI, improve outcome	Hypotension
Endothelin antagonist	N/A	Against Lack of benefit on mortality or outcome and increase risk for AE (strong; high quality)		Pulmonary complications, fluid retention, anemia
Statins	Not recommended (3 no benefit, A)	Against. Lack of benefit (strong; high quality)	No benefit in DCI or mortality	
Magnesium	Not recommended (3 no benefit, A)	Against. Lack of benefit (strong; high quality)	No benefit in cerebral infarction or mortality	
Fluid administration	Maintain euvolemia is beneficial (2a, B-NR)	Target euvolemia, possible goal-directed hemodynamic therapy (conditional recommendation)	Potential increase in cerebral perfusion, reduce DCI, improve functional outcome	Liberal fluid use is associated with pulmonary edema
Blood pressure (BP) and cardiac output augmentation	In symptomatic vasospasm, elevate systolic BP may be reasonable (2b, B-NR)	Insufficient data, no recommendation	Potential increase in cerebral perfusion, reduce DCI, improve functional outcome	An underpowered RCT showed no improvement in functional outcome and more complications in induced hypertension arm.[46] Excessive induced hypertension may be associated with PRES.[62]

Prophylactic hemodynamic augmentation	Should not be performed (3 harm, B-R)	n/a	No benefit in outcome	Higher incidence of complications including congestive heart failure
Intra-arterial vasodilator	In severe vasospasm, IA vasodilator use may be reasonable (2b, B-NR)	N/A	Reverse cerebral vasospasm, reduce progression and severity of DCI	Systemic hypotension, elevated ICP during medication administration
Cerebral angioplasty	In severe vasospasm, angioplasty may be reasonable (2b, B-NR)	N/A	Reverse cerebral vasospasm, reduce progression and severity of DCI; greater durability in angiographic response compared with IA vasodilator	High mortality associated with vessel rupture

do. Both of the latest guidelines recommend against prophylactic hemodynamic augmentation because of a lack of clinical benefit and high incidence of complications.[5,42] In practice, the most commonly used therapeutic approaches for symptomatic vasospasm/DCI include

- Symptoms-driven augmentation of blood pressure and cardiac output to optimize cerebral perfusion
- Endovascular rescue therapies, including intra-arterial infusion of various vasodilators, most commonly calcium channel blockers, into the affected cerebral circulation and cerebral angioplasty of the vessels affected by vasospasm to restore cerebral perfusion

Existing guidelines offer differing guidance on these options, largely because of the limited level of clinical evidence. The only RCT that examined induced hypertension in DCI (HIMALAIA) was stopped early because of slow enrollment and was substantially underpowered to detect outcome differences. Although it did show 2.1-fold increase complications in the induced hypertension arm, baseline differences in SAH severity between the 2 arms preclude any reliable interpretation of the results.[46] **Table 4** summarizes major recommendations and differences in the latest AHA/ASA and NCS guidelines on vasospasm and DCI management in SAH, as well as potential clinical benefits and cautions with each therapeutic approach.

Refractory Vasospasm/Delayed Cerebral Ischemia – Beyond the Guidelines

One of the most challenging clinical scenarios in high-grade SAH patients is refractory vasospasm/DCI, where symptoms are recurrent, progressive, or persistent, despite first-line treatments. Without therapeutic intervention, these patients are at high risk for progressing to cerebral infarction, severe morbidity, and even death. However, potential additional therapeutic approaches in such clinical scenarios are experimental, high-risk, and supported by limited clinical data, generally from smaller retrospective studies or case series. Current clinical practice in severe vasospasm/DCI treatment is highly variable across regions, centers, and even individual partitioners,[47] further limiting the possibility of large, multicenter collaborative studies to generate the much-needed clinical evidence to establish risks, benefits, and patient selection criteria for these therapeutic approaches.

Table 5 summarizes some therapeutic approaches to severe vasospasm/DCI beyond existing guidelines, along with potential benefits and downsides based on the limited clinical evidence available. Intravenous milrinone infusion[48,49] induces cerebral vasodilation and increases cardiac inotropy; it has been studied in larger observational cohort studies of SAH and meta-analysis with relatively abundant data on risk profiles. The major adverse effect is systemic hypotension and higher need for vasopressor support. Repeated intraventricular nicardipine injections (most commonly 4 mg every 8–12 hours) through an external ventricular drain have been reported in smaller, retrospective studies with fewer data on potential adverse events and patient selection.[50] Prophylactic CSF drainage via lumbar drain has been studied in RCTs, with the latest, EARLYDRAIN, demonstrating efficacy on reducing cerebral infarction and improving SAH outcomes 6 months, although by a narrow margin.[14] This beneficial effect is not present on metanalyses combining all existing RCT data.[15] Percutaneous stellate ganglion blockade to reduce sympathetic outflow to cerebral arteries has been used to promote cerebral vasodilation in small RCTs that examined surrogate measures of brain injury with limited data on potential impact on SAH outcomes.

Given the limited evidence and high-risk scenario, treatment approaches to severe or refractory vasospasm and DCI may be best served with a multidisciplinary team

Table 5
Refractory vasospasm and delayed cerebral ischemia therapeutic approaches: beyond the guidelines

Therapeutic Approach	AHA[5] Reccommendations	NCC[42] Reccommendations	Mechanism and Potential Benefit	Caution
Intraventricular nicardipine injections[50]	N/A	None; insufficient data	• Direct cerebral arteriolar vasodilatation through circulation of drug into the intrathecal space • TCD velocities improved following injections, lasting for > 24 h	• Serial injections through EVD may increase infection risk. Overall reported rate is 6% • Small studies with limited data on safety, patient selection, complications
Milrinone intravenous infusion[48]	N/A; future research	N/A	• Increases cardiac inotropy, increase cardiac output • Cerebral vasodilatory effect through phosphodiesterase-III (PDE 3) inhibition • Large case series demonstrate drug is relatively well tolerated	• Vasodilatory effect on systemic circulation • Most common adverse event is hypotension (23%) and increase vasopressor support need • Hypokalemia occurs in 11% • May need adjustment for renal function
Prophylactic CSF drainage (lumbar drain)[63,64]	N/A; future research	N/A	• EARLYDRAIN RCT with lumbar drain for CSF diversion 5 mL/h starting within 72 h of SAH was associated with less cerebral infarctions at discharge and more favorable outcome at 6 mo	• 70% patients in lumbar drain group had an EVD • ICP gradient between cranial and lumbar drain pressures were monitored and lumbar drainage discontinued if the gradient is > 5 mm Hg • Prior RCTs, and meta-analysis including EARLYDRAIN, showed no effect on clinical outcome

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Therapeutic Approach	AHA[5] Reccommendations	NCC[42] Reccommendations	Mechanism and Potential Benefit	Caution
Neural ganglia block[65,66] (stellate ganglia block)	N/A; future research	n/a	• Percutaneous nerve block to reduce sympathetic outflow to cerebral arteries, potentially leading to cerebral vasodilation	• Potential complications include transient recurrent laryngeal nerve paralysis and voice changes • Limited data on impact on SAH outcome

approach and with shared decision making, particularly in areas where risks and benefits are not well established.

DISCUSSION

Outcome after SAH is evolving, and mortality and the mRS are insufficient measures to understand survivor experience and impact on individuals, families, and society. There are increasingly more SAH survivors,[51] including those who survived high-grade SAH. Even in patients who present with initial HH grade of 5, with modern surgical and critical care support, up to 39% achieve a favorable neurologic outcome and good cognitive function.[3,4,52] Despite the overall trend of improving survival and outcomes, significant variabilities in outcomes are seen across the United States and globally.[53] Although many factors may contribute to observed outcomes, existence of large SAH clinical care practice variabilities across individuals, centers, and regions is well documented.[47] There is evidence that protocolized, bundled care is associated with improved patient outcomes in larger population studies that include SAH patients, as discussed in recent published guidelines.[5] Published guidelines often do not address the most refractory and severe cases, as there are generally insufficient data and clinical evidence to support conclusive guidance. This article addresses some of the most common exceptions that are beyond existing guidelines.

Although SAH patients are surviving more and living longer, limited data on the quality of survivorship suggest many SAH survivors may continue to experience disability and altered quality of life many years after ictus.[54] Indeed, the number of people and number of years living with SAH-associated disability may be expanding. Emerging data, although scant, point to a significant burden of pain/headache, fatigue, PTSD, anxiety/depression, cognitive changes, hormonal dysfunction including sexual dysfunction, and social dependence/isolation, loss of work, and financial challenges in survivors.[55,56] There is even less information or clinical studies on potential therapeutic options to optimize quality of life, function, and overall wellness in SAH survivors. This represents an important knowledge gap in the care of SAH patients. The therapeutic course extends much beyond the acute phase of SAH and short-term ICU survival and a global functional outcome at 90 days.

SUMMARY

High-grade SAH patients are at high risk for severe disability and death, and yet favorable outcomes are possible, highlighting the importance of optimal critical care management in this patient population. Common severe complications include respiratory failure, ARDS, and severe cerebral vasospasm and DCI. There is limited randomized clinical trial evidence to guide management of these severe complications, other than the recommended use of enteral nimodipine to reduce DCI risk and improve SAH outcomes. ARDS management strategies in SAH patients require careful consideration of their potential impact on cerebral physiology including intracranial pressure and cerebral blood flow, which requires close monitoring and treatment. DCI remains an important and potentially reversible cause of morbidity and death particularly in high-grade SAH, but optimal treatment strategy for DCI remains controversial, and the current level of clinical evidence remains limited. Angiographic vasospasm has limited association with DCI and SAH outcome, and RCTs found therapeutic agents that reduced cerebral vasospasm did not improve SAH outcome. Prophylactic treatments to induce hemodynamic augmentation in patients with vasospasm but without clinical symptoms lead to high incidence of complications without outcome improvement and should therefore not be used.

CLINICS CARE POINTS

- Current ARDS management strategies such as higher PEEP, limited tidal volume, and prone positioning can improve systemic and cerebral tissue oxygenation but may also raise intracranial pressure, reduce cerebral perfusion, and lower cerebral venous outflow. ICP and CPP monitoring may be reasonable in these situations.
- Sedation and neuromuscular blockade use in ARDS limit clinical neurologic monitoring in SAH patients who are at high risk for DCI.
- Enteral nimodipine use can reduce DCI and improve SAH outcome, and it is a high-level recommendation in all existing SAH guidelines.
- Prophylactic hemodynamic augmentation in SAH leads to high incidence of medical complications without outcome benefit and is not recommended.
- Prophylactic use of endothelin antagonist, statins, and magnesium did not improve SAH outcome, and routine use is not recommended.
- Common treatment approaches to symptomatic vasospasm and DCI include hemodynamic augmentation and endovascular rescue therapies. Other potential treatment approaches, such as intraventricular nicardipine injections, milrinone intravenous infusions, prophylactic CSF drainage by lumbar drain, or stellate ganglia block remain experimental and have limited clinical efficacy and safety data.

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