Update on intrathecal management of cerebral vasospasm: a systematic review and meta-analysis

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OBJECTIVE Aneurysmal subarachnoid hemorrhage (aSAH) accounts for a relatively small portion of strokes but has the potential to cause permanent neurological deficits. Vasospasm with delayed ischemic neurological deficit is thought to be responsible for much of the morbidity associated with aSAH. This has illuminated some treatment options that have the potential to target specific components of the vasospasm cascade. Intrathecal management via lumbar drain (LD) or external ventricular drain (EVD) offers unique advantages in this patient population. The aim of this review was to provide an update on intrathecal vasospasm treatments, emphasizing the need for larger-scale trials and updated protocols using data-driven evidence.

METHODS A search of PubMed, Ovid MEDLINE, and Cochrane databases included the search terms (subarachnoid hemorrhage) AND (vasospasm OR delayed cerebral ischemia) AND (intrathecal OR intraventricular OR lumbar drain OR lumbar catheter) for 2010 to the present. Next, a meta-analysis was performed of select therapeutic regimens. The primary endpoints of analysis were vasospasm, delayed cerebral ischemia (DCI), cerebral infarction, and functional outcome.

RESULTS Twenty-nine studies were included in the analysis. There were 10 studies in which CSF drainage was the primary experimental group. Calcium channel antagonists were the focus of 7 studies. Fibrinolytics and other vasodilators were each examined in 6 studies. The meta-analysis included studies examining CSF drainage via LD ($n = 4$), tissue plasminogen activator in addition to EVD ($n = 3$), intraventricular nimodipine ($n = 2$), and cisternal magnesium ($n = 2$). Results showed that intraventricular nimodipine decreased vasospasm (OR 0.59, 95% CI 0.37–0.94; $p = 0.03$). Therapies that significantly reduced DCI were CSF drainage via LD (OR 0.47, 95% CI 0.25–0.88; $p = 0.02$) and cisternal magnesium (OR 0.27, 95% CI 0.07–1.02; $p = 0.05$). CSF drainage via LD was also found to significantly reduce the incidence of cerebral infarction (OR 0.35, 95% CI 0.24–0.51; $p < 0.001$). Lastly, functional outcome was significantly better in patients who received CSF drainage via LD (OR 2.42, 95% CI 1.39–4.21; $p = 0.002$).

CONCLUSIONS The authors' results showed that intrathecal therapy is a safe and feasible option following aSAH. It has been shown to attenuate cerebral vasospasm, reduce the incidence of DCI, and improve clinical outcome. The authors support the use of intrathecal management in the prevention and rescue management of cerebral vasospasm. More randomized controlled trials are warranted to determine the best combination of pharmaceutical agents and administration route in order to formulate a standardized treatment approach.

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KEYWORDS subarachnoid hemorrhage; vasospasm; intrathecal; intraventricular; lumbar drain; external ventricular drain

SUBARACHNOID hemorrhage is most commonly the result of traumatic injury, with the remaining majority of cases due to ruptured intracranial aneurysm.¹ While aneurysmal subarachnoid hemorrhage (aSAH) accounts for a relatively small portion of strokes (approximately 5%), it comes with high morbidity and mortality. Possible sequelae include hydrocephalus, vasospasm, delayed cerebral ischemia (DCI), cerebral infarction, and death.

In accordance with the uniform definitions outlined by

Vergouwen et al.,² vasospasm is an arterial narrowing after hemorrhage demonstrated on angiography or transcranial Doppler (TCD) ultrasonography. This prolonged arterial constriction is most likely to occur within the first 3 to 14 days following hemorrhage. However, the vasospasm period is considered to extend until 21 days after the initial hemorrhage. While the pathogenesis of vasospasm has yet to be fully elucidated, the mechanism involves early brain injury and subsequent inflammatory cascade. Prolonged vasoconstriction occurs secondary to irritation due

ABBREVIATIONS aSAH = aneurysmal subarachnoid hemorrhage; DCI = delayed cerebral ischemia; EVD = external ventricular drain; GOS = Glasgow Outcome Scale; ICP = intracranial pressure; LD = lumbar drain; mRS = modified Rankin Scale; TCD = transcranial Doppler; tPA = tissue plasminogen activator.

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to blood clotting and inflammatory mediators surrounding the vessel. Some of the key mediators include nitric oxide and endothelin-1, which induce oxidative stress and release free radicals surrounding the calcium channels of vascular smooth-muscle cells.³ Reports have estimated that the likelihood of vasospasm following aSAH ranges between 50% and 90%.⁴

DCI is defined as new neurological deficits such as decreased level of consciousness, aphasia, hemiparesis, or neglect.² In the past, DCI has been attributed to vasospasm; however, past interventions have not been met with resounding results, suggesting that vasospasm is not the sole cause of DCI. Mechanisms, including blood-brain barrier disruption, microthrombosis, cortical spreading depolarizations, and failure of cerebral autoregulation, have also been suggested to play a role.⁴ DCI has a clear association with subsequent cerebral infarction and is one of the most common, and perhaps most preventable, causes of late neurological morbidity in this patient population.

Identifying patients at greatest risk of DCI is essential in preventing neurological and functional decline. Methods that have been historically used, in part, to prognosticate aSAH include the Hunt and Hess grade and World Federation of Neurosurgical Societies grading system. In recent years, there has been an emergence of new clinical prediction models that used pooled patient information from data sets, registries, and clinical trials.⁵ Additionally, computational fluid dynamics is currently being studied as a novel method to predict DCI before aneurysm treatment.⁶

Treatment of vasospasm can be divided into prophylaxis and rescue management. Prophylaxis is administered in the acute period after aSAH, before the occurrence of vasospasm. Rescue management is administered after radiographic or clinical evidence of vasospasm. Currently, the only medication approved by the US FDA that has been shown systematically to improve outcomes from aSAH is the calcium channel blocker nimodipine.

The traditional treatment for DCI was “triple-H” therapy involving induced hypertension, hypervolemia, and hemodilution. However, treatment protocols have shifted after increased morbidity developed from anemia, hyponatremia, a hypervolemic state, and complications from vasopressors. Most protocols currently include fluid repletion to maintain a euvolemic state while achieving a permissively elevated systolic blood pressure. Other common practices include placement of an external ventricular drain (EVD) to combat increased intracranial pressure (ICP) as well as avoidance of anemia and hyponatremia.³

New research continues to emerge regarding the pathogenesis of vasospasm. This has illuminated some treatment options that have the potential to target specific components of the pathology cascade. Our review provides an update on intrathecal vasospasm treatments, emphasizing the need for larger-scale trials and updated protocols using data-driven evidence.

Methods

Systematic Review

Eligibility Criteria

A systematic review of studies involving intrathecal

therapeutic options for prevention and rescue management of vasospasm following aSAH was performed according to PRISMA guidelines. Articles were reviewed by one team member (A.A.G.), and interpretation was verified by a second team member (G.L.E.).

A search of the PubMed, Ovid MEDLINE, and Cochrane databases was conducted for the time period from 2010 to August 13, 2021, with the following search terms: (subarachnoid hemorrhage) AND (vasospasm OR delayed cerebral ischemia) AND (intrathecal OR intraventricular OR lumbar drain OR lumbar catheter).

Studies were included if they 1) included patients with confirmed aSAH; 2) investigated prophylactic or rescue therapy administered intrathecally, intracisternally, or intraventricularly for the management of vasospasm; and 3) presented original research. Animal studies and study protocols with no reported data were excluded from analysis. Reviews, meta-analyses, commentary, letters to the editor, editorials, and articles not accessible in the English language were also excluded.

Data Extraction

The following data points were extracted from each study: therapeutic agent, mode of administration, dosage, and patient population and control. Each data point was extracted, reviewed, and agreed on by the two reviewers. The primary outcomes of our analysis were vasospasm, DCI, cerebral infarction, and functional outcome.

Meta-Analysis

Eligibility Criteria

We conducted a meta-analysis of eligible studies from each therapeutic category (CSF drainage, fibrinolysis, calcium channel antagonists, and other vasodilators). Study inclusion criteria were as follows: 1) An intrathecal experimental group and a nonintrathecal control were included. 2) The therapeutic regimen and control were utilized by more than one study. 3) The incidence of vasospasm, DCI, cerebral infarction, or functional outcome was reported for both groups.

Data Extraction

Each eligible therapeutic regimen was identified and analyzed. Primary endpoints of analysis were vasospasm, DCI, cerebral infarction, and functional outcome. Analysis was conducted using Review Manager version 5.4.1 (The Cochrane Collaboration). Statistical significance was defined as $p \leq 0.05$.

Definitions

Vasospasm was defined as arterial narrowing proven by angiography or TCD ultrasonography, and DCI was defined as new neurological deficits (e.g., decreased level of consciousness, aphasia, hemiparesis, or neglect). Cerebral infarction was identified on CT or MRI, or proven at autopsy. Complications were defined as adverse events following aSAH management, including hydrocephalus, hemorrhage or hematoma, pneumonia, meningitis, ventriculitis, angioplasty, heart failure, requiring a ventriculoperitoneal shunt, and septic shock. Functional outcome

was determined by Glasgow Coma Scale, Glasgow Outcome Scale (GOS), extended GOS, or modified Rankin Scale (mRS) scores, whereby favorable outcome was reported as a Glasgow Coma Scale score of 13 to 15, a GOS score of 3 to 5, an extended GOS score of 6 to 8, or an mRS score of 0 to 3 at the longest follow-up.

Results

Search criteria yielded 256 unique results. Of these, 29 met our criteria and were included in the analysis (Fig. 1). Studies are grouped by therapeutic modality: CSF drainage, fibrinolysis, calcium channel antagonists, and other vasodilators (Tables 1–4).

Ten studies involved CSF drainage via either LD ($n = 8$) or EVD ($n = 1$) (Table 1). The final study compared the use of a lumbar catheter with EVD. Of these studies, 1 showed a significant decrease in vasospasm, 3 showed significant decreases in DCI, 3 demonstrated significantly reduced cerebral infarction, and 5 had improved clinical outcomes. Fibrinolytic therapy was examined in 6 of the studies (Table 2). The experimental agent was tissue plasminogen activator (tPA) in 4 studies and urokinase in the remaining 2. Vasospasm, cerebral infarction, and clinical outcome were improved in 1 study each. None were shown to significantly decrease the incidence of DCI. Seven studies pertained to the intrathecal calcium channel antagonists nicardipine ($n = 5$) and nimodipine ($n = 2$) (Table 3). While 4 of these studies showed significant improvement in vasospasm, none showed a decreased incidence of DCI, cerebral infarction, or improved clinical outcome. Six studies involved other vasodilators (Table 4), including milrinone ($n = 2$), magnesium ($n = 2$), and nitric oxide ($n = 2$). Three of these studies showed attenuation of vasospasm, 2 showed decreased DCI, 1 showed reduced incidence of cerebral infarction, and 1 showed improved clinical outcomes.

Therapeutic regimens included in meta-analysis were CSF drainage via a lumbar drain (LD) versus no LD ($n = 4$), tPA+EVD versus EVD alone ($n = 3$), intraventricular nimodipine versus oral nimodipine ($n = 2$), and cisternal magnesium versus no magnesium ($n = 2$).

Therapies were analyzed for efficacy in reducing vasospasm (Fig. 2), DCI (Fig. 3), and cerebral infarction (Fig. 4) as well as improving outcome (Fig. 5). Intraventricular nimodipine was shown to decrease vasospasm (OR 0.59, 95% CI 0.37–0.94; $p = 0.03$). Therapies that significantly reduced DCI were CSF drainage via LD (OR 0.47, 95% CI 0.25–0.88; $p = 0.02$) and cisternal magnesium (OR 0.27, 95% CI 0.07–1.02; $p = 0.05$). CSF drainage via LD was also found to significantly reduce the incidence of cerebral infarction (OR 0.35, 95% CI 0.24–0.51; $p < 0.001$). Lastly, functional outcome was also significantly better in patients who received CSF drainage via LD (OR 2.42, 95% CI 1.39–4.21; $p = 0.002$).

Discussion

Intrathecal treatment is a promising therapeutic modality in vasospasm. The use of EVDs and LDs is twofold—they allow for both CSF drainage and infusion of pharmaceutical agents. Targeted administration of agents

FIG. 1. Identification of studies via PRISMA guidelines. Data added to the PRISMA template [from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71] under the terms of the Creative Commons Attribution License.

directly into the thecal compartment negates the need for blood-brain barrier penetration, further expanding therapeutic options. EVDs are frequently placed as part of many standard hospital protocols for ICP monitoring, and medication can be easily administered via this route. Promising intrathecal management options are highlighted below, categorized by their mechanism of action.

Blood Clot Clearance

An increased amount of hemorrhage has been reported to be the greatest predictor of vasospasm.³ Research has identified certain blood components as contributors to a proinflammatory environment in aSAH; these include acute platelet activation and release of arginase-1, which leads to dysregulated metabolism of nitric oxide precursors.^{36,37}

CSF Drainage

Drainage via LD or EVD allows expedited removal of blood products from the CSF. In addition to blood, increased protein, sphingosine 1-phosphate, and IL-6 levels in the CSF have been associated with poor outcomes.^{38–40} One meta-analysis found that, when compared with no CSF drainage, patients who received CSF drainage had a decreased incidence of vasospasm and DCI with better long-term outcomes.⁴¹ Aydin et al.¹⁰ demonstrated that patients who received drainage

TABLE 1. Prophylactic CSF drainage

Authors & Year	Study Design	Aneurysm Treatment	Treatment Regimen	Experimental Group (n)	Control (n)	Vasospasm	DCI	Cerebral Infarction	Complications	Functional Outcome
Amato et al., 2011 ⁷	Observational	Mixed	No standardized regimen; provider dependent	Open EVD (24)	Intermittent EVD drainage (13)	±	±	±	+++	±
Maeda et al., 2013 ⁸	Observational	Coiling	CSF drain placed day of op through day 14; target drainage rate was 120–240 ml/day	LD (34)	EVD (17)	±	±	±	±	+++
Ormond et al., 2013 ⁹	Retro-spective	NR	After failed EVD removal, LD placed for a mean of 6.7 days (range 4–16 days) w/ a drainage rate of 10 ml/hr	LD (25)	NA	+	+	NR	Decreased VPS	+
Aydin et al., 2015 ¹⁰	Observational	Clipping	LD placed before op & terminated at 7 days post-op; max 200 ml/day CSF drained until fluid was not visibly hemorrhagic	LD (70)	NA	NR	+	NR	NR	+++
Park et al., 2015 ¹¹	RCT	Mixed	LD placed during aneurysm treatment & left in place for 14 days w/ a drainage rate of 5–10 ml/hr	LD (126)	No LD (108)	NR	+++	+++	Decreased angioplasty	+++
Meguro et al., 2016 ¹²	Case series	Coiling	Mechanically ventilated pts w/ neurogenic pulmonary edema had LD placed following coiling & kept in place for 72 hrs	LD (12)	NA	NR	NR	NR	Pneumonia	+
Borkar et al., 2018 ¹³	RCT	Clipping	LD placed before op; before dural opening, the LD was opened & kept in place for 72 hrs	LD (30)	No LD (30)	+++	+++	+++	±	+++
Liang et al., 2018 ¹⁴	Retro-spective	Coiling	LD placed postop day 1 & continued at a rate of 5–10 ml/hr until fluid was not visibly hemorrhagic	LD (39)	Serial LP (41)	±	±	±	CSF infection	±
Fang et al., 2020 ¹⁵	Retro-spective	Clipping	LD placed before op; drainage rate of 5–10 ml/hr or until fluid was not visibly hemorrhagic (LD was not kept in place >10 days)	LD (113)	No LD (80)	NR	+++	+++	Decreased hydrocephalus	+++
Jeong et al., 2020 ¹⁶	Retro-spective	Mixed	LD placed before posthemorrhage day 4 & continued for ≥3 days; drainage rate of 5–10 ml/hr or until fluid was not visibly hemorrhagic	LD (28)	No LD (79)	NR	±	±	None	±

LP = lumbar puncture; max = maximum; NA = not applicable; NR = not reported; pts = patients; RCT = randomized controlled trial; VPS = ventriculoperitoneal shunt; ± = no significant difference; + = reported improvement; +++ = significant improvement ($p < 0.05$).

via LD had an overall decreased incidence of hydrocephalus and lower ICP values. Those who had visibly clear blood on CSF drainage were less likely to develop DCI. Even more importantly, those patients who did have hemorrhagic CSF were more likely to have DCI resolution once clear CSF was found. Our meta-analysis showed that drainage via LD significantly reduced DCI

and cerebral infarction with a higher rate of favorable outcomes.

A computational model by Abolfazli et al. demonstrated LDs to be an effective means to facilitate blood clearance, with higher drainage rates correlated with increased clot clearance.⁴² It is important to note that CSF drainage in the absence of adequate subarachnoid clot removal

TABLE 2. Prophylactic fibrinolysis

Authors & Year	Study Design	Aneurysm Repair	Treatment Regimen	Experimental Group (n)	Control (n)	Vasospasm	DCI	Cerebral Infarction	Complications	Functional Outcome
Ramakrishna et al., 2010 ¹⁷	Retro-spective	Mixed	tPA (5 mg in 2 ml NS) administered via EVD; EVD flushed with 3 ml NS & then both LD & EVD clamped; LD unclamped after 30 mins & EVD unclamped after 60 mins; tPA regimen was repeated 24 hrs apart × 7	tPA via EVD & LD (41)	EVD (35)	+++	NR	NR	Decreased VPS & angioplasty	±
Kai et al., 2011 ¹⁸	RCT	Coiling	60,000 U urokinase in 20 ml NS injected into the cisterna magna via microcatheter; continuous infusion for 20–30 mins; microcatheter clamped for 2 hrs & repeated until 24-hr scan showed clot resolution	Urokinase (6)	NA	NR	+	NR	NR	+
Etminan et al., 2013 ¹⁹	RCT	Mixed	5 mg tPA in 2 ml NS via EVD every 12 hrs via EVD; EVD clamped for 30 mins; repeated for 48 hrs	tPA via EVD w/ lat rotation therapy (30)	EVD (30)	±	±	±	±	±
Litrico et al., 2013 ²⁰	RCT	Mixed	3 mg tPA (1 mg/ml) via EVD 6–12 hrs after aneurysm repair; 2 ml NS flush; EVD clamped for 1 hr; continued every 12 hrs until postregimen scan showed clot resolution (max tPA 36 mg)	tPA via EVD (11)	EVD (8)	NR	±	NR	±	±
Kramer et al., 2014 ²¹	RCT	Coiling	2 mg IV tissue tPA every 12 hrs (max 10 mg) or placebo	tPA via EVD (6)	Placebo (6)	±	±	±	±	±
Yoshikane et al., 2021 ²²	Retro-spective	Clipping	Irrigation of urokinase (120,000 U/1000 ml) in 0.9% NS > 30 mins after clipping	Urokinase (21)	No urokinase (19)	±	±	+++	Decreased pneumonia & HF	+++

HF = heart failure; IV = intraventricular; NS = normal saline.

can lead to an increased CSF pH and lower CSF PCO₂.⁴³ Therefore, if CSF drainage is not sufficiently removing blood, it has a paradoxically increased risk of acid metabolite buildup, arterial constriction, and DCI.⁴³

Fibrinolysis

Fibrinolysis accelerates the rate of clot clearance through enzymatic breakdown. This was seen in 3 studies included in our review.^{19–21} These medications also inhibit acute platelet activation and the inflammatory cascade. Increased intrathecal levels of cytokines following aSAH and fever have been found to be an independent risk factor for DCI.⁴⁴ Low-frequency head rotation has also been tested in conjunction with intraventricular tPA. This ki-

netic mechanism is thought to augment the effect of fibrinolytics and has been shown to increase the rate of clot clearance.^{19,45} Eicker et al.⁴⁵ showed promising results for DCI in an interim report for a randomized controlled trial involving tPA and lateral rotational head therapy; however, the final results showed no difference in vasospasm, cerebral infarction, or functional outcome.⁴⁶

Our review showed that irrigation with urokinase (120,000 U/1000 ml) in 0.9% normal saline for more than 30 minutes after clipping significantly decreased DCI and improved clinical outcome. Ramakrishna et al.¹⁷ demonstrated decreased severe vasospasm on TCD ultrasonography by administering tPA (5 mg in 2 ml normal saline) via EVD. Currently, Gaberel et al.⁴⁷ are

TABLE 3. Calcium channel antagonists

Authors & Year	Study Design	Aneurysm Treatment	Treatment Regimen	Experimental Group (n)	Control (n)	Vasospasm	DCI	Cerebral Infarction	Complications	Functional Outcome
Rescue management										
Webb et al., 2010 ²³	Retrospective	Mixed	4 mg nicardipine mixed w/ 2 NS given via EVD every 8–12 hrs; EVD clamped for 30 mins	Nicardipine (64)	NA	+++	NR	NR	Ventriculostomy-related infection	NR
Lu et al., 2012 ²⁴	Retrospective	Mixed	No standardized protocol; median nicardipine dose was 4 mg (range 3–7 mg), w/ 7 median doses (range 1–17)	Nicardipine (14)	No nicardipine (14)	+++	NR	NR	None	±
Ko et al., 2016 ²⁵	Retrospective case series	NR	3–4 ml nicardipine (1 mg/ml) via EVD; EVD clamped for 1 hr	Nicardipine (11)	NA	+	NR	NR	NR	NR
Sadan et al., 2022 ²⁶	Retrospective	Mixed	4 mg nicardipine in 2 ml NaCl 0.9% solution via EVD every 8 hrs; EVD flushed w/ 1–2 ml NaCl 0.9%; EVD clamped for 30 mins	Nicardipine (422)	No nicardipine (SAHIT database) (929)	+++	+	NR	Increased VPS; decreased ventriculitis	+
Prophylaxis										
Barth et al., 2011 ²⁷	Prospective	Mixed	4 mg sustained-release nicardipine pellets; pts received either 6 or 10 pellets	IV nicardipine (31)	No nicardipine (16)	+++ (clipping only)	NR	NR	NR	NR
Carlson et al., 2020 ²⁸	RCT	Mixed	1 IV 600-mg dose of sustained-release nimodipine	IV nimodipine (138)	Oral nimodipine (144)	±	±	±	±	±
Macdonald et al., 2020 ²⁹	RCT	Mixed	1 IV 600-mg dose of sustained-release nimodipine	IV nimodipine (5)	Oral nimodipine (1)	±	±	±	±	±

enrolling patients in a phase III randomized controlled trial of intraventricular tPA. The study will compare an EVD alone and an EVD in addition to tPA. This will be the first phase III trial assessing the efficacy of this treatment in the prevention of DCI and other aSAH-related complications.

Targeting Heme Degradation Products

Other intrathecal therapeutic agents targeting specific heme degradation products have been tested in vitro and in animal models. These include haptoglobin, deferoxamine, and vitamin D. An in vitro study by Garland et al.⁴⁸ found that haptoglobin has the ability to bind to CSF hemopexin and could potentially improve outcomes. Studies have suggested that increased iron levels in CSF can be associated with secondary brain injury.⁴⁹ The iron chelator, deferoxamine, was found to be neuroprotective in a mouse model; however, this protective effect was not directly associated with vasospasm.

Vasodilators

Calcium Channel Antagonists

Since the 1980s, nimodipine has been the mainstay for prevention of vasospasm and cerebral infarction secondary to aSAH. It is now considered the standard of care for management of patients with ruptured aneurysms. Interestingly, its mechanism of action is not thought to be due to its vasodilatory effect, and it remains incompletely understood.⁴ Its chemical makeup made nimodipine a favorable drug for vasospasm as it readily crosses the blood-brain barrier. With the development of more advanced catheters and delivery systems, other calcium channel antagonists have been tested in animal studies and in clinical practice, including intrathecal verapamil and nicardipine.^{24,25,50–52} The calcium channel antagonists in our review showed a significant vasodilatory effect and decrease in vasospasm; however, none of these translated to decreased DCI or improved clinical outcome.

Kasuya et al.⁵³ pioneered intrathecal therapy with calci-

TABLE 4. Other vasodilators

Authors & Year	Study Design	Aneurysm Treatment	Treatment Regimen	Experimental Group (n)	Control (n)	Vasospasm	DCI	Cerebral Infarction	Complications	Functional Outcome
Rescue management										
Sadama-sa et al., 2014 ³⁰	Feasibility/safety	Mixed	0.87 mg milrinone (2.6 ml/day) per 7 ml NS for 2 hrs via LD; LD clamped for 2 hrs; cycle repeated until day 14 after SAH	Milrinone (170)	NA	NR	±	±	None	+
Ehlert et al., 2016 ³¹	Case report	Coiling	Continuous intravenous molsidomine & boluses of sodium nitroprusside 7 times over 22 days for DCI (3 or 5 mg each time)	IV sodium nitroprusside w/ intravenous molsidomine (1)	NA	+	+	+	NR	+
Koyanagi et al., 2018 ³²	Prospective	Mixed	0.87 mg milrinone (2.6 ml/day) per 7 ml NS for 2 hrs via LD; LD clamped for 2 hrs; cycle repeated until day 14 after SAH	Milrinone (99)	No milrinone (99)	NR	+++	+++	±	±
Ehlert et al., 2020 ³³	Retrospective, observational	Mixed	Continuous intravenous molsidomine & boluses of sodium nitroprusside w/ DCI (2–10 mg); mean 5.6 mg	IV sodium nitroprusside w/ intravenous molsidomine (18)	NA	+++	+	+	Septic shock	+
Prophylaxis										
Yamamoto et al., 2016 ³⁴	RCT	Clipping	Continuous cisternal infusion of Mg solution (5 mmol/L Mg at 20 ml/hr) from days 4 to 14	Mg (35)	No Mg (35)	+++	NR	±	Bradypnea	±
Takeuchi et al., 2021 ³⁵	RCT	Mixed	Mg w/ or w/o hydrogen groups: continuous cisternal Mg sulfate infusion (2.5 mmol/L Mg sulfate in LR solution at 20 ml/hr) from days 1 to 14	Mg w/ or w/o hydrogen (24)	No Mg (13)	+++	+++	NR	None	+++

LR = lactated Ringer's.

um channel antagonists in 2002 when they first described prolonged-release nicardipine pellets as an effective means to decrease vasospasm and DCI. Further building on this work, Kuori et al.⁵⁴ demonstrated that a nicardipine prolonged-release implant (NPRI) significantly decreased vasospasm and DCI in patients with aSAH undergoing surgical clipping. Additionally, these patients had improved mRS scores at discharge. A phase II trial is currently recruiting to further assess this treatment modality. After aneurysm clipping, 10 NPRI capsules will be placed into the basal cistern, directly abutting the blood vessel walls (registration no. NCT04269408, ClinicalTrials.gov).

Intrathecal use of both dotarizine and flunarizine has been examined in animal models.^{55,56} Both of these were

compared with the standard of care, nimodipine. It was found that dotarizine and flunarizine have marked vasodilatory effects in an experimental model and have the potential to be valid alternatives to nimodipine.^{55,56}

Other Vasodilators

In addition to calcium channel antagonists, other vasodilators that are currently being studied include milrinone,^{30,32} nitric oxide,³³ magnesium sulfate,⁵⁷ cilostazol,⁵⁸ and glyceryl trinitrate.⁵⁹ Milrinone is a phosphodiesterase-3 inhibitor that has been proven to be safe and feasible for the prevention of DCI and in the period following confirmed vasospasm in a clinical setting. Koyanagi et al.³² showed that a treatment regimen of 0.87 mg milrinone per

FIG. 2. Forest plots showing pooled ORs of vasospasm (VSP) by therapeutic regimen. Intra = intraventricular; IV = inverse variance.

FIG. 3. Forest plots showing pooled ORs of DCI by therapeutic regimen.

FIG. 4. Forest plots showing pooled ORs of cerebral infarction by therapeutic regimen.

FIG. 5. Forest plots showing pooled ORs of favorable outcome by therapeutic regimen.

7 ml normal saline for 2 hours via LD was an effective way to decrease incidence of DCI and cerebral infarction. Nitric oxide and magnesium sulfate have also been shown to be effective in patients with aSAH. Cilostazol and glyceryl trinitrate have only been tested in animal models.

Proper Catheter Administration and Maintenance

The optimal management of LDs and EVDs remains controversial. The variables described below have been studied and should be considered during treatment.

Patient Positioning

Tangen et al.⁶⁰ suggested the importance of patient positioning in a study in which they created a CSF dynamics model to assess differing situations of contaminant clearance with lumbar drainage in addition to the rate of blood clearance. The authors found that body position and drainage rates were both essential for effective blood clearance. Their findings emphasized having the patient in an upright position to mitigate infection as any contaminant present is maximally diverted from the cranial CSF compartment.⁶⁰

Intracranial Pressure

Elevated ICP is a common occurrence following aSAH and can contribute to poor outcomes in the acute and subacute settings. In traumatic brain injury, increased ICP is defined as pressure > 20 mm Hg. Some estimates suggest that more than half of all patients with aSAH will experience an ICP value > 20 mm Hg at some point during their hospital stay.⁶¹ During intrathecal therapy, an EVD typically must be clamped for some time to allow the medication to dwell. For this reason, intrathecal management is typically precluded in this patient population. Additionally, vasodilators—a commonly used class of intrathecal medications—can increase ICP. Ko et al. saw an increase in ICP for approximately 1 hour following injection of intraventricular nicardipine.²⁵ However, this effect was transient and did not significantly alter cerebral blood flow or oxidative glucose metabolism, nor did it cause systemic hypotension. Other interventions to counteract increased ICP are mitigating the dwell time by using two catheters or with concomitant use of EVDs and LDs.^{27–29}

Pressure Gradient

A lumbar drainage catheter is sometimes placed intraoperatively to decrease fluid pressure on the brain in patients with aSAH. In rare cases, catheter placement can lead to intracranial hypotension, resulting in brainstem herniation (“brain sag”), causing neurological injury and even death. Cases of transient herniation have been reported due to lumbar catheter overdrainage.⁶² Leaving the CSF bag at the level of the head and using careful pressure-gradient monitoring can help avoid poor outcomes. In a safety and feasibility study of lumbar drainage in patients with poor-grade aSAH, the ideal ventriculolumbar pressure gradient was found to be 6 mm Hg or less.⁶³

Infection

Infections and medical complications following aSAH are common. The infection risk associated with intrathecal

therapy is likely due to accessing the EVD or LD multiple times throughout treatment to deliver medication. Newer drains, which have the dual capability of draining and infusing, may mitigate this risk. Prolonged LD placement has also been associated with increased infection rate. This provides rationale for why Liang et al. found a decreased infection rate following serial lumbar puncture when compared with LD.¹⁴ Park et al.¹¹ described complications they encountered during lumbar drainage. These included CSF infection and microorganism growth when they conducted a routine drainage tip culture. However, CSF infection was easily managed with proper antibiotics, and microorganism growth resolved on its own.¹¹ Moreover, antibiotic-coated EVDs are routine at many institutions.¹⁷

Future of Vasospasm Management

The future role of intrathecal management in aSAH and vasospasm is yet to be fully understood. There is a large amount of heterogeneity in the current studies exploring the topic, sometimes making results difficult to interpret; this includes medication timing and dosage in addition to catheter use. We recognize broad potential for protocolized implementation of these treatments in future trials.

There is no definitive evidence as to whether CSF drainage or medication administration via EVD or LD leads to better outcomes. LDs and EVDs have both shown safety and efficacy in intrathecal management. However, there is still controversy over the preferred method for clearing subarachnoid blood and preventing vasospasm. There have been few studies evaluating them side by side. When Maeda et al.⁸ retrospectively examined this, they found no significant difference in the occurrence of vasospasm, hydrocephalus, or ventriculoperitoneal shunt placement. However, the LD group had faster clot clearance and improved outcomes compared with the EVD group. It was hypothesized that the EVD could lead to hemorrhage stasis. There is currently a randomized controlled trial in the recruitment phase that will examine whether LD or EVD is superior in vasospasm prevention and clinical outcome (registration no. NCT03065231, ClinicalTrials.gov). Concomitant use of LDs and EVDs has also been shown to be effective in management of vasospasm and is an expected area of study.

Advances in biomedical engineering have led to the invention of new catheters. Stereotactic catheter ventriculocisternostomy is a method of obtaining access to the intrathecal space that was recently found to be feasible in a majority of patients with aSAH.⁶⁴ Roelz et al. have employed this method with nimodipine and CSF drainage with success.^{65,66}

There are a number of other intrathecal therapies that have been explored in vitro and in animal models but have yet to be tested in patients; these include MEK 1/2 inhibitors,^{67,68} NDP-MSH,⁶⁹ ebiselen,⁷⁰ nicergoline,⁷¹ acetylcholine,⁷² osteopontin,⁷³ and valproic acid.⁷⁴ In addition to these, there are experimental drugs currently being tested in an intravenous form that have yet to be tested intrathecally, including endothelin antagonists and statin therapy.

Study Limitations

There is an inherent limitation to systematic reviews

and meta-analyses as they are retrospective. There is the potential to miss relevant studies due to the choice of search terms and an inability to access certain articles or journals. The biggest limitation encountered in this report was the heterogeneity of study designs. This was true not only for therapeutic regimens but also for how clinic outcomes were reported. Studies also continue to use different definitions for vasospasm, DCI, and cerebral infarction, which can make interpretation difficult.

Conclusions

This study provides a review of the current options for intrathecal management of aSAH-induced vasospasm. The intrathecal route has obvious advantages in that medications can be delivered directly to the subarachnoid space and do not need to cross the blood-brain barrier. Thus far, the literature is quite heterogeneous with regard to dosing, timing, and delivery method, and no single protocol emerges as the superior therapy. One therapy that has been shown to decrease DCI and cerebral infarction with improved functional outcome is CSF drainage via LD. Other therapies show promise for decreasing the incidence of vasospasm, DCI, and cerebral infarction, although there is not yet significant evidence to recommend their use in routine practice. More randomized controlled trials are warranted to determine the best combination of pharmaceutical agents and administration routes in order to formulate a standardized treatment approach.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: Grossen, Ernst. Analysis and interpretation of data: Grossen, Ernst. Drafting the article: Grossen, Ernst. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Administrative/technical/material support: Grossen. Study supervision: Bauer.

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