Current Topics in Pharmacology
Vol. 17, *1*, 2013

Review

Current pharmacologic management strategies in aneurysmal subarachnoid hemorrhage

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ABSTRACT

Aneurysmal subarachnoid hemorrhage (aSAH) is a particularly devastating neurologic insult as the majority of patients suffer morbidity and mortality at the time of rupture, and from subsequent complications. While at least one-third of patients die shortly after experiencing a ruptured cerebral aneurysm, ~60% of survivors develop debilitating neurologic deficits throughout their course of treatment. In numerous cases, spastic narrowing of large cerebral vessels, termed cerebral vasospasm, has been associated with delayed cerebral ischemia (DCI) and stroke 4 to 21 days post-hemorrhage. Despite decades of animal research and numerous clinical trials, highly effective pharmacological treatment options for aSAH patients are lacking. Herein, results from clinical trials examining pharmacologic therapies for delayed cerebral vasospasm, DCI and functional outcomes in aSAH patients are discussed, including the current status of nimodipine and other dihydropyridines, endothelin receptor antagonists, magnesium sulfate, and 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins).

KEYWORDS: subarachnoid hemorrhage, cerebral vasospasm, pharmacotherapy, cerebral ischemia, functional outcomes

INTRODUCTION

Aneurysmal subarachnoid hemorrhage occurs in ~10 of 100,000 people annually, and is associated with particularly high rates of morbidity and mortality. Over the past few decades, more favorable patient outcomes in industrialized nations have been attributed primarily to improved diagnosis and acute hemodynamic management, whereas progress in the development of effective pharmacotherapies to treat delayed complications (e.g. DCI, stroke, disability, mortality) has been disappointing (Figure 1). At the earliest stage of injury, misdiagnosis is associated with increased morbidity and mortality because it is critical to locate and secure the suspected aneurysm in a timely manner. The gold-standard for accurate diagnosis is non-contrast head CT scan, which approaches 100% sensitivity in the first few days after injury [1]. Since 1985, the rate of misdiagnosis has decreased from an estimated 64% to approximately ~12% [2, 3]. Cerebral digital subtraction angiography (DSA) is performed to identify any aneurysms or other vascular malformations, so the aneurysm can be obliterated by endovascular coiling or microsurgical clipping. The choice to use the less invasive coiling procedure versus clipping depends on several factors, as reviewed elsewhere [4, 5, 6].

Treatment of aneurysms as soon as possible after diagnosis has significantly reduced morbidity and mortality associated with re-bleeding. In fact ultra-early treatment within 24 hours may be especially advantageous in poor-grade patients [7]. Note that cerebral infarctions associated with aneurysm rupture, or treating the aneurysm are not uncommon and should be assessed by CT scan or MRI ~24-48 hours following the procedure to

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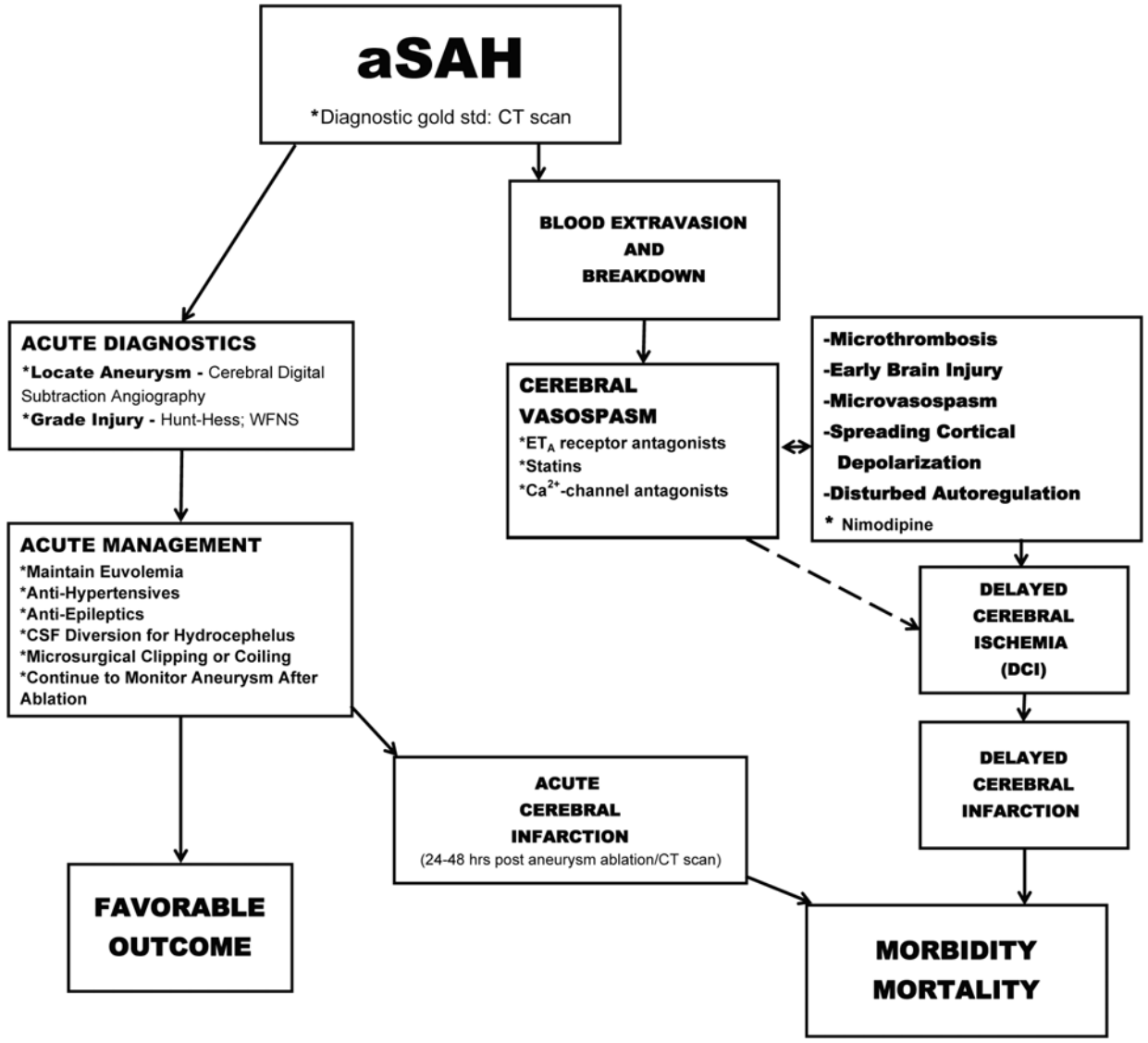

Figure 1. Management strategies for diagnosis and treatment of acute and delayed injury after aSAH. Enhanced outcomes in aSAH patients are largely attributable to improvements in their acute management, including diagnosis, hemodynamic treatments, microsurgical and endovascular techniques, and imaging technologies. Despite these advancements, patients are still at risk for poor outcomes, for example, due to cerebral infarctions associated with aneurysm ablation. Efforts to develop pharmacological interventions to prevent delayed cerebral ischemia (DCI), which can progress to cerebral infarction and long-term disability and mortality, have been disappointing primarily due to an inappropriate emphasis on cerebral vasospasm as the primary causative factor. Emerging evidence points to the need to understand the multi-factorial nature of the injury process leading to DCI, infarction, and disability or death. Areas of interest include early brain injury, thrombosis and spasm of the microvasculature, disturbances in autoregulation, and spreading cortical depolarization. Nimodipine remains the only drug with Class I, level of evidence A benefit for long-term outcome, which is unrelated to effects on cerebral vasospasm.

distinguish them from delayed infarctions [8]. Additional *American Stroke Association* recommendations include: use of a titratable antihypertensive agent such as nicardipine prior to aneurysm obliteration to reduce the risk of re-bleeding due to hypertension, while maintaining euvolemia and cerebral perfusion pressure to avoid ischemia; immediate as well as subsequent

cerebrovascular imaging to monitor growing remnants or recurrence of aneurysms; grading of injury using the Hunt-Hess clinical grading scale, World Federation of Neurological Surgeons Classification System (WFNS); use of antiepileptic drugs to prevent seizures immediately after hemorrhage but not later in the course of injury unless the patient is at risk for delayed seizure disorder; appropriate cerebrospinal fluid (CSF) diversion in patients with acute or chronic symptomatic hydrocephalus [1].

Following the diagnosis, acute treatment, and monitoring of the aneurysm, patients are at risk for multiple complications that appear days or weeks later (Figure 1). Blood contaminates the cerebrospinal fluid (CSF) and bathes the outside walls of cerebral arteries, and blood breakdown products exert complex pathological effects that can lead to stroke, neurological deficits, disability and death. By an uncharacterized mechanism, the toxic effects of the blood breakdown products can cause large arteries that pass through the subarachnoid space to spasm and narrow, a process called cerebral vasospasm that can be measured by digital subtraction angiography. Cerebral vasospasm can restrict the amount of blood and oxygen delivered to brain tissue causing DCI and, presumably, leading to devastating long-term functional deficits from secondary stroke. Cerebral vasospasm typically occurs 4-21 days after aneurysm bleeding, and is observed in approximately ~70% of patients [9-12] with up to 40% developing stroke symptoms. It is a well-known clinical phenomenon that greater amounts of blood in the CSF increase the likelihood and severity of vasospasm and neurological damage. Due to its delayed onset, and our understanding of receptors and signaling cascades mediating vasculature contractility, vasospasm would appear to be an ideal target for drug therapy. Thus, a major focus of study and drug development in both animal models and clinical trials has been prevention of cerebral vasospasm, the rationale being that DCI and stroke are direct consequences leading to poor functional outcome.

Numerous studies have investigated different management strategies with the aim of improving overall outcome in aSAH patients, and successful attenuation of vasospasm has been documented with different classes of pharmacotherapies, however, there is a lack of compelling evidence linking the anti-vasospastic efficacies of these agents with improved long-term outcomes in aSAH patients. Consistent with this, many patients with severe vasospasm show no symptomatic evidence of ischemic damage or compromised function, while others with no vasospasm or mild vasospasm are severely impacted nonetheless [13-16]. This lack of concordance between large artery vasospasm and long-term clinical outcomes has motivated investigators to renew their efforts to unravel the complex and multifactorial underpinnings of the injury process, in an effort to identify alternative targets for effective drug therapy.

Nimodipine and other dihydropyridines

Calcium-channel antagonists reduce the influx of calcium from the extracellular milieu into the cell by blocking specific types of voltage-dependent calcium channels. In aSAH patients, the drugs used most commonly occlude L-type channels on vascular smooth muscle cells to decrease contractility [17]. By inference, they are predicted to decrease the incidence and severity of vasospasm, protect against DCI and cerebral infarctions, thereby improving functional outcomes. These agents also bind to channels on neurons and other cell types, possibly affording other forms of protection that remain to be characterized. For example, nimodipine may attenuate iron-induced toxicity through effects on voltage-gated calcium channels and N-methyl-D-aspartate (NMDA) receptor-channels [18, 19], and can also block T-type calcium-channels albeit with lower affinity than L-type channels [20, 21]. While several calcium-channel antagonists are available, nimodipine, a dihydropyridine, is preferred as it is well-tolerated and lipid soluble, crosses the blood-brain barrier, and modestly improves outcome in aSAH patients.

One of the earliest randomized, double-blind, placebo controlled clinical trials tested the effects of nimodipine on cerebral vasospasm using angiography at the time of neurologic change. The study included 116 aSAH patients without neurologic deficit presented to the hospital within 96 hours of onset, who were randomized to a

group receiving oral nimodipine with an initial dose of 0.7 mg/kg followed by 0.35 mg/kg dose every 4 hours for 21 days (e.g., 49 mg initially and 24.5 mg thereafter in a 70 kg patient) or a placebo group. Patients in the treatment group showed fewer neurologic deficits from vasospasm, but vasospasm was not completely prevented. The authors suggested optimization of the dosage, and expanding the treatment group to include more severely graded aSAH patients [22].

Petruk and colleagues performed a somewhat larger multicenter randomized double-blind trial comparing placebo versus nimodipine treatment in 154 poor grade (Hunt and Hess grade 3 or worse) aSAH patients. Patients were given oral nimodipine (90 mg every 4 hours for 21 days) or placebo. At 21 days and 3 months post-hemorrhage, significantly more patients in the treatment group showed improvement using the Glasgow Outcome Scale, and few side effects were noted. The benefits were primarily noted in patients with a Hunt and Hess grade of 3 or 4, however, there were no differences in occurrence of delayed ischemic deficits, vasospasm, or incidence of re-bleeding in the group receiving nimodipine, compared to patients in the placebo group. Moreover, there appeared to be a higher mortality rate in patients treated with nimodipine, although it was not statistically significant [23]. In another study of aSAH patients (all grades) receiving oral nimodipine (60 mg every 4 hours for 21 days) or placebo, Mee and colleagues reported a decrease in mortality at 3 months in the nimodipine group. However, this benefit was not positively correlated with an increase in cerebral blood flow, assessed angiographically, and the number of patients was small [24].

Ohman and associates specifically examined the effects of nimodipine on patients with good grade Hunt and Hess scores who underwent early clipping of their aneurysms. Patients (n = 213) were randomized to nimodipine (intravenous dose of 0.25 μg/kg/min increased after two hours to 0.5 μg/kg/min for 7-10 days followed by 60 mg orally every 4 hours for 21 days) versus placebo. A decrease in delayed neurologic events and associated mortality was reported in the treatment group receiving both early surgery and nimodipine [25]. This group also examined the long-term effects of nimodipine on outcome, specifically on occurrence of cerebral infarcts. Using the same patient population, they found that nimodipine significantly reduced the mortality associated with delayed ischemic deterioration but not overall mortality. Additionally, at 1-3 years post rupture, there were significantly fewer areas of infarction seen on CT scan when comparing the treatment group to the placebo group [26]. This study is one of the only randomized control trials of aSAH patients to show long-term benefit from a specific therapy. Such results could be indicative of the natural course of aSAH patients after an extended period of time, or could point to long-term protection after nimodipine treatment, but further studies with similar duration of follow up are needed.

One of the largest trials to date assessed 554 patients randomized to oral nimodipine (60 mg every 4 hours for 21 days within 96 hours after hemorrhage) versus placebo. Nimodipine significantly reduced the number of cerebral infarcts following aSAH, and decreased the incidence of poor outcome defined as death, vegetative state, and severe disability. Reported side effects occurred in 24 patients (14 nimodipine and 10 placebo) and were primarily cardiovascular or hepatobiliary [27].

Nimodipine and related agents can be administered in multiple forms including oral, intravenous, intra-arterial, and time-released implants. Oral nimodipine is commonly used as it is inexpensive and effective; however, it has a low bioavailability due to high first-pass metabolism in the liver [28, 29]. To date, results from studies involving small patient numbers or simple case reports do not show significant advantages of intravenous [30, 31] or, in cases of severe vasospasm, intra-arterial [32-36] nimodipine over oral nimodipine. In a larger North American Cooperative Study, intravenous nicardipine did not improve overall outcome in aSAH patients, though it decreased the incidence of symptomatic vasospasm, and was safe and well-tolerated [37, 38]. The results of 16 well-controlled trials in more than 3300 aSAH patients treated with calcium-channel antagonists or placebo were recently reviewed [39-40]. Only oral nimodipine reduced the relative risk (RR) of poor outcome with a RR value of 0.67 (95%

confidence interval); however, statistical significance was dependent on inclusion of data from a single large study. Of emerging interest are the results of a small prospective, randomized, double-blind study in severely affected aSAH patients who received prolonged release implants of nicardipine in their basal cisterns when microsurgical clipping was being performed. Significant reductions in angiographic vasospasm in conjunction with significantly improved Rankin Scale Scores were reported [41].

In summary, there is a general agreement that oral nimodipine reduces cerebral ischemia and the risk of poor outcome, and is well-tolerated, though it does not reliably decrease cerebral vasospasm [23, 42] suggesting it exerts beneficial effects on other targets. Hence, it received Class I, level of evidence A recommendation for administration to all aSAH patients based on recent guidelines from the *American Stroke Association* [1].

Endothelin receptor antagonists

Endothelin-1 (ET-1) binds with high affinity to ET_A receptors on vascular smooth muscle cells, producing potent and sustained vasoconstriction. A second receptor subtype, the ET_B receptor, is localized to both endothelial and vascular smooth muscle cells where it mediates vasodilation, but this effect is often masked by concurrent ET_A activation. ET-1 is generated from its larger precursor protein in response to several factors, including vascular shear stress, hypoxia, and inflammation. Notably, ET-1 is elevated in the CSF and plasma of aSAH patients in a manner that is positively correlated with cerebral vasospasm [43-47]. ET_A receptor antagonists provide definitive therapeutic benefit in patients with pulmonary hypertension [48], and investigators are actively exploring their potential utility in cerebral vasospasm and functional outcomes in aSAH patients [49-58].

One of the first randomized control trials studied the effects of TAK-044, a nonselective $ET_{A/B}$ receptor antagonist. A total of 420 aSAH patients were randomized to receive TAK-044 (escalating to a maintenance intravenous dose of 50 mg 3 times/day for 10 days) or placebo, with the primary endpoint being incidence of delayed neurological deterioration due to cerebral ischemia. The TAK-044 treatment group demonstrated an RR value of 0.8 corresponding to a relative risk reduction of 20% (95% confidence interval), but the sample size was deemed insufficient to show a statistically significant difference between the two groups, and hypotension was a common adverse effect. Additionally, both groups were also treated with oral nimodipine; thus it was difficult to determine whether the combination of TAK-044 plus nimodipine affected the outcome. Furthermore, since TAK-044 binds to both endothelin receptor subtypes, the vasodilatory effect of blocking ET_A receptors could have been diminished by concurrent blockade of ET_B receptors [51].

Clazosentan is a selective non-peptide antagonist of the ET_A receptor and has been extensively studied in aSAH patients. Vajkoczy and colleagues conducted a randomized double-blind placebo-controlled study using clazosentan in 32 severely graded aSAH patients (Hunt and Hess score III or IV and Fisher grade $\geq$3) to assess the safety of this drug in this patient population. Subjects were treated with clip ligation of their aneurysms, and received placebo or a continuous intravenous infusion of clazosentan (0.2 mg/kg/hr for 14 days). Clinical exam, CT scans on admission and at 14 days, and TCD were used to determine drug tolerability. A decrease in the incidence of angiographic vasospasm and fewer cerebral infarctions on CT scan were observed in the treatment group. No differences in adverse events were observed between the two groups. Based on these results, it was concluded that treatment with clazosentan was safe and well-tolerated, warranting a larger randomized control trial [52].

After clazosentan was shown to be safe in humans, the first Clazosentan to Overcome Neurological iSChemia and Infarct Occurring after Subarachnoid hemorrhage (CONSCIOUS) trial was conducted [53]. Investigators used a randomized, double-blind design to determine the optimum dosing regimen. A total of 413 patients were randomly divided into groups receiving increasing drug dosages (1, 5, 15 mg/hr started intravenously within 56 hours of injury and continued up to 14 days) or placebo. The investigators observed a significant dose-dependent reduction of moderate or severe cerebral vasospasm, and a trend towards reductions in delayed ischemic

neurological deficits, and new cerebral infarctions. There were no apparent changes in morbidity and mortality between the experimental group and placebo group; but the study was not sufficiently powered to show effect on clinical outcome. Common side effects in the treatment group included hypotension, anemia, and pulmonary complications. Based on the reduction of vasospasm and trend towards fewer mortalities in the treatment group, investigators planned subsequent trials to study the overall outcome of patients receiving clazosenten with surgical clipping (CONSCIOUS-2) or endovascular coiling (CONSCIOUS-3) of their aneurysms [54-56].

CONSCIOUS-2 was a phase III randomized, double-blind control trial involving 1147 aSAH patients treated with surgical ligation of their aneurysms. Subjects were randomized to a placebo (n = 383) or a treatment group receiving 5 mg/hr clazosentan for up to 14 days (n = 764). While the drug decreased the risk of vasospasm, there was no difference in incidence of CT findings of cerebral infarction, mortality or vasospasm-related morbidity 6 weeks after the injury, or 12-week outcome as measured by Glasgow Outcome Scale. Similar results were reported in the CONSCIOUS-3 study, although it was terminated early based on non-significant findings from the parallel CONSCIOUS-2 study. Consistent with these findings, meta-analyses were performed by pooling data from several randomized control trials using clazosentan in more than 2000 aSAH patients [59, 60]. Both groups concluded its effectiveness in attenuating cerebral vasospasm and vasospasm-related delayed ischemic neurological deficits and morbidity and mortality. However, significant benefit was not found for new cerebral infarction detected by post-operative CT scan, poor outcome or overall mortality. Moreover, its use is associated with adverse side effects. Altogether, these studies do not support the use of clazosentan as standard treatment in aSAH patients, and further demonstrate that attenuation of radiographic vasospasm is not directly linked to improved functional outcomes.

Magnesium sulfate

Magnesium (Mg^{2+}) is a divalent inorganic cation that, like dihydropyridines, acts as a vasodilator by antagonizing calcium entry through voltage-dependent calcium channels. It also interferes with calcium entry though NMDA receptor-channels and glutamate release suggesting a possible neuroprotective effect against glutamate excitotoxicity in addition to attenuation of cerebral vasospasm [61-65]. Additionally, it may exert neuroprotection by interfering with the actions of ET-1 and formation of reactive oxygen species [66, 67]. Mean serum concentrations are ~0.86 mmol/L and a subgroup of aSAH patients exhibit hypomagnesemia [68], that may increase the incidence and severity of cerebral vasospasm. Magnesium therapy has proven to be beneficial in obstetrics and cardiovascular pathologies, where it is safe and well-tolerated [69, 70]. Moreover, in several animal models of aSAH, the majority of studies observed vasodilation of the cerebral vasculature in response to magnesium administration [65].

Several clinical trials have investigated the potential benefits of magnesium sulfate ($MgSO_4$) in aSAH patients. In a prospective pilot study, 60 aSAH patients were randomized to a placebo group receiving saline, or a treatment group receiving $MgSO_4$ (intravenous infusion of 80 mmol/day for 14 days within 48 hours of aSAH; plasma magnesium concentration was elevated to ~2x the basal value, but was <2.5 mmol/L to avoid hypotension and bradycardia). All patients also received intravenous nimodipine. $MgSO_4$ shortened the duration of cerebral vasospasm assessed by transcranial Doppler (TCD) imaging; however at 6 months there was no difference in functional recovery or Glasgow Outcome Score between the treatment and placebo groups. There was also no difference in adverse events such as hydrocephalus, infection and brain edema. The investigators concluded that a larger sample size would be needed to further delineate any therapeutic benefit of magnesium administration, noting it was well-tolerated in this patient population [62].

The Magnesium in Aneurysmal Subarachnoid Hemorrhage (MASH) study was a larger randomized phase two trial in which aSAH patients received intravenous $MgSO_4$ infusion (64 mmol/L per day for 14 days), and were assessed for the development of DCI as measured by hypodensity on CT scan in conjunction with

neurologic deterioration. Patients were included if they presented within 4 days of SAH, were over 18 years of age, and did not have renal dysfunction or imminent death. While there was a trend towards reduction of DCI and improved outcome in the 283 patients included, the difference was not significant and the investigators concluded that a larger sample size was needed [71].

Subsequently, two phase III double-blinded, randomized placebo-controlled multicenter trials using intravenous $MgSO_4$ in aSAH patients were conducted [72, 73]. In the Intravenous MASH (IMASH) study, patients in the treatment group received $MgSO_4$ infusion within 48 hours of injury for 10-14 days. Serum magnesium concentration was titrated to twice the baseline concentration. Based on the extended outcome Glasgow scale, nearly identical 6-month outcomes were observed in the 169 patients in the treatment group, when compared to the 158 patients in the placebo group. No differences in secondary outcome analyses, including clinical vasospasm, were observed. Notably, there was a positive correlation between serum magnesium concentration and incidence of side effects in aSAH patients [74]. Results from the larger MASH-2 multicenter trial also failed to show improvement in functional outcome between the $MgSO_4$ treatment group versus the placebo group. Thus, although both trials were adequately powered to determine a significant difference, intravenous $MgSO_4$ did not change the incidence of DCI, vasospasm, or improve general outcome, compared to patients in the placebo group.

The IMASH and MASH-2 trials used a standard dosing regimen. To more reliably control the delivery of magnesium, a recent randomized, placebo-controlled study adjusted the dosing every 12 hours, as needed, based on the patient's serum magnesium concentration [75]. A trend towards better 1 year outcomes was reported, but treatment was terminated in over half of the experimental group due to untoward side effects, such as hypotension and hypocalcemia. The investigators noted that patients in whom the magnesium infusion was discontinued received higher doses on average, possibly accounting for the increased incidence of side effects.

Proponents of magnesium therapy in aSAH could argue that it does not readily cross the blood-brain barrier. Thus, while the serum magnesium concentration was elevated in clinical studies, the CSF concentrations may not have been sufficient to cause vasodilation of the cerebral blood vessels in the subarachnoid space [76-78]. Accordingly, a subset of 13 patients (9 receiving $MgSO_4$ and 4 controls) from the IMASH clinical trial were examined for serum, CSF, and urine magnesium concentrations over a period of 9 days [77]. While serum magnesium concentrations were significantly higher, CSF concentrations showed significant differences only on day 2, and days 5 through 8. Though the sample size is small, this subset analysis suggests further studies are needed to determine whether a greater magnesium concentration in the CSF could provide therapeutic benefit without significant side effects.

A proposed method to assure a more direct access to the CSF is an intra-arterial route of administration. Shah and colleagues followed 14 patients with medically-resistant vasospasm who were treated with intra-arterial nicardipine and $MgSO_4$, in combination with balloon angioplasty if indicated. Successful treatment was defined as a 60% increase in blood vessel diameter relative to the initial measurement. Mean arterial pressure and intracranial pressure did not change significantly in response to $MgSO_4$ infusion. Of the 58 vessels treated in 14 patients, 40 responded to $MgSO_4$ plus nicardipine administration alone, and 18 vessels required angioplasty as well which completely reversed vasospasm. A majority of patients showed clinical improvement following treatment, with no evidence of infarction on follow up CT scans. Direct administration of $MgSO_4$ was well-tolerated while exerting a vasodilatory effect; thus, the investigators argue this therapy warrants a larger randomized study to provide additional data.

Intrathecal administration of $MgSO_4$ has been studied in animals as a means to specifically increase its concentration in the CSF [79]. Using a double-blood injection model of SAH to induce vasospasm in canines, $MgSO_4$ was injected into the cisterna magna, and CSF concentrations as well as arterial diameters were measured at 1, 3, and 6 hours after the second blood injection.

Increases in arterial diameters (vasodilation) were positively correlated with increases in CSF magnesium concentrations (1 and 3 hours), and this effect was lost after CSF magnesium concentration returned to baseline (6 hours). Chi square analysis of CSF magnesium concentrations showed that 3 mEq/L was sufficient to produce a vasodilatory effect that lasted for at least 6 hours. Similar results were reported when an intrathecal microcatheter was used to continuously administer $MgSO_4$ into the cisterna magna in experimental SAH [80]. These results demonstrate that raising the concentration of $MgSO_4$ in the CSF can effectively dilate cerebral blood vessels following experimental SAH, suggesting the potential benefits of an intrathecal route of administration in humans. However, further studies are needed to address the ambiguous relationship between $MgSO_4$ concentrations in CSF, cerebral vasospasm, and functional outcome in aSAH patients. Even if $MgSO_4$, like clazosentan, effectively attenuates cerebral vasospasm in aSAH patients when administered intrathecally, there is no reason to presume that it would improve functional outcome unless it impacts a relevant target.

Statins

Statins are 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors that include the natural product from fungi, lovastatin, its 2,2 dimethyl butyrate analogue simvastatin, and other structurally related analogues. In addition to attenuating vasospasm by arterial dilatation, statins exhibit multifactorial effects that may enhance their therapeutic actions. Many of these actions have been characterized in animal models of SAH, where statins exhibit pleiotropic effects [80-86]. They reduce production of inflammatory mediators such as TNF-α and IL-1β, and improve cerebral blood flow through effects on the endothelium and endothelial nitric oxide synthase (eNOS). There is also evidence that simvastatin inhibits the formation of microthrombi and activation of the coagulation cascade to potentially limit delayed ischemic neurological deficits [87, 88], inhibit apoptosis, limit edema, maintain integrity of the BBB, and prevent vasospasm [82, 89] possibly by decreasing perivascular leukocyte infiltration [90, 86]. In humans, ascertaining the benefits of statin has proven difficult, with studies reporting conflicting results.

Lynch and associates conducted a prospective randomized trial of 39 aSAH patients receiving placebo or simvastatin (80 mg/day for 14 days). Patients were evaluated 3 times a week by TCD, and daily blood tests measured predictors of brain injury using von Willebrand factor as a marker for endothelial injury, and S100β protein as a marker for astrocyte activation [89]. Significantly decreased rates of vasospasm were reported in the statin group (26%), compared to controls (60%), in conjunction with significantly decreased amounts of S100β and von Willebrand factor, leading the authors to draw favorable conclusions about the potential benefits of simvastatin in aSAH patients. However, the study has been criticized for being insufficiently powered, and showing higher than normal rates of DCI in placebo groups, possibly accounting for the differences found. In the same year, Tseng and colleagues reported the results of a phase II randomized controlled trial in 80 aSAH patients in which half of the patients received oral pravastatin (40 mg/day up to 14 days within 72 hours of injury) and the other half received placebo. Pravastatin reduced the duration and incidence of severe vasospasm identified by TCD compared to controls [91]. The post-hemorrhage period of dysfunctional cerebral autoregulation was also significantly shortened on both the contralateral and ipsilateral sides, and both vasospasm-related deficits and mortality were significantly reduced. The authors concluded that pravastatin was safe and well-tolerated, and showed significant clinical promise in aSAH patients. Benefits of statin therapy was also reported in aSAH patients receiving atorvastatin [92], where a reduction in volume of ischemic lesion on CT in the statin group which underwent uncomplicated coiling was also noted. A meta-analysis by Sillberg and colleagues also supported the benefits of statins using vasospasm, delayed ischemic deficits and mortality as outcome measures [93]. However, the authors acknowledged that the sample size was small, indicating the need for large randomized control trials.

Other clinical trials have failed to find benefit from acute statin treatment after aSAH. Vergouwen and colleagues conducted a prospective, randomized,

double-blind trial in a total of 32 aSAH patients, with 16 patients each in the treatment and placebo groups [94]. The treatment group received simvastatin (80 mg/day for 14 days). Aside from cholesterol-lowering effects, no difference between statin and non-statin users was observed in regards to incidence of vasospasm, assessed radiographically or clinically, functional outcomes (Glasgow Outcome Scale), or markers of endothelial function and coagulation. Similar results were obtained in a retrospective review of 71 aSAH patients who received simvastatin (80 mg/day for 14 days) compared to 79 patients who did not receive simvastatin [95]. In a pilot study using simvastatin at the same dose, 39 Fisher grade 3 subjects were randomized to treatment and placebo groups. Simvastatin was reported to be well-tolerated, and a trend towards lower mortality with no effect on vasospasm was noted [96]. In a study involving a larger number of patients, pravastatin (40 mg/day for 14 days) failed to reduce vasospasm or global outcome at discharge [97]. Another trial examined the effects of statin plus magnesium administration on vasospasm and functional outcomes, but failed to find significant benefit of either the combination or simvastatin alone [98]. The authors reported a trend in decreased mortality in statin only patients, but this failed to reach significance.

A criticism of the failure to detect differences in statin use among some reports has been postulated to be an effect of the retrospective nature of the studies, frequently including a high degree of variability between comparison groups. McGirt and colleagues conducted a prospective controlled cohort study of 340 patients with aneurysmal SAH [99]. A total of 340 patients were included with 170 receiving 80 mg of parenteral simvastatin daily initiated on admission for a minimum of 14 days. Significant differences were not found between groups in any of the primary endpoints, including length of hospitalization, symptomatic vasospasm, in-hospital death, or poor outcome. In this prospective trial, the authors addressed some of the limitations that confounded previous retrospective trials that failed to demonstrate a significant difference in vasospasm with statins. Baseline characteristics of the experimental and control groups were largely matched, group sizes were equal, and the authors utilized an objective definition of vasospasm. They invoked variations in definition of vasospasm such as dependence on TCD criteria that may have been impacted by statins. The lack of evidence for acute statin therapy as standard care after aSAH was also underscored by a recent meta-analyses in which eligibility criteria were met by 6 RCTs, and five cohort and one case control study involving over 1800 patients. Statins did not have significant effects on poor outcome or mortality, though a potential trend towards lower mortality was suggested. The authors suggested the need for further evaluation in larger trials [100].

A limited number of studies have assessed whether a statin use before injury affords protection against cerebral vasospasm, DCI, or improves functional outcomes in aSAH patients. In a retrospective study involving 115 aSAH patients, 43% experienced symptomatic vasospasm. Fifteen patients were taking statins at least one month prior to injury. Using multivariate logistic regression analysis, the authors reported an 11-fold reduction in vasospasm with prior statin use [101]. Additional therapeutic benefits of pre-hemorrhage statin use was obtained in a matched, controlled cohort study of 20 aSAH patients on statins and 40 control aSAH patients. Patients taking statins prior to injury demonstrated significant improvement in functional outcome at 14 days, and significantly decreased rates of DCI and cerebral infarctions [102], though significant differences were not observed in mortality or global outcome, assessed by the modified Rankin Scale. In another retrospective study involving 308 patients, a trend towards decreased vasospasm was reported in the group taking statins before injury [103]. However, the number of patients in the statin group was quite small (n = 26), compared to the control group (n = 282). A recent study including a total of 117 aSAH patients and 304 control patients with newly diagnosed unruptured aneurysms reported a significantly higher rate of statin use in the control group. After adjusting for potential confounders, the investigators reported an inverse relationship between prior use of statins and aneurysm rupture, and suggested further studies are warranted [104].

Acute statin therapy in aSAH patients is generally safe and well-tolerated [92, 91, 104, 96, 87], and

experimental evidence in animal models indicates that they influence multiple pathways that could impact the multimodal injury process. However, the consensus of clinical trials and meta-analyses do not support statin use to improve functional outcome or reduce mortality in aSAH patients though several groups recommend further study. Regarding use of statins as prophylactic therapy to reduce the risk of aneurysm rupture, additional studies appear warranted based on the limited data obtained thus far.

DISCUSSION

The emphasis on cerebral vasospasm as the major target for drug development and testing in aSAH patients was based on the rationale that significant narrowing of basal cerebral arteries leads to decreased blood flow and oxygen delivery to distal perfused territories, causing DCI and increasing the likelihood of cerebral infarction, long-term disability and death. The argument that vasospasm is the principle causal factor leading to DCI was supported by studies measuring angiographic vasospasm, ischemia, and functional outcomes in aSAH patients [105-108]. However, a preponderance of evidence obtained in recent years indicates large vessel cerebral vasospasm is not the principle causal event leading to disability and death in these patients, and thus should not be the primary target for drug development. Some of the most compelling evidence derives from clinical trials and observational studies. For example, Dankbaar and colleagues assessed the association between vasospasm, DCI and cerebral perfusion in 37 aSAH patients. CT angiography and CT perfusion analyses were performed on admission and within 14 days of admission, and cerebral vasospasm was classified as absent, moderate, or severe. An association between vasospasm and decreased perfusion was shown, but it corresponded to the least perfused territory in only two-thirds of patients. Moreover, 4 of 7 patients with severe vasospasm, 6 of 16 patients with moderate vasospasm, and 3 of 14 patients with no vasospasm had DCI. These results led investigators to conclude that vasospasm does not necessarily cause DCI, and DCI is not uncommon in patients with no evidence of cerebral vasospasm [109]. Along these lines, further analysis of the CONSCIOUS-1 trial data revealed 57% of aSAH patients with moderate to severe vasospasm did not develop neurologic deterioration, and cerebral infarction commonly occurred independent of angiographic vasospasm [14]. Dhar and associates investigated the relationship between vasospasm, regional hypoperfusion and oxygen extraction in 25 aSAH patients using positron emission tomography. These studies revealed a poor correlation between cerebral vasospasm and matched regional hypoperfusion. Although vasospasm was associated with decreased blood flow, oxygen extraction was higher in the impacted areas suggesting compensation by collateral circulation or autoregulatory vasodilatation. Moreover, regions of hypoperfusion and low oxygen extraction were frequently observed in territories with no concurrent vasospasm [110]. Finally, as described above, significant attenuation of cerebral vasospasm with ET_A receptor antagonists did not translate into improved patient outcomes [43-58]. Collectively, these and similar studies have led investigators to conclude that cerebral vasospasm is not a reliable predictor of DCI, cerebral infarction, or clinical outcome in aSAH patients [111-113].

There is general agreement that multiple factors can cause DCI, and investigators have renewed their efforts to unravel these complex processes. There is currently no straightforward means to assess DCI, whereas cerebral infarctions are readily measured and their presence is associated with poor functional outcomes [113-116]. To promote uniformity in terminology and methodologies, which have made it difficult to compare studies by different laboratories, an international panel of experts published a consensus statement. They acknowledged the discrepancy between diagnosis of cerebral vasospasm, and occurrence of DCI and functional outcome when reviewing clinical trials, and suggested outcome measures for future studies should focus on prevention of DCI as opposed to cerebral vasospasm. As primary outcome measures, the group proposed new cerebral infarctions in conjunction with functional outcomes be used. Their definition of new cerebral infarction is: “The presence of cerebral infarction on CT or MR scan of the brain within 6 weeks after SAH, or on

the latest CT or MR scan made before death within 6 weeks, or proven at autopsy, not present on the CT or MR scan between 24 and 48 hours after early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment. Hypodensities on CT imaging resulting from ventricular catheter or intraparenchymal hematoma should not be regarded as cerebral infarctions from DCI" [117]. It was further suggested that the term vasospasm be restricted to describing a radiologic test as opposed to substituting it to describe clinical manifestations of cerebral ischemia. This consensus report reflects the paradigm shift away from cerebral vasospasm to investigation of other methods to assess and treat brain injury after aSAH.

Emerging evidence supports a complex pathogenesis underlying DCI and cerebral infarction including disturbances in autoregulation, which can be measured non-invasively using near-infrared spectroscopy and TCD [118-120], and microthrombosis and microvasospasm [121-123]. Also, a phenomenon characterized by cortical spreading depolarization is associated with cerebral infarction and poor functional outcome and may provide a useful clinical biomarker of injury [124-126, 15]. These mass depolarizations often occur in clusters, and are linked to a breakdown in ionic homeostasis, rises in extracellular potassium, decreased NO availability, reduced oxygen supply, increased oxygen consumption, neuronal swelling, as well as an inverse hemodynamic response reflecting vasoconstriction in the microcirculation which further exacerbates tissue damage by hypoperfusion. In a study involving 13 aSAH patients undergoing aneurysm clipping, subdural electrodes were placed to measure cortical spreading depolarization, and prolonged release nicardipine was also implanted to eliminate or attenuate vasospasm. Results showed a positive correlation between DCI and spreading depolarization, but not cerebral vasospasm [15]. While this area of research is promising, direct measurement of spreading depolarization in the clinic is complicated by the need to implant delicate opto-electrode strips as monitoring devices. As research continues in this area, less invasive monitoring will need to be developed, perhaps in conjunction with use of nimodipine and NO donors which theoretically may attenuate spreading ischemia [124].

In essence, the underlying processes leading to DCI and cerebral infarction represent a continuum involving acute, subacute and delayed stages of injury, as opposed to a single process such as delayed cerebral vasospasm. The relevant pathways are likely to interact and collectively contribute to overall outcome in aSAH patients, and they are not well understood. Early brain injury occurs after the initial aneurysmal rupture and over the first 72 hours, and prior to vasospasm [127-131]. In the acute stages following blood accumulation in the basal cisterns, increased intracranial pressure and decreased cerebral perfusion pressure lead to global ischemic injury, with poorest outcomes in patients exhibiting the greatest increases in intracranial pressure [132, 133]. In a sub-population of patients, edema further enhances the risk for morbidity and mortality [134-136]. Concurrent with these hemodynamic disturbances, blood and blood breakdown products induce inflammation and oxidative stress, which are also predictors of poor outcome [137-144]. This has generated interest in accelerating the clearance of toxic blood breakdown products and attenuating the inflammatory response. For example, in a systematic review and meta-analysis of 5 randomized controlled trials including 465 aSAH patients evaluating the effect of intrathecal thrombolytics, their use was associated with improved outcomes, and investigators suggested the need for larger, more rigorous trials [140]. Also, an on-going preliminary phase I feasibility study is examining the efficacy of etanercept, a TNF-α antagonist [145]. Etanercept and other pharmacotherapies targeting pathways mediating both caspase-dependent and independent apoptosis have generated considerable interest as loss of endothelial cells, neurons and glia are observed in the acute stages of injury [127]. Based on the number and complexity of pathways involved, the most effective drug therapies will need to target multiple stages of this evolving and interrelated injury process.

CONCLUSIONS

Current evidence indicates that cerebral vasospasm, whether it is assessed clinically or radiographically, is not the appropriate target for drug development. Accordingly, its presence in aSAH patients is not consistently associated with cerebral infarctions leading to poor outcomes, and many patients in whom cerebral vasospasm is mild or absent nonetheless suffer long-term disabilities and mortality. Moreover, pharmacological therapies that effectively attenuate cerebral vasospasm do not significantly improve long-term outcomes, perhaps best exemplified in clinical trials using ET_A receptor antagonists. Nimodipine, the only pharmacologic therapy shown to improve outcome following aSAH, does not reliably attenuate cerebral vasospasm. It is evident that a more comprehensive understanding of the injury process is needed, with further research into developing treatment strategies for thrombosis and vasospasm in the microvasculature, impaired cerebral autoregulation, spreading cortical depolarization, and early brain injury. Recent efforts to eliminate ambiguities in the use of terms and procedures to assess delayed cerebral ischemia should also enhance progress in this important field.

CONFLICT OF INTEREST

None of the authors, Margaret Riordan, Michele Kyle, Tonia Tiewul, Eric Deshaies and MaryLou Vallano have a conflict of interest to report.

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