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Statins and Anti-Inflammatory Therapies for Subarachnoid Hemorrhage

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Opinion Statement

Aneurysmal subarachnoid hemorrhage induces a potent inflammatory cascade that contributes to endothelial dysfunction, imbalance of vasoactive substances (excess endothelin, depletion of nitric oxide) and arterial vasospasm. This process results in delayed cerebral ischemia, a major cause of neurological disability in those surviving the initial hemorrhage. The only therapy shown to be effective in improving neurologic outcomes after SAH is the calcium-channel antagonist, nimodipine (although it achieved this without reducing vasospasm). A number of novel therapies have been explored to inhibit the development of vasospasm and reduce the burden of ischemia and cerebral infarction. Statins are promising candidates, as they block multiple aspects of the inflammatory pathway that contributes to ischemic brain injury. Early clinical trials, however, have produced conflicting results and adoption of their use in clinical practice should await the results of larger more definitive studies. While endothelin-receptor antagonists showed promise in significantly reducing vasospasm in preliminary trials, their failure to improve clinical outcomes in phase III studies has been disappointing, highlighting the complex link between vasospasm and ischemia. Future directions in the quest to improve outcomes of patients with SAH may need to approach ischemia as a multifactorial process with inflammatory, vasoactive, and ionic/metabolic components.

Introduction

The rupture of an intracranial aneurysm is a devastating cerebrovascular event that results in subarachnoid hemorrhage (SAH). The acute release of blood into the subarachnoid space and rise in intracranial pressure initiates a cascade of events over the ensuing days that culminates in arterial vasospasm, seen in up to 70% of patients with aneurysmal SAH [1], placing patients at risk for delayed cerebral ischemia (DCI). Ischemia, resulting in neurological deficits in 20–30% of patients, as well as cerebral infarction, is the leading cause of morbidity in survivors of SAH [2]. While the risk and distribution of arterial narrowing correlates with the volume and location of blood clot [3], ischemia is not simply related to the presence of blood or even vasospasm alone [4,5].

Inflammation and endothelial dysfunction are increasingly being recognized as playing central roles in the pathophysiology of this complex and potentially devastating process (Figure 1) [6,7•]. Aneurysmal rupture and subarachnoid blood activate the release of inflammatory cytokines such as interleukin-6 (IL-6) and tumor-necrosis factor-alpha [8–10]. Neutrophils are attracted to the sites of cerebral inflammation, binding to vascular

endothelium in a process mediated by cellular adhesion molecules such as ICAM-1 and the selectins [11,12]. Activated leukocytes within the subarachnoid space contribute to vasospasm by promoting production of endothelin-1, a potent vasoconstrictor, depleting nitric oxide (NO), and producing reactive oxygen species [13]. Free radicals enhance lipid peroxidation and oxidation of bilirubin, both of which can injure smooth muscle cells [14]. This inflammatory mechanism for vasospasm is evidenced by infiltrates of inflammatory cells seen in walls of affected intracranial vessels [15], and the observation that polymorphisms in the eNOS (endothelial nitric oxide synthase) gene affects susceptibility to vasospasm [16].

Experimental studies support a causative role for inflammation, demonstrating a reduction in arterial narrowing by inhibiting various steps of the inflammatory pathway [17,18]. Studies of patients with SAH have shown a correlation between inflammatory markers and vasospasm/DCI [19–21]. The recognition of the role that inflammation may play in genesis of vasospasm and DCI has led to considerable interest in drugs that block these pathways as a means of ameliorating vasospasm and preventing morbidity from ischemia after SAH.

Treatment

Diet and Lifestyle

Smoking is a well-established risk factor for SAH and increases the risk for aneurysmal rupture in those with unruptured aneurysms [22,23, Class II]. This risk appears to be eliminated within a few years of smoking cessation [22, Class III]. Smoking is also a risk factor for the development of vasospasm and cerebral infarcts after SAH [24–27, class II]. There has been a concern about use of nicotine replacement therapy (NRT) in patients with acute SAH given the vasoactive properties of nicotine and potential to worsen endothelial damage [28]. However, a recent retrospective study found that NRT appeared safe in SAH patients with no excess incidence of DCI, perhaps even associated with better outcomes (albeit with a higher incidence of delirium and seizures) [29, class III].

Pharmacologic Treatment

To minimize the burden of DCI after SAH and prevent cerebral infarction, most therapies have centered on reducing the incidence and severity of arterial vasospasm [30••]. Interestingly, nimodipine, the only drug clearly indicated in SAH has been shown to improve neurological outcome without reducing angiographic vasospasm [31, class I]. Instead, its beneficial mode of action may rely more on suppression of calcium-mediated free radical release and ischemic brain injury. Newer therapies have focused on blocking the central pathways leading to arterial constriction and ischemia, many focusing on the inflammatory cascade and endothelial dysfunction.

Corticosteroids—Corticosteroids possess anti-inflammatory properties including the ability to inhibit cyclooxygenase, lipid peroxidation, and free radical production [32]. Three randomized trials of corticosteroids in SAH were analyzed in a Cochrane review [33]. Only one tested a glucocorticoid (hydrocortisone), which was started in those already exhibiting deficits attributed to DCI [34]. Steroid therapy did not improve outcomes in these patients but was associated with an increase in adverse events, mainly related to steroid-induced hyperglycemia (class II). Hydrocortisone does appear to prevent natriuresis and hyponatremia, a common problem in patients with SAH, as demonstrated a single small randomized trial [35, class II]. A preliminary non-randomized study evaluated methylprednisolone compared to matched controls in patients at high risk for vasospasm and found improved outcomes in treated patients [36]. Recently a larger randomized trial in 95 patients evaluated high-dose methylprednisolone given early after aneurysmal rupture [37].

Treatment did not reduce the incidence of delayed ischemic deficits attributable to vasospasm or cerebral infarction, although a SAH associated spike in C-reactive protein levels was attenuated compared to controls. However, 1-year functional outcome tended to be better in steroid-treated patient, with 69% achieving a good outcome defined as a modified Rankin scale of 0–2 compared to 54% with placebo ($p=0.13$, class II). Further confirmation of this benefit will be required before steroids can be adopted as standard treatment for SAH.

Free Radical Scavengers—Tirilazad is a synthetic non-glucocorticoid 17-aminosteroid that inhibits lipid peroxidation and endothelial/smooth muscle cell injury by scavenging free radicals and stabilizing cell membranes [38]. It has been studied in 5 randomized trials of 3821 patients with SAH [39]. Although fewer patients developed symptomatic vasospasm/DCI (OR 0.80, 95% CI 0.69–0.93), no improvement in death or poor outcome (including cerebral infarction) was seen in a recent meta-analysis (Class I).

Edaravone, another free radical scavenger, has recently been evaluated as a means of inhibiting the development of vasospasm after SAH. A study of 91 patients randomized to treatment or placebo found a trend to reduction of ischemic deficits (10% vs. 21%, $p=0.12$) [40, class II]. Cerebral infarction was reduced from 21% to 4% ($p=0.01$). Favorable outcome occurred in 92% of treated patients compared to 83% of controls ($p=0.09$). Larger randomized studies are needed to verify these promising but preliminary findings.

Non-Steroidal Anti-inflammatory Drugs—Acetylsalicylic acid (ASA) is an anti-inflammatory as well as anti-platelet agent; both of these properties may be beneficial in prevention of ischemia after SAH. Based on a meta-analysis of preliminary studies suggesting reduction in ischemic deficits with ASA treatment, a larger randomized, placebo-controlled trial (using 100 mg ASA rectally) was performed in 161 SAH patients [41]. ASA tended to increase the incidence of ischemic deficits with no change in number of infarcts or neurological outcome (class I). At this point, treatment with ASA cannot be recommended in SAH. No human studies of ibuprofen have been performed, but experimental studies have found a reduction in vasospasm possibly mediated through the drugs ability to inhibit leukocyte-endothelial interactions [42,43].

Statins—HMG-CoA reductase inhibitors (“statins”) exhibit pleiotropic actions which may be beneficial in attenuating some of the inflammatory and vasoactive disturbances underlying vasospasm and DCI. They restore eNOS activity, increase NO levels [44,45], and block the activation and migration of inflammatory leukocytes [46,47]. Statins are able to stabilize endothelial and autoregulatory function, may possess antiplatelet and antithrombotic properties, prevent neuronal apoptosis, and scavenge free radicals (Table 1) [48,49]. Experimental evidence has supported their ability (albeit when given at much higher doses than used in humans and either prior to or early after SAH) to attenuate development of vasospasm in animal models, inhibiting inflammatory infiltration of vessel walls [45,47].

Four small randomized controlled trials which enrolled a total of 190 patients have now been published evaluating the use of simvastatin and pravastatin in patients with SAH (see Table 2), while 2 additional trials have been published only in abstract form [50–53]. These have assessed whether early statin treatment can reduce vasospasm and DCI, and improve outcomes. A meta-analysis of these published trials (using a random effects model) found no reduction in vasospasm (defined by TCD criteria), a non-significant trend to reduction in ischemic neurological deficits (OR 0.57, 95% CI 0.29–1.13) and mortality (OR 0.37, 95% CI 0.13–1.10) [54•, class I]. Poor neurological outcome was unaffected by statin treatment. Another recent systematic review used a fixed effects model (which may be inappropriate

when combining small heterogeneous studies) and found that statins appeared to reduce incidence of delayed ischemic deficits and mortality [55]. AHA guidelines do not recommend statins for patients with SAH, pending results of a larger multi-center randomized trial (with simvastatin 40-mg, *ISRCTN75948817*) that is aiming to enroll 800 SAH patients in the United Kingdom [56].

Standard dosage: simvastatin 40–80 mg daily or pravastatin 40 mg daily. Not approved for SAH.

Contraindications: avoid if liver disease (including elevated transaminases) or if pregnant, caution if muscle disease (or elevated creatine kinase, CK). Use of simvastatin 80 mg recently discouraged by an FDA advisory, based on a higher risk of myopathy and rhabdomyolysis in clinical trials and post-marketing surveillance. Myopathy (with CK 10x ULN) was 45 times more common with 80 vs. 20-mg of simvastatin [57]. Incidence of rhabdomyolysis was 0.4% (approximated at 2 per 1000 in the first year of treatment). If this dose is to be used, close monitoring of CK is recommended. While the trials of statins in SAH were underpowered to detect rare adverse effects, no clear excess of myopathy was noted in any of the available studies.

Main drug interactions: simvastatin is metabolized by the cytochrome P-450 system and levels will be increased by drugs (such as protease inhibitors, erythromycin, verapamil, diltiazem, amiodarone, digoxin, cyclosporin, azole antifungals, and warfarin) that inhibit enzymatic activity of this system. Pravastatin is not metabolized through this pathway and its use should avoid such interactions. The combination of statins with drugs like niacin or fibrates may increase the risk of rhabdomyolysis or liver failure.

Main side effects: elevation in transaminases and/or CK, muscle pain and/or myopathy.

Special points: for patients on statins prior to SAH, abrupt withdrawal after admission may be associated with elevated risk of vasospasm [58,59]. Statin withdrawal has been linked to acutely worsening inflammation, suppression of eNOS, and a rise in free radical production. Statins should be continued in any patient taking them prior to admission.

Cost: Relatively inexpensive and cost-effective if able to prevent disability from DCI

Endothelin antagonists—Endothelin is a powerful vasoconstrictor and has been implicated in the pathophysiology of cerebral vasospasm. Endothelin levels are elevated in the CSF of patients with SAH [60], with a profile that mirrors the time course of vasospasm [61]. Activated leukocytes contribute to endothelin production [62], again tying inflammation into the vasoactive theory of DCI. Preliminary clinical studies found that clazosentan, an endothelin-1 receptor antagonist significantly reduced angiographic vasospasm in a dose-dependent manner [1]. A phase III trial was recently reported testing clazosentan in SAH patients who had undergone surgical clipping of a ruptured aneurysm [63]. No improvement in the primary endpoint (mortality, vasospasm-related infarction, delayed ischemic deficits due to vasospasm, and rescue therapy for vasospasm) was seen (21 vs. 25%, $p=0.1$) and poor functional outcome actually was more common in the clazosentan-treated patients (Class I). This might have been due to an increased risk of extra-cerebral adverse events including hypotension, anemia, and pulmonary edema. While results of the CONSCIOUS-3 study in coiled patients are not reported [64], use of clazosentan is neither approved nor recommended in SAH.

Erythropoietin—Erythropoietin (EPO) may not only augment hemoglobin production but also possesses a variety of neuroprotective and immunomodulatory properties. It may

interact with endothelial EPO receptors to augment eNOS expression and NO production [65]. It exhibited promise in experimental studies of ischemic stroke [66], but a recently published clinical trial found a significantly higher mortality rate in treated patients [67]. A small phase II proof-of-concept study was performed administering 3 doses of EPO acutely after SAH [68]. It found no change in overall rate of vasospasm but, using TCD-criteria, severity of vasospasm was reduced and ischemic deficits were less frequent (class II). Phase III studies will be required to confirm the role of EPO in SAH and exclude risk as demonstrated in ischemic stroke trials.

Interventional Procedures

Conventional catheter angiography remains the gold-standard for diagnosing cerebral vasospasm. Furthermore, angiography not only allows accurate diagnosis of vasospasm but provides opportunity for therapeutic interventions to reduce arterial narrowing.

Angioplasty—Standard procedure: a balloon is inflated after a micro-catheter is passed across the segment of arterial narrowing producing a sustained increase in luminal diameter. Clinical improvement may be seen in 60% or more of patients. No controlled studies have been performed to demonstrate better outcomes.

Contraindications: intracranial aneurysm in the same vessel segment, inability to access the affected segment (common for A1 or other distal vessels).

Complications: vessel perforation or rupture (often fatal), dissection, and hemorrhage from an unsecured aneurysm [69].

Special points: angioplasty is a relatively durable treatment option with most segments not requiring retreatment (i.e. recurrent vasospasm is rare). Early treatment (shortly after onset of deficits, rather than waiting for hours to days for failure of medical therapies) may be better to prevent permanent sequelae [70]. Prophylactic angioplasty did not reduce DIDs or TCD-defined vasospasm in high-risk patients, with similar functional outcomes but a number of procedural-related deaths [71]

Cost: Expensive, requires special expertise (only available in certain centers).

Intra-arterial vasodilators—Standard procedure: a vasodilator (such as nicardipine, verapamil, magnesium, or milrinone) is infused through the intracranial microcatheter into the affected vessel. This allows treatment of smaller, more distal arteries that may not be accessible to angioplasty.

Contraindications: inability to pass micocatheter.

Complications: Use of papaverine has largely been abandoned with the advent of safer options and recognition of various complications including raised intracranial pressure [72], seizures [73], and paradoxical worsening of vasospasm [74]

Special points: the dilatory response is more transient than seen with angioplasty and often treated vessel segments require retreatment for recurrent vasospasm.

Cost: expensive, requires special expertise.

Surgery

Definitive aneurysm treatment is essential to prevent rebleeding, which carries very high mortality. Surgical clipping or endovascular coiling are both options. Once the ruptured

aneurysm has been secured, it is also safer to initiate hemodynamic therapies (such as induced hypertension) safely should ischemic deficits develop.

Emerging therapies

Cortical spreading depression (CSD) describes a wave of neuronal depolarization that propagates across the cerebral cortex; it is frequently recorded in patients suffering from ischemia after SAH and may be associated with microvascular spasm and worsening tissue hypoxia [75]. Endothelin, ionic/membrane alterations, and oxidative stress appear to contribute to CSD. Therapies aimed at mitigating this potentially harmful electrical phenomenon might prevent further neuronal injury; ketamine, a NMDA-receptor antagonist has been proposed but studies in SAH are lacking.

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Table 1

Putative pleiotropic effects of statins relevant to subarachnoid hemorrhage

Site of Action	Mechanism
Endothelium	Restores eNOS activity and blocks iNOS Increased NO results in vasodilatation (as does inhibition of endothelin-1 expression) Improved autoregulatory function and CBF Inhibits smooth muscle proliferation Reduces matrix metalloproteinases
Inflammatory Cascade	Inhibits leukocyte adhesion (and CNS infiltration) Reduces pro-inflammatory cytokines and CRP
Free Radicals	Reduces production/scavenges free radicals
Thrombosis	Inhibits platelet aggregation/adhesion Augments fibrinolysis (tPA)
Neurons	Blocks neuronal apoptosis

Modified from: Sabri and Macdonald [76•]

Abbreviations: CBF = cerebral blood flow; CNS = central nervous system; CRP = C-reactive protein; eNOS = endothelial nitric oxide synthase; iNOS = inducible nitric oxide synthase; NO = nitric oxide; tPA = tissue plasminogen activator.

Table 2

Published randomized trials of acute statin therapy in subarachnoid hemorrhage

Study	N	Statin/Dose	Duration	Vasospasm (TCD)	DID	Poor Outcome	Mortality
Tseng [51]	80	Pravastatin 40 mg once daily	14 days or discharge	43 vs. 63% (p=0.006)	5% vs. 30% (p<0.001)	43% vs. 53% (p=0.7)	5% vs. 20% (p=0.04)
Lynch [50]	39	Simvastatin 80 mg once daily	14 days	n/a	26% vs. 60% (p=0.03)	N/A	N/A
Chou [52]	39	Simvastatin 80 mg once daily	Max 21d (or ICU discharge)	68% vs. 50% (p=0.24)	37% vs. 50% (p=0.41)	63% vs. 50% (p=0.41)	0 vs. 15% (p=0.23)
Vergouwen [53]	32	Simvastatin 80 mg once daily	14 days	75% vs. 69% (p=0.024)	38% vs. 31% (p=0.71)	56% vs. 69% (p=0.63)	13% in both groups

Rates of each outcome are reported as statin vs. placebo

Abbreviations: DID = delayed ischemic deficits, TCD = Transcranial Doppler