EXPERT REVIEWS

Aneurysmal subarachnoid hemorrhage: pathobiology, current treatment and future directions

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Aneurysmal subarachnoid hemorrhage is the most devastating form of stroke. Many pathological mechanisms ensue after cerebral aneurysm rupture, including hydrocephalus, apoptosis of endothelial cells and neurons, cerebral edema, loss of blood–brain barrier, abnormal cerebral autoregulation, microthrombosis, cortical spreading depolarization and macrovascular vasospasm. Although studied extensively through experimental and clinical trials, current treatment guidelines to prevent delayed cerebral ischemia is limited to oral nimodipine, maintenance of euvolemia, induction of hypertension if ischemic signs occur and endovascular therapy for patients with continued ischemia after induced hypertension. Future investigations will involve agents targeting vasodilation, anticoagulation, inhibition of apoptosis pathways, free radical neutralization, suppression of cortical spreading depolarization and attenuation of inflammation.

Eighty-five percent of all cases of spontaneous subarachnoid hemorrhage (SAH) are due to cerebral aneurysm (CA) rupture [1]. SAH caused by rupture of a CA still carries high mortality (30–50%) and morbidity in spite of advances in management [2]. Initial management of aneurysmal SAH (aSAH) involves surgical or endovascular obliteration of the CA to prevent rerupture. Subsequent to securing the CA, attention is directed at prevention of further neurological damage from multiple pathological mechanisms.

In recent years, the pathological mechanisms of aSAH initiated at ictus and causing neuronal cell death in the first 72 h have been termed early brain injury (EBI) [3,4]. More delayed pathological mechanisms leading to infarction are termed delayed cerebral ischemia (DCI) [5]. The neuronal cell death from the combined pathological processes in EBI and DCI lead to subsequent diffuse cerebral atrophy and long-term neuropsychological deficiencies [6]. The pathological mechanisms of EBI and DCI appear to only occur when two

criteria are met: an initial severe elevation in intracranial pressure with consequent cerebral ischemia due to reduced cerebral perfusion and the presence of a large amount of blood in the subarachnoid space. In non-aneurysmal SAH (e.g., SAH due to arteriovenous malformation rupture or angiographically negative SAH), EBI and DCI rarely occur [7,8].

The magnitude and duration of initial intracranial hypertension after CA rupture and the amount of blood within the subarachnoid space correlate directly with the presenting clinical condition of the patient as well as the severity of the ensuing neuronal injury from EBI and DCI [9,10]. Because these factors are determined before the patients arrive at the hospital, improvement of outcomes after aSAH is a difficult task.

Macrovascular vasospasm is correlated in nearly three-fourths of delayed strokes after aSAH [11,12]. Accordingly, most therapy has been directed at altering the molecular pathways of macrovascular vasospasm. However, trials reducing angiographic vasospasm have

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not obtained the expected improvement in clinical outcomes [13–15]. This has led many investigators to evaluate other pathological mechanisms after aSAH, besides large vessel vasospasm, that may account for neurological damage. The other possible pathological mechanisms include: early induction of apoptosis after intracranial hypertension, cerebral edema, loss of blood–brain barrier (BBB) integrity and cerebral autoregulation, hydrocephalus, microvascular vasoconstriction and microthrombosis and cortical spreading depolarization (CSD). In this review, we discuss recent research on the pathobiology of aSAH, summarize the current management of aSAH and offer the future clinical implications of ongoing research.

Mechanisms of EBI
Intracranial hypertension after initial aneurysm rupture; Apoptosis

After rupture of a CA, patients present in varying clinical conditions from awake and alert to comatose. In the most severe clinical scenario, the opening of the arterial tree into the subarachnoid space after CA rupture causes an immediate increase in the intracranial pressure to the mean arterial pressure for several minutes. This leads to cerebral circulatory arrest that stops the hemorrhagic event [16]. Additionally, acute vasoconstriction occurs at this time, independent of intracranial pressure or cerebral perfusion pressure [17]. The combination of elevated intracranial pressure and acute vasoconstriction reduces cerebral perfusion pressure resulting in a diffuse cerebral ischemic event.

If the hemorrhage results in sustained severe intracranial hypertension, it can result in prolonged cerebral ischemia and immediate death of the patient, which is seen in 12% of aSAH cases [18]. More commonly however, bleeding from the aneurysm stops, intracranial pressure lowers, cerebral perfusion pressure increases and patients present for medical care in varying clinical conditions ranging from comatose to awake and neurologically intact.

Apoptosis is the most significant pathological process in EBI [19]. Park et al. found that experimental aSAH led to apoptosis in endothelial cells resulting in increased BBB permeability and increased cerebral water content. They also observed apoptosis in the hippocampal and cortical neurons [20]. In postmortem examination of aSAH patients, 80% of patients had apoptosis in the granule layer of the dentate gyri with the highest density of apoptotic cells seen at 2–11 days after ictus [21]. The extent of apoptosis has been shown to correlate with the duration of reduced cerebral blood flow in the animal model [22].

Hydrocephalus

Symptomatic hydrocephalus after aSAH occurs acutely in about 15% of aSAH patients [23]. The incidence of hydrocephalus tends to correlate with clinical grade in aSAH, where poorer grade patients have a higher incidence of hydrocephalus [24]. Hydrocephalus results in increased intracranial pressure, which reduces cerebral perfusion leading to cerebral ischemia. Cerebral perfusion was assessed by computed tomography (CT) in

139 consecutive aSAH patients with hydrocephalus by van Asch et al. Most of the reduction in blood flow occurred in the basal ganglia and periventricular areas while only slight reductions were seen in the cerebral cortex [25].

Schmidt et al. evaluated regional cerebral blood flow with positron emission tomography in six aSAH patients before and immediately after a release of 20 ml of cerebrospinal fluid (CSF) by lumbar puncture. Interestingly, the removal resulted in improved cerebral blood flow near the treated aneurysm and reduced cerebral blood flow away from the treated aneurysm. The observed changes in cerebral blood flow were described as 'spatial heterogeneity' and supported disturbances in autoregulation to be discussed later [26]. Due to elevated intracranial pressure from hydrocephalus, it is initially managed with temporary CSF diversion by ventricular or lumbar drain placement. Approximately 30% of patients requiring temporary CSF diversion will go on to require permanent CSF diversion with a ventricular shunt [10].

BBB dysfunction, loss of autoregulation, cerebral edema

The BBB becomes more permeable after aSAH. In an experimental aSAH model, BBB permeability increased significantly at 24–36 h peaking at 48 h [27]. BBB dysfunction is likely attributed to microvascular and basal lamina damage [28]. The loss of BBB integrity may continue for several weeks after aSAH [29].

Autoregulation has also shown disturbances in aSAH patients. Voldby et al. assessed autoregulation in 34 aSAH patients using Xenon-CT. They found that poor grade patients had dysfunctional autoregulation whereas good grade patients had intact autoregulation [30]. Patients with more disturbances in autoregulation have demonstrated more ischemic lesions at 1 year and worse neuropsychological testing [31].

Cerebral edema is often found after aSAH. This edema is from both vasogenic and cytogenic mechanisms. In an experimental aSAH model, cytotoxic edema was found in the distal middle cerebral artery territory within 2 min of hemorrhage [32]. Liu et al. used MRI to assess cerebral vasogenic edema in 100 aSAH patients at an average of 9 days after aSAH. Vasogenic edema was found through much of the cerebral white matter and deep gray matter with minimal cortical gray matter abnormalities [33].

Global cerebral edema is a distinct clinical phenomenon described by Claassen et al. It is seen in aSAH patients in 8% of admission CT scans and in another 12% of delayed CT scans. Global cerebral edema on admission is predicted by loss of consciousness at ictus and poor Hunt-Hess grade and is also an independent risk factor for poor outcome. Global cerebral edema after aSAH may be due to ischemic injury from decreased cerebral perfusion pressure, diffuse inflammation, neurotoxic effects of aSAH, impaired autoregulation and/or loss of BBB integrity [34]. Aquaporin overexpression after aSAH may also contribute to cerebral edema [35].

Endothelial cell and microvascular damage are likely the common mechanism underlying BBB dysfunction, loss of

cerebrovascular reactivity and cerebral edema after aSAH. Whether these mechanisms are causal for neurological damage or merely markers for other mechanisms is unclear. Future trials demonstrating improved clinical outcomes with apoptosis inhibitors, which preserve the BBB and reduce cerebral edema, may suggest a causal mechanism [36–38].

Mechanism of DCI
Macrovascular vasospasm & inflammation
At 3 days after aSAH, macrovascular vasospasm becomes the most significant cause of neurological morbidity [10]. On average, this phenomenon peaks at 7 days after aneurysm rupture [11]. Vasospasm is most severe with large amounts of hemorrhage [39]. Three-fourths of ischemic strokes after aSAH are attributed to vasospasm [12]. The presence of spasmogenic molecules (oxyhemoglobin, endothelin, calcium, prostaglandins, thromboxanes, leukotrienes, free radicals) or lack of vasodilatory molecules (nitric oxide [NO], magnesium) have been suggested as pathways for macrovascular vasospasm [40]. These molecular pathways eventually lead to vascular smooth muscle cell hyperplasia and contraction resulting in macrovascular vasospasm after aSAH. However, the administration of medications to resolve angiographic vasospasm does not always lead to the expected improvement in clinical outcomes (TABLE 1) [13].

Inflammation likely plays a significant role in the development of macrovascular vasospasm. The nadir of the inflammatory cytokines (IL-1β, IL-6, TNF-α) in the CSF and serum after aSAH occurs on SAH day 7, which also correlates with the peak severity of vasospasm [11,41]. The CSF levels of cytokines are much higher than control levels (e.g., IL-6 increased 10,000-fold) and increased levels of IL-6 correlate with poorer outcomes [41]. Leukocyte–endothelial interaction through cell adhesion molecules plays a significant role in vasospasm [42]. Leukocytes are recruited into the CSF by E-selectin, among other adhesion molecules, and this adhesion molecule has been found in much higher concentrations in the CSF of aSAH patients [43]. The inhibition of E-selectin with a monoclonal antibody demonstrated reduced macrovascular vasospasm in an animal aSAH model [44].

Microvascular vasoconstriction & microthombosis
Microvascular vasoconstriction and microthrombosis in cerebral arterioles likely contribute to neurological deficit after aSAH. In a mouse aSAH model, vasoconstriction is seen in 70% of arterioles with microthrombi present in 30% of arterioles [45]. Ulm et al. compared pial arterioles and venules of aSAH patients intra-operatively to patients with unruptured aneurysms undergoing clip ligation. In aSAH patients, they found vasoconstriction in 55% of arterioles versus only 13% of arterioles in patients without aSAH [46]. In post-mortem examination of 53 aSAH patients, Neil-Dwyer et al. described a diffuse microangiopathy with ischemic lesions in 77% of cortices and 50% of hypothalami [47]. Transcranial Doppler ultrasound shows microembolic signals (indicating microthrombosis) in 70% of aSAH patients and 32% of all vessels monitored in these patients [48]. Mechanisms for microvascular constriction and thrombosis include reduced vasodilators (namely NO) and increased P-selectin, which results in fibrin and platelet aggregation [49]. Ostergaard et al. proposed a multifactorial etiology of capillary flow disturbances including vasoconstriction by pericapillary oxyhemoglobin reducing NO, capillary wall damage and mechanical compression by cerebral edema [50].

Further evidence of the role of microthombosis in aSAH can be gleaned from trials investigating transexamic acid. Transexamic acid was historically used to prevent aneurysm rerupture by inducing a hypercoagulable state. Meta-analysis of all randomized controlled trials (RCTs) comparing transexamic acid to placebo found a reduction in rerupture rates with increased rates of infarction [51]. One of these trials also reported angiographic vasospasm. This trial found more DCI in the transexamic acid group (44 vs 22%) with the same incidence of vasospasm (24 vs 22%) [52]. This could be explained by an induced hypercoagulable state worsening microthrombosis and gives more evidence for microthrombosis playing a significant role in DCI.

Cortical spreading depolarization
CSD is a cerebral electrical phenomenon seen in many neurological disorders including ischemic stroke, traumatic brain injury, intracerebral hemorrhage and aSAH [53–55]. At the neuronal level, there is complete loss of the cellular ion gradient, complete depolarization and loss of electrical activity resulting in cytotoxic edema of neurons. The vascular response to a short CSD is vasodilation resulting in hyperemia. This hyperemic response is followed by vasoconstriction with a reduction in cerebral blood flow resulting in spreading oligemia [53]. In severe pathological states (e.g., poor-grade aSAH) with clusters of CSD lasting longer than 3 min, there is prolonged vasoconstriction resulting in spreading ischemia [56,57].

CSD and spreading ischemia after aSAH follow a similar time course as macrovascular vasospasm [58]. The Co-Operative Studies in Brain Injury Depolarizations group recorded 603 CSD in 12/13 aSAH patients. In five patients, clusters of CSD were found which were associated with vasoconstriction and consequently spreading ischemia [59]. Similar to vasospasm, endothelin-1 also induces CSD [60]. However, the pathological processes of CSD and vasospasm may not be completely linked. Confirming the separation of these two pathological processes, Woitzik et al. placed nicardipine pellets intracranially and had no angiographic vasospasm but found CSD in 10 of 13 patients [61]. Research into understanding the pathobiology of CSDs is a new frontier in neurocritical care and therapy to attenuate CSDs will be the subject of future clinical trials [62].

Current management of aSAH
CSF diversion & blood-clearing after aSAH
Acute symptomatic hydrocephalus is present in about 15% of aSAH patients [23]. The most efficacious method of CSF drainage after aSAH to reduce chronic hydrocephalus and vasospasm is debated. In a case–control series comparing lumbar drainage

Table 1. Literature review of all randomized, placebo-controlled trials of medications to prevent delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage patients with at least 30 patients and long-term outcomes (≥3 months).

Study (year)	Patients (n)	Treatment	Angiographic/ sonographic vasospasm	Symptomatic vasospasm/ DIND	Stroke (imaging)	Good neurological outcome	Ref.
Magnesium							
Bradford et al. (2013)	162	Magnesium	−	−		−	[89]
Dorhout Mees et al. (2012)	1204	Magnesium				−	[95]
Wong et al. (2010)	327	Magnesium	−	−		−	[87]
Westermaier et al. (2010)	110	Magnesium	↓	−	↓	−	[88]
Muroi et al. (2008)	58	Magnesium		−	−	−	[90]
Wong et al. (2006)	60	Magnesium		−		−	[91]
van den Bergh et al. (2005)	238	Magnesium		−	−	−	[92]
Boet et al. (2005)	45	Magnesium		−		−	[94]
Veyna et al. (2002)	36	Magnesium	−	−	−	−	[93]
Endothelin antagonist							
MacDonald et al. (2013)	577	Clazosentan		↓	↓	−	[15]
MacDonald (2011)	1157	Clazosentan	↓	↓	−	−	
MacDonald et al. (2008)	413	Clazosentan	↓	−	−	−	[85]
Vajkoczy et al. (2005)	66	Clazosentan	↓		−	−	[86]
Shaw (2000)	420	TAK-044			↓	−	[159]
HMG-CoA reductase inhibitors (statins)							
Kirkpatrick et al. (2014)	803	Simvastatin		−	−	−	[113]
Garg et al. (2013)	38	Simvastatin	−	−		−	[98]
Vergouwen et al. (2009)	32	Simvastatin	−	−		−	[99]
Chou et al. (2008)	39	Simvastatin	−	−	−	−	[100]
Tseng et al. (2007)	80	Pravastatin		↓		−	[102]
Tseng et al. (2005)	80	Pravastatin	↓	↓		−	[101]
Tirilazad							
Lanzino et al. (1999)	819	Tirilazad		↓	↓	−	[109]
Lanzino and Kassell (1999)	823	Tirilazad	−	−		−	[110]
Haley et al. (1997)	897	Tirilazad	−			−	[108]

↓: Decreased incidence in the treatment arm; ↑: Increased incidence in the treatment arm; −: No difference; DIND: Delayed ischemic neurological deficit; tPA: Tissue plasminogen activator.

Table 1. Literature review of all randomized, placebo-controlled trials of medications to prevent delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage patients with at least 30 patients and long-term outcomes (≥3 months) (cont.).

Study (year)	Patients (n)	Treatment	Angiographic/ sonographic vasospasm	Symptomatic vasospasm/ DIND	Stroke (imaging)	Good neurological outcome	Ref.
Tirilazad (cont.)							
Kassell et al. (1996)	1023	Tirilazad		−	−	↑	[107]
Haley et al. (1995)	245	Tirilazad		↓	−	−	[106]
Nicardipine							
Barth et al. (2007)	32	Nicardipine implants	↓		−	↑	[125]
Haley et al. (1993)	906	IV Nicardipine	↓	↓	−	−	[124]
Nimodipine							
Ohman et al. (1991)	213	IV Nimodipine				↑	[73]
Desbordes et al. (1989)	127	IV Nimodipine				↑	[74]
Pickard et al. (1989)	554	PO Nimodipine			↓	↑	[75]
Jan et al. (1988)	188	IV Nimodipine				↑	[76]
Petruk et al. (1988)	152	PO Nimodipine	−		↓	↑	[77]
Neil-Dwyer et al. (1987)	75	PO Nimodipine				↑	[78]
Philippon et al. (1986)	70	PO Nimodipine	−			−	[79]
Rho kinase inhibitors							
Yoneda et al. (2014)	162	Eicosapentaenoic acid		↓	↓	−	[117]
Shibuya et al. (1992)	276	Fasudil	↓		↓	↑	[116]
Neuroprotectives							
Munakata et al. (2009)	91	Edavarone		−		↑	[121]
Saito et al. (1998)	286	Ebselen		−	↓	↑	[118]
Asano et al. (1996)	162	AVS			↓	−	[119]
Thrombolytics							
Etminan et al. (2013)	60	Intraventricular tPA		−	−	−	[65]
Yamamoto et al. (2010)	40	Cisternal tPA			−	↑	[67]

↓: Decreased incidence in the treatment arm; ↑: Increased incidence in the treatment arm; −: No difference; DIND: Delayed ischemic neurological deficit; tPA: Tissue plasminogen activator.

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Table 1. Literature review of all randomized, placebo-controlled trials of medications to prevent delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage patients with at least 30 patients and long-term outcomes (≥3 months) (cont.).

Study (year)	Patients (n)	Treatment	Angiographic/ sonographic vasospasm	Symptomatic vasospasm/ DIND	Stroke (imaging)	Good neurological outcome	Ref.
Thrombolytics (cont.)							
Hamada (2000)	110	Intrathecal Urokinase	↓			↑	[66]
Findlay (1995)	100	Cisternal tPA	–	–		–	[68]
Erythropoietin							
Tseng et al. (2009)	80	Erythropoietin	–	↓	↓	↑	[145]
Springborg et al. (2007)	73	Erythropoietin	–	–	–	–	[144]
Anticoagulation							
Senbokuya et al. (2013)	109	Cilostazol	↓	↓	↓	–	[129]
van den Bergh et al. (2006)	161	Aspirin		–	–	–	[132]
Wurm et al. (2004)	120	Enoxaparin	↓	↓	↓	↑	[130]
Siironen et al. (2003)	170	Enoxaparin		–		–	[133]
Hop et al. (2000)	50	Aspirin		–	–	–	[131]
Suzuki et al. (1989)	285	Ozagrel	↓		↓	–	[135]
Shaw et al. (1985)	677	Dypiridamole				–	[134]
Ono et al. (1984)	133	Ticlopidine	–	↓		↑	[136]
Anti-inflammatory							
Gomis et al. (2010)	95	Methylprednisolone		–	–	–	[123]

↓: Decreased incidence in the treatment arm; ↑: Increased incidence in the treatment arm; –: No difference; DIND: Delayed ischemic neurological deficit; tPA: Tissue plasminogen activator.

to ventricular drainage, patients with lumbar drains had significant reductions of symptomatic vasospasm (17 vs 51%), DCI (7 vs 27%) and poor outcome (Glasgow Outcome Scale 1–3, 29 vs 65%) [63]. Shunting was equivalent in both treatments. The major confounders in the series are the retrospective nature of the review and that the ventricular drain arm also included patients with no CSF diversion. Results from a recently completed RCT of lumbar drainage versus external ventricular drainage are forthcoming [64].

Active clearing of blood from the subarachnoid space has been attempted after aSAH to prevent vasospasm and chronic hydrocephalus [65–68]. Blood clearing is done by instilling a thrombolytic into the lumbar or basal cisterns. A meta-analysis of five studies found a significant reduction in angiographic vasospasm, DCI, poor outcome and chronic hydrocephalus with intrathecal thrombolytics [69]. Conversely, a more recent

RCT reported no improvement of outcomes with intraventricular administration of tissue plasminogen activator and low-frequency head rotation [65]. It is currently not the standard of care to actively clear blood from the subarachnoid space after aSAH [70].

Prevention & management of DCI

The current standard of care for prevention of DCI only includes maintenance of euvolemia with prophylactic oral nimodipine [70]. Nimodipine is a dihydropyridine calcium channel blocker that improves outcome after aSAH without improvement in angiographic vasospasm. However, this agent also increases fibrinolytic activity and has been shown to inhibit CSD in the rat model [71,72]. Either of these mechanisms could explain nimodipine's efficacy. Nimodipine is the only well-validated medication for prevention of DCI with six of seven

RCTs demonstrating improved outcomes (TABLE 1) [73–79]. As a result of this overwhelming evidence, nimodipine is the only class I, level A recommendation in the current SAH treatment guidelines [70].

Hemodynamic & endovascular management of DCI after aSAH

Hyperdynamic, hypertensive, hemodilutional (HHH) therapy has been a mainstay of vasospasm management since the 1980s. Often hypervolemia is instituted by administering intravenous crystalloid or colloid solutions. However, a Cochrane review indicates hypervolemia has little benefit of preventing DCI in aSAH [80]. In fact, hypertension is likely the only component of HHH therapy that increases CBF [81]. There has been a trend away from traditional HHH therapy toward only maintaining euvolemia with augmentation of hypertension if DCI is diagnosed. The current aSAH guidelines recommend induction of hypertension for patients with DCI unless already hypertensive or a precluding cardiac status exists (class I, level B) [70]. The Hypertension Induction in the Management of AneurysmaL subArachnod haemorrhage with secondary IschemiA trial will further evaluate hypertensive therapy in aSAH patients by randomizing aSAH patients with DCI to receive hypertensive augmentation or not receive any hypertensive augmentation [82].

Many case series have reported the efficacy of endovascular therapy with symptomatic vasospasm [83]. There has not been an RCT of this treatment compared with medical management alone. However, an RCT evaluating the prophylactic use of balloon angioplasty has been studied. Zwienenberg-Lee *et al.* randomized patients to receive prophylactic balloon angioplasty within 96 h of aSAH versus standard medical therapy with therapeutic balloon angioplasty if medical management failed. They found a small non-statistically significant reduction in DCI and non-statistically significant reduction in poor outcome [84]. The use of endovascular therapy, including intra-arterial vasodilators and balloon angioplasty, is recommended at class IIa, level B, if hypertensive therapy is not improving the clinical status rapidly [70].

Failed therapy for prevention of DCI

Four agents (clazosentan, magnesium, statins and tirilazad) for the prevention of DCI had much enthusiasm surrounding their potential but definitively failed to show efficacy in large RCTs. Clazosentan is an endothelin receptor antagonist that drastically reduces angiographic vasospasm [85,86]. Despite this angiographic reduction in vasospasm, clazosentan did not lead to improved clinical outcomes in the CONSCIOUS trials [14,15]. Magnesium sulfate had drawn interest to reduce vasospasm through vasodilatory effects. Eight small RCTs failed to show efficacy of magnesium in aSAH and most recently a large Phase III RCT (MASH-2) with 1204 patients failed to show improved outcomes at 6 months (poor outcomes; magnesium sulfate = 26.2% vs placebo = 25%) [87–95].

Inhibitors of HMG-CoA reductase (statins) have positive pleiotropic effects on cerebral vasculature by upregulation of endothelial nitric oxide synthase [96,97]. Several small RCTs failed to demonstrate efficacy of statins in aSAH [98–102]. Recently, results from a large RCT called Simvastatin Treatment for Aneurysmal Subarachnoid Hemorrhage (STASH) trial with 803 patients have been reported. This trial found no reduction in stroke, no reduction in symptomatic vasospasm and no improvement in outcome [103].

Upon conversion of oxyhemoglobin to methemoglobin, superoxide radicals are released which convert to hydroxyl radicals. This increased oxidative environment leads to lipid peroxidation, which may be deleterious in aSAH patients [104]. Tirilazad is a non-glucocorticoid aminosteroid that blocks lipid peroxidation. This medication has failed to show efficacy as a neuroprotective agent in spinal cord injury, traumatic brain injury and ischemic stroke [105]. Five large RCTs have evaluated tirilazad in aSAH [106–110]. Only the study by Kassell *et al.* showed improved clinical outcomes and this was seen predominantly in men for unclear reasons [107]. A meta-analysis of these five RCTs showed less DCI with no difference in clinical outcome in patients treated with tirilazad [111]. Further study of clazosentan, magnesium, statins or tirilazad in aSAH patients is not warranted, given the conclusive results of these negative trials.

Promising therapy requiring further validation

Several medications have been found to be efficacious in small or single-center studies and require further validation in large multicenter RCT before entering treatment guidelines. Fasudil is a Rho kinase inhibitor that prevents the effects of extracellular calcium on smooth muscle contraction, reduces smooth muscle hypertrophy and suppresses expression of cell adhesion molecules, thus attenuating inflammation by reducing endothelial–leukocyte interaction [40,112–115]. In an RCT of 267 patients, fasudil reduced angiographic vasospasm, symptomatic vasospasm, low-density regions on head CT and improved clinical outcome [116]. Like fasudil, eicosapentaenoic acid also inhibits Rho kinase. Eicosapentaenoic acid was evaluated in an RCT of 162 patients. This trial showed a statistically significant reduction in angiographic vasospasm (7 vs 21%; p = 0.012), symptomatic vasospasm (15 vs 30%; p = 0.022) with no improvement in outcomes (good outcomes at 6 months, 88 vs 85%; p = 0.65) [117]. Larger multicenter placebo-controlled trials are warranted to evaluate Rho kinase inhibitors in aSAH patients.

Medications targeting oxidative end products have shown some promise. An inhibitor of lipid peroxidation, ebselen, has been evaluated in a multicenter RCT (n = 286). This trial found decreased low-density regions on head CT and improved Glasgow Outcome Scale at 3 months [118]. AVS ((±)-*N,N*-propylenedinicotinamide; nicaraven) is a hydroxyl radical scavenger. In a multicenter RCT, 162 patients were randomized to receive AVS or glucose intravenously. Outcomes showed a non-significant improvement at 3 months with a statistical improvement in cumulative death rate in the AVS arm [119]. Edaravone is a free radical scavenger that has shown improved outcome in ischemic strokes [120]. In a single-center RCT of

aSAH patients, edavarone demonstrated less DCI and better outcomes at 3 months [121]. Larger multicenter trials are needed to determine the efficacy of medications targeting oxidative end products in aSAH patients.

Steroids are the only immune-suppressing agents that have been used to target inflammatory pathways for preventing vasospasm and/or DCI after aSAH. One study randomized 140 patients to receive hydrocortisone or placebo after aSAH. They noted improvement in short-term neurological outcomes in the treatment arm [122]. More recently, Gomis et al. randomized patients to receive methylprednisolone after aSAH and showed improved functional outcomes at 1 year with a non-significant improvement in clinical outcome [123]. Given the negative side effects of steroids, more controlled studies would need to show efficacy before this therapy would be recommended.

Intravenous nicardipine was studied in an RCT showing improvement in angiographic vasospasm and reducing symptomatic vasospasm without a significant improvement in clinical outcome [124]. The placement of nicardipine pellets into the basal cisterns during surgical clipping has shown promising results in a small single-center RCT (n = 32). Drastic improvements were noted in proximal vessel vasospasm (7 vs 73%), ischemic lesions of head CT (14 vs 47%) and death (6 vs 38%) [125]. Placement of nicardipine pellets through ventricular drains, which may allow their use in patients receiving endovascular treatment for ruptured aneurysms, has been evaluated in a small feasibility study with positive results [126]. Vehicles for direct intracranial delivery of drugs avoid systemic side effects of these medications and will likely be involved in future clinical trials [127,128].

Antiplatelet therapy and anticoagulants have been evaluated in the aSAH population [129–136]. Cilostazol has antiplatelet properties in addition to anti-inflammatory and vasodilatory attributes [137]. A meta-analysis including four small Japanese RCTs/quasi-RCTs on cilostazol in aSAH showed reduced vasospasm, reduced infarctions and better outcomes in the cilostazol-treated patients [138]. A meta-analysis looked at seven RCTs of other antiplatelet therapies in aSAH (including aspirin, ticlopidine, dipyridamole and ozagrel) and found a strong trend toward better outcomes that was not statistically significant [139].

Anticoagulants have been evaluated in aSAH patients with inconclusive results. Low-dose intravenous heparin after aSAH has been evaluated in a retrospective case–control study. A 14-day low-dose continuous heparin infusion in aSAH patients showed drastically reduced DCI compared with patients without anticoagulation (21 vs 0%; p = 0.003, respectively) [140]. Two RCTs of enoxaparin at differing doses have been conducted in aSAH with conflicting results. Enoxaparin 40 mg daily resulted in slightly more intracranial hemorrhages in the enoxaparin group with no change in rate of stroke or neurological outcome at 3 months compared with placebo [133]. Enoxaparin 20 mg daily resulted in less DCI, less strokes due to vasospasm and improved outcomes at 1 year in the enoxaparin arm versus placebo with no difference in hemorrhagic

complications [130]. It would seem from these data that low-dose anticoagulation may offer benefit for aSAH patients, whereas high-dose anticoagulation negates the benefit due to intracranial hemorrhages. Further clinical studies are warranted to evaluate antiplatelet medications and low-dose anticoagulation in aSAH patients.

Erythropoietin is a hormone produced in the kidney that increases hematocrit and has pleiotropic effects. Additionally, erythropoietin is present in CSF and CNS receptors for erythropoietin have been identified. This finding creates the possibility for erythropoietin to have neurotrophic or neuroprotective effects in addition to its hemodynamic effect [141]. Erythropoietin has been found to decrease vasospasm in an animal model and increase cerebral oxygenation in a small cohort of aSAH patients [142,143]. However, a small RCT (n = 54) of aSAH patients found no difference in cerebral metabolism by microdialysis or in neurological outcome at 6 months [144]. Another small RCT of erythropoietin found less severe vasospasm, less DCI and less impairment of autoregulation in the erythropoietin arm, with no difference in strokes or neurological outcome at 6 months [145]. The initial results with erythropoietin have not been very encouraging but more study in larger trials is warranted before this agent should be dismissed.

Expert commentary

The clinical sequelae of aSAH continue to devastate many patients with only small improvements in outcomes made over several decades of managing these patients. As TABLE 1 reveals, there have been many more failures than successes. Even the mechanism of action leading to therapeutic benefit in the only successful agent, nimodipine, is not certain. Future investigations into pathobiology of aSAH must 'look outside the box' for different approaches to achieve meaningful results.

Five-year view

Many agents will soon be investigated in aSAH patients to prevent DCI. Prostacyclin is a vasodilator that also inhibits platelet function. Both of these properties make it ideal for prevention of DCI and an early clinical trial is underway [146]. Sodium nitrite acts as a reservoir of NO, a potent vasodilator. NO is depleted after aSAH and the systemic administration of sodium nitrite is thought to increase the local availability of NO [147]. A trial is currently enrolling patients to evaluate the efficacy of sodium nitrite in aSAH [148]. A novel method of vasodilation through blockade of the cervical sympathetic chain with clonidine and bupivacaine is being investigated in a small pilot study [149]. The use of hypercapnia to induce cerebral vasodilation during the vasospasm period and thus improve cerebral oxygenation has been evaluated in a small Phase I feasibility study with results pending [150].

In a large retrospective analysis of the effect of multiple sedatives and analgesics in patients with traumatic brain injury, stroke and aSAH, ketamine was associated with a reduction in CSD [62]. Ketamine is an NMDA antagonist. Whether the reduction of CSD would improve clinical outcomes in an

aSAH population is unknown. The observed reductions in CSDs in patients receiving ketamine will likely serve as the basis for a prospective trial suppressing CSDs with ketamine.

Remote ischemic preconditioning is a therapy that involves making a limb ischemic by tourniquet for several minutes. This therapy has been shown to prolong coagulation times in aSAH patients [151]. This may improve outcomes by prevention of microthrombosis and an RCT is currently evaluating remote ischemic preconditioning in aSAH patients [152].

Rosiglitazone is PPAR agonist. Rosiglitazone has recently been shown to increase the expression of caveolin-1, a membrane protein, which reduces vascular smooth muscle cell proliferation and vasospasm in an experimental SAH model [153]. This agent will likely be introduced into small clinical trials in the near future. PDGF has been demonstrated to induce vasospasm in a rabbit model. Trapidil and imatinib, both inhibitors of PDGF, have prevented vasospasm and attenuated vascular smooth muscle cell proliferation in animal models and may be evaluated in clinical trials in the future [154–156]. Given the efficacy of intracisternal nicardipine pellets in preventing DCI, small feasibility studies are also evaluating intracisternal nimodipine [157,158].

Inhibition of apoptosis has shown promise in experimental models. A p53 inhibitor, pifithrin-α, inhibits endothelial cell apoptosis and vascular smooth muscle cell proliferation [36]. A pan-caspase inhibitor has demonstrated reduced BBB permeability and brain water content [20]. c-Jun N-terminal kinase inhibition has been shown to suppress aquaporin-1, matrix metalloproteinase-9, VEGF and caspase-3 activation with reduction in brain swelling, BBB preservation, reduction in neural injury and improved overall neurological outcomes [37]. Many other apoptotic pathways have been inhibited in experimental models with decreased brain edema and improved neurological outcomes [38]. Apoptosis inhibition in aSAH clinical trials has not been performed.

In addition to large vessel vasodilation, future targets for prevention of DCI after aSAH will focus on antiplatelet or low-dose anticoagulation therapy for microthrombosis, suppression of CSDs, neutralization of free radicals, apoptosis inhibition and attenuation of inflammatory pathways.

Financial & competing interests disclosure

Key issues

- After the initial aneurysm hemorrhage, multiple pathological mechanisms account for neuronal injury including: hydrocephalus, apoptosis, cerebral edema, loss of blood–brain barrier, abnormal cerebral autoregulation, microthrombosis, cortical spreading depression and vasospasm.
- Current treatment of delayed cerebral ischemia (DCI) involves nimodipine, maintenance of euvolemia, induced hypertension for symptomatic DCI and possible endovascular treatment for patients with DCI symptoms refractory to induced hypertension.
- Cortical spreading depolarization is the latest mechanisms targeted for in DCI after aneurysmal subarachnoid hemorrhage and future trials will use ketamine to suppress cortical spreading depolarizations.
- Other future therapy for DCI will include agents to block apoptotic pathways, agents to prevent smooth muscle cell contraction and proliferation and low-dose anticoagulation to prevent microthrombosis.

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