Neuroprotection in Subarachnoid Hemorrhage

Daniel T. Laskowitz, MD, MHS; Brad J. Kolls, MD, PhD

Abstract—Despite advances in aneurysm ablation and the initial management of patients presenting with aneurysmal subarachnoid hemorrhage, delayed cerebral ischemia remains a significant source of morbidity. Traditionally, delayed cerebral ischemia was thought to be a result of vasospasm of the proximal intracranial vessels, and clinical trials have relied largely on radiographic evidence of vasospasm as a surrogate for functional outcome. However, a number of trials have demonstrated a dissociation between angiographic vasospasm and outcome, and more recent data suggest that other mechanisms of injury, such as microvascular dysfunction and complex neuronal-glial interactions, may influence the development of delayed ischemic deficit after aneurysmal subarachnoid hemorrhage. Our evolving understanding of the pathophysiology of delayed cerebral ischemia may offer the opportunity to test new therapeutic strategies in this area and improve clinical trial design. (Stroke. 2010;41[suppl 1]:S79-S84.)

Key Words: subarachnoid hemorrhage ■ delayed cerebral ischemia ■ vasospasm ■ spreading depression

Although aneurysmal subarachnoid hemorrhage (aSAH) accounts for <5% of all strokes, it represents a disproportionate source of morbidity and mortality, as afflicted individuals tend to be younger and often have worse outcomes than do those with ischemic stroke.1-4 A significant proportion of the mortality associated with aSAH occurs soon after the ictus, and in recent years, considerable advances have been made in the initial diagnosis and management of ruptured aneurysms, which have resulted in improved survival in hospitalized patients.5 For example, noninvasive imaging techniques such as magnetic resonance and computed tomography angiography have become increasingly sensitive at detecting aneurysms in the cerebral vasculature. Rebleeding is associated with an extremely high mortality, and current practice at most institutions is in favor of early aneurysm ablation, which is consistent with the results of a large trial on the timing of aneurysm surgery.2 Endovascular techniques have also advanced rapidly and become widely adopted, facilitating the early ablation of aneurysms in patients who might otherwise have been considered poor operative risks. Despite these advances, patients remain at considerable risk for neurologic and medical complications after aneurysm ablation. In particular, subacute neurologic deterioration due to delayed cerebral ischemia (DCI) remains one of the most feared complications associated with neurologic morbidity. Traditionally, DCI was believed to be primarily due to vasospasm of the proximal cerebral vasculature, and luminal narrowing on conventional angiography may be present in up to two thirds of patients.6 Although smooth muscle contraction may play an important role in contributing to luminal narrowing, the term “vasospasm” itself may be an oversimplification, as preclinical and clinical studies have suggested morphological changes in the vasculature, including smooth muscle and endothelial proliferation.7-9

Because vascular changes and luminal narrowing may be dramatic on angiography, it would seem intuitive that vasospasm is the cause of DCI, and in fact, these terms have been used interchangeably in the older literature. However, it is worth noting that an imperfect correlation exists between angiographic vasospasm and DCI.10 For example, only a subset of patients with angiographic vasospasm will manifest clinical symptoms of delayed ischemic deficit, and of these patients, not all will have clinical symptoms referable to the involved vascular distribution.11 Similarly, although up to half of patients with delayed ischemic deficits will develop cerebral infarction, the area of infarct often is not correlated with the territory of angiographic vasospasm and may appear pathologically as scattered, laminar, cortical and subcortical infarcts rather than large-vessel stroke.12-14 Moreover, not all clinically symptomatic patients will have angiographic evidence of vasospasm; this is presumably due to the involvement of smaller vessels that are not adequately imaged. Thus, although angiographic vasospasm is certainly correlated and likely contributes to DCI, infarct, and poor outcome, an argument may be made that it is as much a marker for a more diffuse microvascular disease than it is the proximal cause of all delayed ischemia.12

Rethinking Angiographic Vasospasm as a Primary Outcome for Therapeutic Trials

Despite a number of clinical trials, little progress has been made either in the pharmacologic prophylaxis or treatment of DCI or in improving long-term functional outcomes associated with this complication (Table). At present, the only pharmacologic treatment that has been demonstrated to mod-
estly improve outcome after aSAH is nimodipine, a dihydropyridine-type calcium channel blocker. Although the original rationale for the use of nimodipine was to reduce vasospasm by blocking calcium influx into vascular smooth muscle, there was no clear effect on angiographic vasospasm despite improvement in functional outcome. Thus, its mechanism of action remains controversial, and may be, in part, to direct neuroprotective effects. Interestingly, nicardipine, a calcium channel blocker with a similar mechanism of action, demonstrated improvement in angiographic vasospasm but did not demonstrate improvements in functional outcome. Nonetheless, at many institutions, the transient improvement in radiographic vasospasm guides the use of intra-arterial administration of nicardipine and other smooth muscle relaxants, despite the lack of evidence that this strategy improves long-term outcomes.

Although the majority of therapeutic trials have tested interventions designed to directly target the cerebral vasculature to reduce vasospasm, several neuroprotective strategies have also been tested. In general, these studies have also demonstrated a dissociation between angiographic vasospasm and functional outcomes. For example, a recent meta-analysis of tirilazad, a nonglucocorticoid 21-aminosteroid designed to reduce lipid peroxidation, demonstrated a reduction in vasospasm but no improvement in clinical outcomes as assessed by the Glasgow Outcome Score. In addition to its vasoactive properties, magnesium also has several potentially protective mechanisms of action after aSAH, including blockade of the N-methyl-D-aspartate–glutamate receptor and voltage-dependent calcium channels; however, clinical trials have remained inconclusive.

More recently, therapeutic trials have targeted endothelin, an endogenous mediator of vasoconstriction that is believed to play an important role in vasospasm. Based on early clinical work suggesting that clazosentan, an endothelin receptor A antagonist, reduced angiographic vasospasm, a larger, phase IIb study (CONSCIOUS-1) was initiated. The CONSCIOUS 1 trial confirmed that clazosentan improved the primary end point of angiographic vasospasm in a dose-dependent fashion. However, once again, despite an improvement in this angiographic end point, there was no associated improvement in functional outcomes.

Thus, a dissociation between proximal vascular changes identified by angiography and improvement in functional outcomes has been demonstrated in a number of clinical and therapeutic trials.
preclinical studies. Clearly, a surrogate end point that is mechanistically related to DCI and predictive of outcome is appealing for early clinical trials and would address the prohibitively large sample sizes that would be necessary if functionally relevant end points were used. However, the poor track record of angiographic vasospasm might call into question its appropriateness as a primary surrogate end point predictive of functional outcome.

Other Causes of Treatable Injury Amenable to Targeted Treatment

In addition to the vascular changes associated with DCI, there are a number of other mechanisms of brain injury after aSAH that might be amenable to specific therapeutic interventions. For example, aneurysmal rupture is associated with acute brain injury owing to mechanical compression of brain tissue and secondary ischemia due to the hypoperfusion associated with increased intracranial pressures. These early destructive events may be mitigated by early management of intracranial hypertension and administration of therapies designed to interrupt the ischemic cascade of excitotoxicity and neuronal calcium influx. Although conventional angiographic techniques have focused on the proximal cerebral vessels, there is increasing evidence of microvascular dysfunction, which is suggested by the pattern of infarcts observed in some cases. Endothelial dysfunction, platelet aggregation, microthrombosis, and microembolization have been described and suggested as a possible basis for DCI. Although microembolization has been postulated as a mechanism of injury, trials of antplatelet and anticoagulant therapies such as aspirin and enoxaparin have met with limited success.

One of the interesting mechanisms of delayed cerebral injury that has gained increasing attention is cortical spreading depression (CSD). CSD refers to a wave of mass neuronal depolarization and has been described in a variety of acute brain injury paradigms. The normal physiologic vascular response in the setting of CSD is vasodilation and hyperemia (Figure). However, in the setting of brain injuries such as SAH, a paradoxical vasoconstriction may be observed. This process, termed cortical spreading ischemia (CSI), is believed to be the result of inverse coupling between neuronal and astroglial interaction with cerebral blood flow. Although the exact mechanisms have not been fully defined, experimental evidence suggests that endothelin-1, which is upregulated after SAH, is a potent inducer of CSD and reduces Na+/K+ ATPase activity. In situations of decreased nitric oxide, such as may occur in the presence of oxyhemoglobin, the normal physiologic vasodilation is converted to vasoconstriction, which may exacerbate secondary neuronal injury in vulnerable areas of the brain. There are several observations that suggest that CSI may be a clinically relevant phenomena after aSAH. For example, CSI has been demonstrated to produce laminar cortical infarcts similar to those seen in autopsy studies of patients with DCI. Moreover, recent clinical observations have confirmed episodes of CSI in patients with SAH on electrocorticography and perfusion monitoring. In many instances, these observed depolarization and perfusion changes were associated with a clinical worsening characteristic of DCI. Interestingly, although CSD may not be considered a primary vascular event, calcium channel blockers, such as nimodipine, have been demonstrated to partially block CSI and reinstate a more physiologic hyperemic response. However, these effects may occur in

Figure. After SAH, mediators of inflammation, including endothelin, may initiate mass neuronal depolarization. In the presence of decreased availability of nitric oxide (NO), an inverse coupling between neuronal and astroglial interaction with cerebral blood flow may result in spreading ischemia. TNF indicates tumor necrosis factor; IL, interleukin.
smaller vessels, and thus, resolution of angiographic vasospasm may not be the most appropriate surrogate.

Clinical Implications
A more complete understanding of the mechanisms that contribute to DCI may have direct therapeutic and clinical research implications. For example, in addition to vasoactive therapies that target vasospasm, novel strategies that target neuronal and glial function may also hold promise. A recent report has demonstrated that administration of leviteracetam, an anticonvulsant that targets a presynaptic neuronal vesicular protein, reduces vasospasm and histologic injury and improves functional outcomes in a murine model of SAH.51 Similarly, a therapeutic peptide derived from the apolipoprotein E protein, which modulates glial activation and reduces glutamate excitotoxicity, has also demonstrated promise in murine SAH models.27,52 Although traditional neuroprotective strategies that target glutamate excitotoxicity and oxidative stress have been difficult to translate into clinical trials of acute stroke, they may have potential in reducing DCI, as the drug can be started before the onset of ischemic symptoms in a tightly controlled setting.

In addition to suggesting new therapeutic targets, an increased understanding of the pathophysiology of DCI may also have implications for postoperative management strategies in the care of at-risk patients. Understanding the real-time effects of therapeutic interventions such as manipulating hemodynamics or oxygenation is facilitated by the fact that multimodal monitoring, including parenchymal oximetry, is now widely available at many institutions. For example, in experimental models, hyperoxia may reduce CSD, and a recent clinical study has demonstrated that clusters of CSD are associated with local tissue hypoxia.42 This demonstrates the importance of monitoring and optimizing tissue oxygen pressures through hemodynamic control and ventilator management. Similarly, although hyperglycemia has been associated with poor outcome after SAH,53 recent prospective trials of tight glucose control in aSAH have been mixed.54,55 Hyperglycemia may in fact attenuate CSD,56 and overly aggressive glycontrol increases the risk for episodes of hypoglycemia that might exacerbate tissue injury.57

Given the seemingly obvious causal relation between vascular changes observed on angiography and DCI, most therapeutic trials have relied on angiographic surrogates of vasospasm. As noted earlier, however, the majority of clinical trials have demonstrated a dissociation between angiographic vasospasm and functional outcome. A more complete understanding of the role that microvascular dysfunction and CSI play in contributing to secondary neurologic deterioration would also suggest the importance of incorporating more global measures of diffuse brain injury and neurocognitive dysfunction into clinical trials58,59 rather than focusing primarily on proximal vasospasm and large-vessel stroke.

Role of Neuroprotectants in SAH: Broader Implications for Stroke
Ultimately, the testing of neuroprotectant strategies in the setting of SAH may have broad implications for trials of acute stroke and cerebrovascular disease. Traditionally, stroke trials have been difficult to perform for a number of reasons,60 including initiating therapy soon enough after symptom onset for a neuroprotective agent to be effective. The historical failure of stroke neuroprotection trials, coupled with the expense and logistic difficulties associated with these trials, has led to an unfortunate reduction in enthusiasm for acute stroke research. However, patients with aSAH in the neurocritical care unit may offer a number of advantages for early trials in cerebrovascular disease. Aneurysmal SAH is one of the few situations in which cerebral ischemia occurs in a reproducible and delayed time frame, allowing patients to be enrolled and the drug started before the onset of ischemia. Moreover, unlike most acute stroke trials, aSAH trials take place in a controlled setting, and trials can be enriched for patients likely to experience DCI by selecting those with a large subarachnoid clot burden. Thus, testing for neuroprotection in aSAH may ultimately be an ideal way to provide proof-of-concept data before testing an agent for neuroprotection in acute ischemic stroke.

Disclosures
D.T.L. serves as a consultant for NeurOp, Inc and Cognosci, Inc.

References


Neuroprotection in Subarachnoid Hemorrhage
Daniel T. Laskowitz and Brad J. Kolls

Stroke. 2010;41:S79-S84
doi: 10.1161/STROKEAHA.110.595090
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/10_suppl_1/S79

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/