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Delayed Cerebral Ischemia: Is Prevention Better Than Treatment?

"An ounce of prevention is worth a pound of cure."
—Benjamin Franklin, 1736

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating subtype of stroke affecting up to 30,000 individuals annually in the United States.[1] Despite significant advances in diagnosis and treatment, aSAH is associated with an up to 50% mortality rate and permanent disability in 30% to 50% of survivors.[1,2] Whenever patients survive the ictus of the aneurysm rupture, they are at risk of rebleeding and delayed cerebral ischemia (DCI). Although historically common, aneurysmal rerupture is no longer the major cause of delayed death and disability due to adoption of early securing of the aneurysms. In contrast, DCI remains the most common cause of late major morbidity after aSAH. It can result in prolonged periods of intensive care and rehabilitation, and admission to long-term care facilities, at a significantly increased physical, social, and financial cost to individuals, families, and health care systems.[1,2]

In the mid-1980s, several groups studied the outcomes of early surgery (0 to 3 d) and compared them to delayed intervention (>4 to 7 d) after aSAH; these studies reported significantly improved outcomes when aSAH patients were treated early.[3] Spetzler et al[4] later reported greater outcome improvements when patients underwent early coiling rather than open surgery, especially when it involved the posterior cerebral circulation. That approach represented a radical departure from the traditional management of aSAH, which often required prolonged intensive care unit admission to determine fitness for surgery. Now is the time also to change our approach to DCI. We need to establish better animal models and risk stratification to determine which aSAH patients are at risk for DCI. Only then can we decrease DCI incidence and reach a new milestone to fill this unmet need.[5]

DCI must be considered when the Glasgow Coma Scale decreases by 2 points for 1 hour, or tissue perfusion worsens ~4 to 14 days after the initial hemorrhage. Any decrease in level of consciousness must be distinguished from an acute ischemic event and other causes of neurological deterioration. Although the etiology of DCI remains largely unknown, it is likely multifactorial and is possibly related to large vessel vasospasm, microspasm (arteriolar), inflammation, metabolic disturbances, microthrombus and cortical spreading depolarizations with their paradoxical vasoconstriction.[2] Although radiographic vasospasm occurs in about 70% of patients with aSAH, only 30% ultimately develop DCI which may not involve the same vascular territory as the spasm itself.[2] To date, there is no reliable method to predict the occurrence of DCI.

The strategic goal in the management of DCI is preservation of cerebral perfusion. This can be achieved via pharmacologic treatments, hemodynamic manipulations and endovascular therapies. The only evidence-based strategy available for the prevention of DCI remains nimodipine, which prevents and possibly reverses arteriolar vasospasm or microspasm but has no effect on radiographic or large vessel vasospasm.[6] It has a cytoprotective effect the mechanism of which is poorly understood. Nimodipine is standard of care in all patients with aSAH as it prolongs survival and improves neurological outcomes. However, nimodipine does not prevent the occurrence of DCI completely.[6]

Hypervolemia, hypertension and hemodilution (triple H therapy) previously used for aSAH patients without radiographic vasospasm led to the development of various complications including cerebral edema, ischemic infarcts, and cardiopulmonary complications.[7] This approach has since been refined to euvolemic hypertension in an effort to decrease the rate of complications.[8] Endovascular strategies have been utilized for symptomatic radiographic spasm and have included intra-arterial (IA) vasodilators, balloon angioplasty, and deployment of various intracranial stents. Subarachnoid and ventricular blood evacuation during open aneurysm clipping was shown to be effective at preventing vasospasm since it decreased the amount of oxyhemoglobin around large intracranial vessels, which has been implicated in inciting vasospasm since it acts as a nitric oxide sink.[2]

There are other strategies that have a slightly less clear therapeutic value. Statins have low quality evidence of benefit. It is recommended to continue statins if the patient is already receiving them but not to initiate them in statin-naive patients.[2] Tranexamic acid is somewhat effective in the prevention of rebleeding early after aSAH but does not have a clear benefit in preventing DCI.[2] Low-dose intravenous high–molecular-weight heparin reduces DCI by half compared with subcutaneous heparin at similar dosages.[9] It also reduces delayed cognitive deficits that are frequently associated with aSAH; this is thought to be related to greater bioavailability and potential anti-inflammatory activity in addition to the anticoagulant effect of the intravenous heparin.[9] White blood cell counts and neutrophil to lymphocyte ratios may be predictive for the development of DCI, and early neutrophil depletion shows promise for preventing DCI in a mouse SAH model.[2] There are also many more pharmacologic and biological strategies currently under investigation.

Milrinone has been identified as a promising therapeutic agent for DCI and, in this issue of JNA, Bernier et al[10] review milrinone DCI treatment studies. Milrinone is a phosphodiesterase III inhibitor that increases cAMP, improves cardiac lusitropy and contractility and thus perfusion; it also increases cGMP and incites vasodilation. Milrinone does not have any known direct neuronal effects. The protocols in the studies reviewed by Bernier et al[10] included IA, intravenous (IV) or

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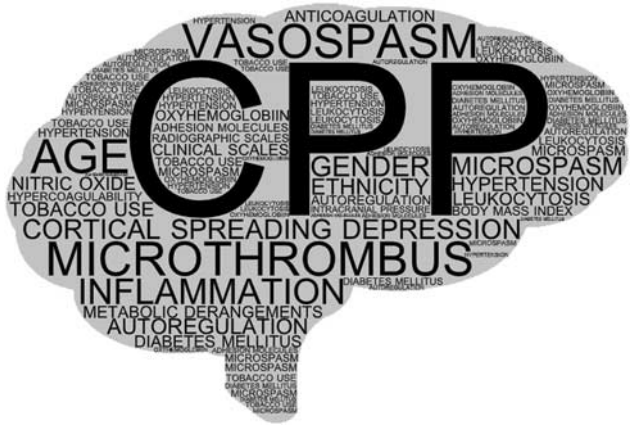

FIGURE 1. Selected factors to consider for risk stratification for compromised cerebral perfusion pressure and subsequent delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. CPP indicates cerebral perfusion pressure.

both IA and IV administration of milrinone with widely variable dosing regimens. Hypotension requiring pressor therapy was the main complication reported. Bernier et al[10] conclude that the available evidence suggests that IA and IV milrinone are safe and effective treatments for DCI and associated with improved long-term functional outcomes. However, studies to date are limited to retrospective case series and single-center cohorts. Bernier et al[10] propose a multicenter randomized study with uniform protocols involving escalating doses of IV and IA milrinone to treat DCI, with primary clinical neurological and safety outcomes. Since early aggressive therapy of DCI is promising, consideration should also be given to adding a preventive aspect to the proposal. We challenge the readership of JNA to tackle the milrinone project proposed by Bernier and colleagues.

There has been little or no change in long-term neurological outcomes after aSAH since early aneurysm occlusion was introduced in the 1980s. We now need to dramatically change the way we approach aSAH—to identify predictors of DCI utilizing neuroinformatics and large data studies.[11] This could allow for analysis of many potential risk factors, including multimodal neuromonitoring, clinical, laboratory, and radiographic findings, to identify actionable sets of derangements before DCI occurs in order, ultimately, to avoid secondary brain injury (Fig. 1). In individuals with positive predictors of DCI, preventive therapies should be promptly initiated. If DCI occurrence is prevented in the first place, then improved neurological outcomes will follow.

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Twitter Journal Clubs in Perioperative Neuroscience: Opportunities and Challenges

Journal clubs have been a pillar of medical knowledge dissemination and scientific evaluation for decades. They offer students and medical trainees an opportunity to grow in scientific study and review, and for established medical professionals they provide an opportunity to acquire new knowledge, debate controversial findings with peers, and to mold the next generation of scientific leaders.

The rapid growth of social media and the COVID-19 pandemic have dramatically impacted how medical professionals connect. We foresee a growing opportunity

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