Controversy: Does Prevention of Vasospasm in SAH Improve Clinical Outcome?

Does Prevention of Vasospasm in Subarachnoid Hemorrhage Improve Clinical Outcome? No

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In those who survive the initial impact of aneurysmal subarachnoid hemorrhage (aSAH), delayed ischemic neurological deficit (DIND) is the leading cause of morbidity and mortality.1 Despite therapeutic advances leading to decreased case fatality rate of 0.9% per year from 1960 to 1992,2 mainly attributed to improved prevention of rebleeding, the 30-day case fatality rate has remained static,3 and advances in treating DIND is the Holy Grail in aSAH research.

The exact pathogenesis of DIND is incompletely understood. Angiographic visualization of proximal arterial vasoconstriction was the first laboratory finding to be associated with DIND reported by Ecker and Riemschneider.4 The axiom that aSAH produces proximal arterial narrowing and subsequent ischemia causing infarction and poor outcome has thus become the research and clinical focus in the treatment of aSAH.

This article, based on a presentation given at the 2012 Princeton Conference, discusses the significance of delayed vasospasm in the pathogenesis of DIND by attempting to answer the following questions. What is the threshold of vasoconstriction that causes brain injury and how frequently is it reached in the setting of aSAH-induced vasospasm? What causes vasospasm, and is it a necessary and sufficient condition for DIND?

Vasospasm: Effect on Cerebral Perfusion and Threshold of Injury

Seventy percent of patients after aSAH have development of proximal vasospasm in the critical period of DIND.5 It is intuitive to postulate that vasospasm, which reduces cerebral blood flow (CBF), causes cerebral infarction and accompanying neurological deficit. However, in previous clinical studies, 50% to 70% of subjects with aSAH who had development of moderate-to-severe angiographic vasospasm were asymptomatic, and 20% to 25% who had development of DIND had no signs of vasospasm.6

Voldby et al7 used 133Xe injection to correlate changes in CBF with angiographic vasospasm (n=38) and showed that only severe diffuse vasospasm (>50% to 67%) produced a significant decline in CBF. This finding was later replicated by Ohkuma et al8 (n=58) using 3-dimensional single-photon emission computed tomography; they reported that the greatest decrease in cortical regional CBF occurred in patients with peripheral vasospasm rather than proximal vasospasm alone.

Dankbaar et al9 used computed tomography perfusion to measure regional CBF (n=37) and showed that proximal vasospasm was correlated with poor global CBF, but in 35% of subjects, the flow territory of the vessels with the most severe vasospasm did not correspond to the least perfused regions of the brain. These data indicate that proximal vasospasm and microvascular autoregulatory dysfunction are distinct processes, and that DIND is likely related, at least in part, to microcirculatory changes where CBF is primarily regulated by the arterioles.

Türeyen et al used an intraluminal filament middle cerebral artery occlusion murine model to elucidate the degree of luminal obstruction necessary to cause persistent fall in CBF.10 A 180-µm-thick filament reduced CBF and caused infarction after 90 minutes of occlusion, whereas 130-µm-thick filaments failed to show these effects. These data indicate that >75% obstruction is required to produce brain injury and neurological deficit. The exact threshold for vasospasm-induced brain injury secondary to aSAH is currently unknown, but it is likely that moderate vasospasm (34% to 66%) alone is insufficient to cause brain injury, and even severe vasospasm (≥67%) will not affect all patients.

Is Vasospasm a Necessary and Sufficient Condition for Delayed Neurological Deficit?

The clot placement nonhuman primate model is the most successful animal model for inducing angiographic vasospasm.11 The presence of hematoma alone led to significant delayed vasospasm (31% to 100%) in 87% (26/30) of animals. However, only 1 animal displayed neurological deficit. Subsequent studies confirmed high vasospasm incidence in which moderate (31% to 50%) and severe (≥50%) vasospasm was evident in 30% to 80% and 20% to 70% of animals, respectively.12,13 However, delayed neurological deficit was observed in merely 0% to 28%. Furthermore, removal of the clot was found to be very effective at preventing the development of delayed vasospasm in subsequent studies, significantly reducing the incidence from 100% moderate-to-severe vasospasm to approximately 0%.

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20% mild-to-moderate vasospasm. These studies isolated a single pathogenic factor, namely the hematoma encasing proximal vessels, as the cause of delayed vasospasm. Delayed vasospasm per itself in this model was insufficient for causing severe delayed neurological deficit.

Weir et al attempted to simulate early brain injury in a comparable model by giving weekly injection of 4 mL autologous blood via a needle into the subfrontal subarachnoid space of rhesus monkeys. Acutely elevated intracranial pressure temporarily exceeded the mean blood pressure and regional CBF, and cerebral perfusion pressure acutely decreased. Vasospasm, conversely, was short-lived and mild, amounting to −24% at 15 minutes and −6% on day 7. Nevertheless, a high overall mortality of 75% was observed over a 4-week period. Notably, the authors reported that “the degree of vasospasm in the animals which were dead the following day and the animals which were sitting up and eating normally was identical in the post-SAH angiograms,” refuting the relationship between delayed vasospasm and poor outcome. Espinosa et al injected 4 mL autologous blood to reach a peak intracranial pressure of 141 mmHg. Neurological deficit was observed in 100% of animals, ranging from lethargy and no spontaneous attempt to stand upright (67%) to obtundation with new cerebral infarctions, DIND, and extended GOS at 3 months. To date, nimodipine is the only intervention, based on 5 randomized, placebo-controlled trials, associated with improvement in functional outcome. However, none of these studies was able to demonstrate a reduction in angiographic vasospasm.

Collectively, a beneficial therapy with no impact on angiographic vasospasm and interventions that alleviated angiographic vasospasm, but that did not affect clinical outcome, suggest that the role of proximal arterial vasospasm in the pathogenesis of DIND is probably smaller than previously assumed, and the pathophysiological spectrum of delayed brain injury in aSAH is more complex.

**Early Brain Injury, Delayed Brain Injury, and Delayed Neurological Deficit**

Recent studies have demonstrated a host of critical, interrelated pathological pathways arising in the subacute phase of aSAH as a result of early brain injury, which we designate as “delayed brain injury.” With advances in understanding the pathophysiology of delayed brain injury, it becomes clear that the mechanisms leading to delayed vasospasm and delayed brain injury are not mutually exclusive. In fact, many of the pathogenic triggers of both conditions are interrelated, such that astrocytes and leukocytes release endothelin-1 in response to inflammation and ischemia after aSAH; and hemolyzed blood induces both vasospasm and cortical spreading depolarization. Thus, we suggest vasospasm is not a separate entity but is a subset of a number of mechanisms implicated in delayed brain injury.

**Conclusion**

Many hopeful neuroprotective therapies aimed to reverse delayed vasospasm have failed to demonstrate significant benefit in humans. Given the emerging recognition of the importance of early and delayed brain injury, it is clear that alleviation of a single pathological process may not provide sufficient protection. Future efforts must focus on all pathogenic aspects of aSAH and how they relate to each other, and they must act in concert to cause DIND. A multipronged approach on multiple processes may be required.

Furthermore, mounting evidence that the pathological derangements of early brain injury start immediately postictus and evolve with time emphasizes the importance of very early intervention. A possible explanation for the lack of effect of previously tested neuroprotective agents could be the delay in starting therapy, and efforts to minimize time to treatment should be the focus of future human trials of aSAH.

**Glossaries**

**Early Brain Injury**

Early brain injury is the immediate pathophysiological events induced by subarachnoid hemorrhage, including increased intracranial pressure, decreased cerebral perfusion pressure, acute vasoconstriction and distal vasoparalysis, no-flow phenomenon, and transient global ischemia.
Delayed Brain Injury

Pathological changes occur as a result of propagated early brain injury, leading to delayed vasospasm, microcirculatory autoregulation dysfunction, blood–brain barrier disruption, inflammation, oxidative stress, activated cell death mechanisms, microthrombosis, cortical spreading depolarization and ischemia, metabolic derangements, and electrolyte disturbances. These changes act in concert to cause delayed ischemic neurological deficit.

Disclosures

None.

References


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