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

Does Prevention of Vasospasm in Subarachnoid Hemorrhage Improve Clinical Outcome? Yes

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Controversy has arisen over the results of, among other studies, clinical trials of clazosentan in patients with aneurysmal subarachnoid hemorrhage (SAH). In a double-blind, dose-finding study, where patients were randomized to placebo or 1 of 3 doses of clazosentan, the drug significantly reduced angiographic vasospasm (aVSP) as assessed by independent, blinded review of angiograms done on all patients. There was no effect on 90-day outcome on the extended Glasgow outcome scale. The study was not powered to detect a difference in 90-day clinical outcome. In 2 phase 3 studies, clazosentan was associated with a trend toward or with a significant reduction in aVSP-related morbidity but again no effect on clinical outcome at 90 days. This led to the suggestion that reducing aVSP does not improve outcome after aneurysmal SAH because aVSP is an epiphenomenon or marker of other processes that are the true causes of poor outcome, an idea that has been around for <35 years. The other processes that are postulated to cause poor outcome include early brain injury, microthromboemboli, and cortical spreading ischemia (Figure). Whether aVSP is an epiphenomenon, the clazosentan trials are consistent with meta-analysis of clinical trials of drugs to improve outcome after SAH, which found that drug treatment significantly reduced aVSP, but that there was only a statistically insignificant trend toward improvement in clinical outcome. Other hypotheses to explain this disconnection include (1) rescue therapy, which in many studies was used more frequently in the placebo groups, improves outcome in the placebo groups to the same extent as the drug treatment in the drug treatment groups, (2) drug side effects counterbalance any benefit, (3) the sample sizes of the trials were too small, and (4) the outcome measure was too crude to measure the drug’s effect.

What evidence would exclude these possibilities and prove that aVSP does not affect outcome? The best would be a molecular manipulation that specifically prevented aVSP in some animal model or in humans (currently impossible to do) and that did not improve outcome on a scale known to be responsive to treatments that affect outcome. An experiment showing a drug improves outcome without affecting aVSP does not answer the question because the drug could reduce any of the other processes that theoretically contribute to poor outcome after SAH (Figure).

Animal and human studies of SAH that can guide understanding of the question whether aVSP causes poor outcome were reviewed in a nonsystematic fashion. The animal studies could permit scientific studies to be performed, but to date, no experiments in animals have shown specific molecular manipulations that improved outcome without affecting aVSP. Some molecular manipulation studies have been reported in superoxide dismutase knockout mice, but they show that superoxide dismutase knockout improved both aVSP and outcome. Studies by several investigators in rats have shown that the severity of aVSP, assessed usually at 1 time after the SAH, sometimes does not correlate with the degree of brain injury. This is not surprising because we already know that there are other causes of brain injury after SAH, especially early brain injury, as reported in animal models and reflected in humans by the powerful influence of initial neurological condition on overall outcome. The decrease in cerebral blood flow and the severity of aVSP is probably not enough to cause brain injury in many patients.

There are a number of animal studies that are consistent with the hypothesis that reducing aVSP improves outcome. One review noted that caspase inhibitors in rats, hydroxy-3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in rats and mice, erythropoietin in rabbits, ibuprofen in dogs, c-Jun N-terminal kinase inhibitors in dogs, and levetiracetam in mice reduced aVSP and improved behavioral outcomes. The caveat to these studies would be whether aVSP was secondary to some other effect and that the drug reduced that effect, improved outcome and thus, secondarily, aVSP. The problem with this idea is decades and dozens of experiments show that the link between SAH and aVSP fulfills the postulates of Koch. Blood by itself is associated with aVSP and when the blood is removed early on then aVSP does not develop. Some animal studies are similar to the human meta-analysis. Mesis et al administered carboxyimidotriazole or vehicle to mice and showing the drug decreased aVSP but worsened outcome. All the explanations...
for the disconnection in the human trials apply to these sorts of studies, except that animals are not usually treated with rescue therapy.\textsuperscript{15} Another study demonstrated that the mitogen-activated protein kinase inhibitor, U0126, improved behavior in dogs, despite the presence of severe aVSP, although the spasm was only moderate (≈50%).\textsuperscript{16} This is the reverse of the question at hand. It shows outcome can improve without affecting aVSP. This is simply evidence that other pathophysiological mechanisms of brain injury after SAH can be successfully treated, at least experimentally.

Thus, overall, the animal studies, although useful for elucidating pathophysiological mechanisms, have not specifically determined whether preventing aVSP matters to outcome after SAH in humans. They demonstrate that aVSP has to be severe before cerebral blood flow is affected.

What can we learn about the relation of aVSP to outcome from human studies? The data suggest that the connection between sustained severely reduced blood flow and outcome is true but that it is difficult to demonstrate because of the drug side effects, beneficial effects of rescue therapy in placebo patients, use of suboptimal outcome measures, and the contribution of other mechanisms to poor outcome (Figure). In human studies, it is difficult to determine the exact contributions of any of these factors. Systematic reviews of population-based studies of SAH show that outcome is improving at a rate of ≈1% per year.\textsuperscript{17} Why is this? One possible reason is a reduction in the incidence of and improved treatment of aVSP. In a meta-analysis of clinical trials of drug treatments for SAH that collected data on aVSP, delayed cerebral ischemia (DCI) and outcome, drug treatments significantly reduced aVSP.\textsuperscript{5} As previously mentioned, there was no significant improvement in outcome, but the trend was toward improved outcome. Data from a nicardipine trial showed that the increase in DCI in the placebo group was balanced by an increase in rescue therapy. Thus, assuming rescue therapy works, it could be difficult to improve outcome unless a new treatment was very efficacious.\textsuperscript{18} This does not mean that such treatment should not be sought; rescue therapy is arduous, expensive, and risky. The next issue is the effect size or relative contribution of aVSP and DCI to poor outcome. Outcome is assessed using crude, usually dichotomized scales that were not developed for SAH (modified Rankin Scale and extended Glasgow outcome scale). Modeling various effect sizes on data from the Columbia University SAH outcomes project and studies of tirilazad found that unless a treatment for DCI was very effective, it might require thousands of patients to see an effect on the dichotomous modified Rankin Scale.\textsuperscript{19} The sensitivity of the outcome scale to treatments that affect outcome after SAH is a relative one. Endovascular coiling of ruptured aneurysms was associated with a statistically significant 23% relative and 7% absolute risk reduction in death or dependency compared with neurosurgical clipping on the dichotomous modified Rankin Scale at 1 year in the International Subarachnoid Aneurysm Trial (ISAT).\textsuperscript{20} Thus, at least some treatment effects can be detected in patients with SAH with this scale.

The next problem is drug side effects. In the trials of clazosentan, drug treatment was associated with doubling of the incidence of lung complications and tripling of the risk of hypotension.\textsuperscript{1–3} Given the attention paid to blood pressure and pulmonary function in neurocritical care of SAH, it is reasonable to consider these side effects could counterbalance any benefit of reducing aVSP.\textsuperscript{21}

Another potential factor is that outcome has improved with treatments that were not directed at aVSP but that reduced it nevertheless. In ISAT, a randomized clinical trial that compared outcomes in patients treated by endovascular coiling with neurosurgical clipping, outcome was better after coiling.\textsuperscript{20} DCI was less in the coiled patients, and this is certainly 1 possible reason for the better outcome.\textsuperscript{22} Data from a randomized, blinded study of clazosentan also suggested that the reason DCI is less after coiling is because coiling is associated with less aVSP.\textsuperscript{23} Thus, improved outcomes after coiling may be in part because of reduced aVSP, in keeping with the pathway from aVSP to DCI to outcome (Figure).

In summary, it is likely that severe and sustained aVSP can lead to DCI and to poor outcome, but multiple factors limit detection of this phenomenon in clinical trials. Why only some patients with aVSP develop DCI is not that mysterious. Investigators in ischemic stroke have deduced that many factors determine whether infarction develops, including duration and severity of ischemia, the presence and length of stenosis, and collateral pathways.\textsuperscript{24} The aVSP and SAH literature is contaminated with numerous studies diagnosing mild aVSP noninvasively and then not surprisingly showing no correlation.
of the supposed aVSP with DCI and outcome. There are multiple other pathways beside aVSP that lead to DCI and poor outcome (Figure). Treatments that target multiple may be needed to further improve the outcome of patients with SAH.

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References

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