Pharmacologic Management of Subarachnoid Hemorrhage

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Subarachnoid hemorrhage (SAH) remains a condition with suboptimal functional outcomes, especially in the young population. Pharmacotherapy has an accepted role in several aspects of the disease and an emerging role in several others. No preventive pharmacologic interventions for SAH currently exist. Antiplatelet medications as well as anticoagulation have been used to prevent thromboembolic events after endovascular coiling. However, the main focus of pharmacologic treatment of SAH is the prevention of delayed cerebral ischemia (DCI). Currently the only evidence-based medical intervention is nimodipine. Other calcium channel blockers have been evaluated without convincing efficacy. Anti-inflammatory drugs such as statins have demonstrated early potential; however, they failed to provide significant evidence for the use in preventing DCI. Similar findings have been reported for magnesium, which showed potential in experimental studies and a phase 2 trial. Clazosentane, a potent endothelin receptor antagonist, did not translate to improve functional outcomes. Various other neuroprotective agents have been used to prevent DCI; however, the results have been, at best inconclusive. The prevention of DCI and improvement in functional outcome remain the goals of pharmacotherapy after the culprit lesion has been treated in aneurysmal SAH. Therefore, further research to elucidate the exact mechanisms by which DCI is propagated is clearly needed.

In this article, we review the current pharmacologic approaches that have been evaluated in SAH and highlight the areas in which further research is needed.

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH) is responsible for approximately 5% of all strokes, but because of its young age of onset, primarily in the 5th to 6th decade of life, and high mortality, the loss of productive life years is comparable with that of the more common ischemic and hemorrhagic strokes (29). The mortality rate, however, varies with age, race, and region, but is overall approximately 45% (29). Of the remaining cases, approximately one third of patients are left with permanent neurologic deficits (39). The incidence of SAH is 6–7 per 100,000 per year, in most populations but around 20 per 100,000 per year in Japan and Finland (39). At any point in time, approximately 2%–3% of the population will be harboring asymptomatic intracranial aneurysms that have the potential to rupture and cause acute SAH (64).

Pharmacotherapy has an accepted role in several aspects of SAH and an emerging role in several others. No preventive pharmacologic interventions for SAH currently exist. Antiplatelet medications as well as anticoagulation have been used to prevent thromboembolic events after endovascular coiling. The main focus

Key words
- Mortality
- Outcome
- Subarachnoid hemorrhage
- Therapy

Abbreviations and Acronyms
AF: Antifibrinolytic
CBF: Cerebral blood flow
CONSCIOUS: Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage
CSF-1: Cerebrospinal fluid
DCI: Delayed cerebral ischemia
DFO: Deferoxamine
ET-1: Endothelin-1
HIF-1: Hypoxia-inducible factor-1
MASH: Magnesium in Aneurysmal Subarachnoid Hemorrhage
MLB: Magnesium lithospermate B
NAC: *N*-acetylcysteine
NO: Nitric oxide
PAR1: Proteinase-activated receptor 1
SAH: Subarachnoid hemorrhage
SP: Substance P

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of pharmacologic treatment of SAH, however, is the prevention of delayed cerebral ischemia (DCI). Currently the only evidence based medical intervention is nimodipine. Other calcium channel blockers have been evaluated without convincing efficacy. Anti-inflammatory drugs such as statins may prove promising in the prevention of DCI and currently are being evaluated in large-scale clinical trials. Similar findings have been reported for magnesium, which showed potential in experimental studies and a phase 2 trial. Clazosentane therapy, a potent endothelin receptor antagonist, did not translate into improved functional outcome. Various other agents have been used to prevent DCI; however, the results have been, at best, inconclusive. Prevention of DCI and improvement in functional outcome remain the goals of pharmacotherapy after the culprit lesion has been treated in aneurysmal SAH. Therefore, further research to elucidate the exact mechanisms by which DCI is propagated is clearly needed.

In this article, we review the current pharmacologic approaches that have been evaluated in SAH. Specifically, we will discuss 3 key categories of intervention: (1) treatment to prevent aneurysm re-bleed; (2) treatment to reduce the risk of DCI or vasospasm; and (3) treatment that may attenuate the harmful effects of subarachnoid blood or ischemia on neurons (**Figure 1**). As such we hope to highlight the best treatments available and highlight the areas where further research is required.

MEDICAL TREATMENT TO PREVENT ANEURYSM REBLEEDING

Antifibrinolytic Therapy

Before the development of effective methods to secure aneurysms, antifibrinolytic (AF) therapies such as tranexamic acid and ε-aminocaproic acid were used as a first-line prevention of aneurysmal rebleeding (14). The 2003 Cochrane Review demonstrated that although there was a clear decrease in rebleeding, there also was an increased risk of DCI that was associated with an absence of improvement in functional outcome (59). As a result there was a sharp decrease in the use of AF therapies in the majority of the neurosurgical units (14). Nevertheless, this review included studies that used historical management of SAH (i.e., late aneurysm exclusion and no medical prevention of DCI) (59). The evolution of treatment has made this a more promising option. Current practice is to secure the aneurysm as soon as possible after ictus, and this considerably reduces the overall risk of rebleeding (71). Additionally, the development of agents, such as calcium antagonists, significantly has reduced the risk of DCI (12). In keeping with this protocol, the addition of AF use in the pre-exclusion period of ruptured aneurysms treatment demonstrated promising results (38).

The impact of AF therapy in aneurysmal SAH on functional outcome, rebleeding, and delayed ischemic deficits was reviewed in a recent meta-analysis (14). Specifically focusing on the rate of re-bleeding and DCI, it was demonstrated that the risk was no different to control (8). Furthermore, improved functional outcome was demonstrated when AFs were used for short periods and associated with a medical prevention of ischemic deficit (63). Aneurysmal SAH presents a 9.6% risk of rebleeding in the first 24 hours after rupture and a 5.7% risk for the first 3 days (23). In summary, the use of AF on a short-term basis just before aneurysm exclusion may be re-evaluated because it might play a role in preventing early re-bleeding (38).

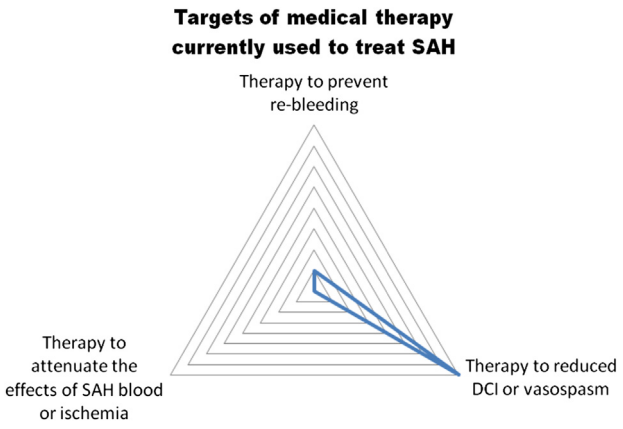

Figure 1. Spider chart of medical therapies used to treat subarachnoid hemorrhage (SAH). Currently the majority of medical therapy is aimed at reducing the effects of delayed cerebral ischemia or vasospasm. These 8 individual therapies in this area can be compared with only one, which works to prevent rebleeding and currently there are no products available that reduce the harmful effects of SAH blood or ischemia on neurons.

MEDICAL THERAPY TO REDUCE THE RISK OF DCI OR VASOSPASM

Hemodynamic Therapy

Disturbed cerebral autoregulation is prominent in patients with SAH (70). In the presence of vasospasm or microthrombosis, this may result in decreased cerebral blood flow (CBF) and thereby DCI (70). When autoregulation is affected, CBF becomes dependent on cerebral perfusion pressure and blood viscosity. To increase CBF different combinations of hemodilution, hypervolemia, and hypertension have been used for many years (35).

There is a distinct lack of randomized clinical trials on hemodynamic therapy and clinical outcome; as a result, hemodynamic therapy has only ever been analyzed in this context of supporting CBF. The induction of hypervolemia (47) and hypertension (65) in isolation, or in combination (10), was demonstrated to improve CBF, although none of these studies was adequately controlled.

The main drawbacks from these early studies is sample size (<10 patients), and a large heterogeneity in CBF outcome measure induces further variability. Both the techniques used to analyze CBF and the anatomical regions measured varied throughout the studies. The pathology resulting from the aneurysm is likely to occupy a proportionally small area of the parenchyma distal to rupture (58). As such, the changes induced by hemodynamic therapy are likely to be larger in that part of the brain. Quantitative disparities of CBF in such areas can be nullified or enhanced depending on the accuracy of measurement (9).

Further work will have to be done to consolidate the relationship between CBF and SAH outcome. An increase in CBF is the mechanism by which hemodynamic therapy and its components should improve outcome; however, this increase may only be transient or not sufficient to prevent ischemia and infarction. In