

Review Article

Intracranial Aneurysms and Antiplatelet Therapy

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Abstract

Subarachnoid hemorrhage secondary to ruptured aneurysms is one of the major concerns of neurosurgeons when performing the currently available invasive rupture prevention treatments. Assuming that antiplatelet therapy not only reduces the formation of thrombi but also acts on the physiology of inflammation and decreases its progression, several studies have recently trying to establish a beneficial relationship of the aneurysms rupture prevention with antiplatelet therapy against the hypothesis of causing rates increase in aneurysms bleeding. The aim of the present study was to analyze the published literature on the relationship between antiplatelet therapy and its effect on the rupture of intracranial aneurysms.

ABBREVIATIONS

UIAs: Unruptured Intracranial Aneurysms; SAH: Subarachnoid Hemorrhage; IA: Intracranial Aneurysm; COX: Cyclooxygenase; AA: Arachidonic Acid; PGH₂: Prostaglandin H₂; ISUIA: International Study of Unruptured Intracranial Aneurysms Investigators

INTRODUCTION

Unruptured intracranial aneurysms (UIAs) have a prevalence of 2% to 3% in general population. They may remain clinically asymptomatic for a long period of time; its rupture causes subarachnoid hemorrhage (SAH).

Stroke is the third most common cause of death in developed countries, exceeded only by coronary heart disease and cancer. Estimates from the World Health Statistics (WHO) show a trend towards a progressive increase in deaths attributed to cerebrovascular diseases, which could reach around 12.1% of world mortality by 2030 [1]. About 80% of non-traumatic SAH in the patients are related to rupture of saccular aneurysm. This disease is estimated to occur in 30,000 patients annually in the United States, where someone dies of stroke every three minutes, generating an annual rate of aneurysmal SAH of 10 to 28 per 100,000 inhabitants. Patients with SAH from a ruptured aneurysm have a poor prognosis with lethality rates up to 50%. Of these, 10 to 15% die before reaching medical care and about 66% of those who underwent successful aneurysm clipping have irremediable sequelae, suggesting that treatment of UIAs before their rupture is beneficial [1-5].

PHYSIOPATHOLOGY

Many studies show that inflammation in response to hemodynamic stress is a relevant element behind the

physiopathology of the formation and rupture of the cerebral aneurysm, playing a key role in its propagation and destabilization leading to an eventual rupture [6-9].

Chyatte et al., found inflammation evidence with the presence of T and B lymphocytes, macrophages, immunoglobulins (IgG and IgM), and components of the complement system (C3c and C9) in aneurysm wall tissue samples collected at the time of microsurgical repair of 23 aneurysms unruptured and 2 ruptured [10].

Frosen found histological findings of macrophage and T cell infiltration in surgical tissues of 24 unruptured aneurysms and 42 that had ruptured [11], also demonstrated in another study the evidence of increased expression of various inflammatory receptors, and attributed to the factor of growth of beta-R2 transformation (TGFbeta-R2) and vascular endothelial growth factor (VEGF) -R1 association with aneurysmal rupture [12-14].

CURRENT MANAGEMENT FOR ANEURISM

The current effective options to prevent IA rupture are microsurgical interventions and coiling, both of which are considered invasive procedures presenting a risk of adverse complications. Currently, no treatment has been recorded demonstrating its effectiveness in preventing rupture of an unruptured intracranial aneurysm. Evidence of the efficacy of the systemic pharmacological treatment option aimed at minimizing the inflammatory process involved in IA formation and rupture is promising [7,15-17].

Antiplatelet agents and anticoagulants are medications that may present a dilemma in the management of UIA and the purpose of this review is to critically analyze the relationship between antiplatelet therapy and its effect on rupture of IA.

ASPIRIN AND REDUCTION OF INFLAMMATION

Known for its efficacy as an antiplatelet drug, aspirin is also a powerful weapon for the inhibition of inflammation. The described pathway through which aspirin acts on the inflammatory response is through inhibition of COX thus decreasing the conversion of arachidonic acid (AA) to prostaglandin H₂ (PGH₂). PGH₂ is converted to thromboxane A₂ (TXA₂) and prostacyclin, and also in other types of prostaglandins D₂ (PGD₂), E₂ (PGE₂) and F_{2α} (PGF_{2α}), all of which act by signaling mechanisms autocrine or paracrine, playing important roles in triggering the inflammatory process. The combined effect of prostaglandins derived from PGH₂ in humans is the increase in proinflammatory signaling and is minimized by the use of aspirin [8].

Gross et al studied 747 patients with cerebral aneurysms, comparing the rate of hemorrhagic complications in patients taking aspirin and patients who were not taking aspirin. They also evaluated the clinical outcomes, for one year, among patients with SAH between those taking aspirin and patients who were not taking aspirin. The authors found that the rate of hemorrhagic presentation was significantly lower in patients taking aspirin (28% vs. 40%) [14]. The great relevance of this study lies mainly in the observation that, in patients presenting with SAH, the use of aspirin did not negatively affect the results, minimizing the concern of worsening bleeding and consequently the prognosis in case of aneurysmal rupture.

Hasan et al. found that the use of aspirin is a protective factor against rupture of the cerebral aneurysm. In a case-controlled study of the International Study of Unruptured Intracranial Aneurysms Investigators (ISUIA), these authors found that patients who took aspirin at least 3 times a week had a lower risk of SAH (odds ratio, 0.27; 95%, 0.11-0.67, P = 0.03) compared to patients who never took aspirin [7]. Such evidence was later confirmed in a large European study (1340 cases of SAH and 10,000 controls) in which aspirin intake was associated with a decreased risk of SAH (odds ratio, 0.82, 95% confidence interval, 0, 67-1.00), with aspirin use for more than 3 years having the best protective effect against SAH [15]. They found that the use of aspirin was not associated with an increased risk of intracerebral hemorrhage.

Believing that the protective effect of aspirin against aneurysm rupture is related to its antiplatelet effects by the formulation that the inhibition of platelet activation reduces endothelial injury, mural thrombus formation and subsequent inflammation of the aneurysm wall, Hasan et al., also evaluated the effect of other antiplatelet agents. Although this mechanism may be possible, the study did not demonstrate any protective effect for Clopidogrel (a more potent antiplatelet agent) against SAH argues against the hypothesis by antiplatelet effects. In addition, they found that aspirin did not increase hemorrhagic complications after rupture of the aneurysm and may have a general beneficial effect on outcome [7].

As well as the severity of aneurysmal SAH, data from an analysis of 305 selected surgical cases showed no apparent increase in the initial severity of bleeding and no complication at the long-term outcome in patients with aneurysmal SAH who were taking aspirin before the rupture [16]. They concluded that,

based on these preliminary data, the presence of an IA is not a contraindication to the use of aspirin.

DISCUSSION & CONCLUSION

Considering all the facts, from the detection of an unruptured aneurysm, the natural history of the aneurysm should be evaluated for the choice of interventional action, with consideration of innumerable factors regarding to the aneurysm and the patient. Aneurysm size, location, morphology and presentation, and patient factors, including age, family history of SAH, presence of medical conditions, such as clear indication for administration of anticoagulants such as atrial fibrillation, previous ischemic stroke or stroke transient ischemic disease [17]. In such situations, antiplatelet therapy should not be considered a contraindication. Thus, the decision should be individualized according to the best estimates of risks and benefits, carefully analyzing mainly the risk of spontaneous rupture of the aneurysm and, on the other hand, the risk of thrombosis or stroke if the antiplatelet treatment is not administered.

Concerning the possibility of a second hemorrhage, few studies have evaluated the use of aspirin in the post-hemorrhagic period and re-bleeding. In a study that analyzed 11,549 patients with previous diagnosis of SAH and who underwent conventional treatment (microsurgical or coiling), 245 were on aspirin and 108 were given other types of anticoagulants. The authors believed that both drugs were not associated with differential mortality rates or greater complications following SAH [19]. On the other hand, Toussaint LG et al. although concluding that prior aspirin use was not a significant worsening factor in the overall post-aneurysmal SAH result, reported an increase in the rate of re-bleeding in aspirin users (14,3%) compared to the rate of non-users (4,7%) (p = 0.06), with significant difference between rates [16]. Given such controversies, there is a need for greater effort to establish a clear effect of aspirin on re-bleeding, since in our department in cases of ruptured aneurysm we do not take the chance of re-bleeding and patients are referred preferentially to endovascular procedure or in some particular cases to microvascular surgery. We think, in those cases, aspirin treatment could represent an unnecessary risk to the patient's survival.

There are certain limitations of our study. First, the data are derived from existing evidence from recent studies, evidencing the need for further investigation, considering more variables of the patients that influence the evolution of the clinical picture. Second, there was a certain heterogeneity between classifications for some items, which emphasizes the uncertainty about the natural history of UIAs, clinical history of patients and other medications patients may be taking, which may influence the results.

However, given the strong evidence that aspirin can prevent rupture of the aneurysm and does not have a negative outcome effect in patients with SAH so far, it is reasonable to consider the possibility of preventive pharmacological management with aspirin as one of the treatments for aneurysms to accompany endovascular therapy.

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