Cerebral Aneurysm rebleeding; Do We Know Enough?

Omar Elwardany, MD
Nothing to Disclose
Introduction

Despite the improvement in the outcome after aneurysmal subarachnoid hemorrhage (aSAH) in the last few decades, rebleeding remains a significant contributor to morbidity and poor prognosis. (1)

Mortality associated with rebleeding has been reported as high as 80% compared to 40% in acute aSAH patients. (2)

Fifty years ago, Antifibrinolytic therapies such as tranexamic acid (TA) and ε-aminocaproic acid (EACA) have been used as a preoperative treatment to prevent aneurysmal rebleeding after aSAH. However, their safety and effectiveness are still very controversial. (3)

Improving our understanding of this phenomenon and identifying patients at risk have the potential to enable better management and minimize the devastating consequences.

Methods

Up-to-date, reviewing the literature concerning rebleeding after aneurysmal subarachnoid hemorrhage as regards to incidence/timing, risk factors, prevention and management.
Results

Although rebleeding from a ruptured cerebral aneurysm has been extensively investigated in many studies, a lot of contradicted data, controversies and unanswered question are still there.

As high as 80% Mortality has been reported in patients with rebleeding, while it is only 41% in patients without rebleeding. (4) These mortality rates for patients have been reported by studies investigating rebleeding that happens after hospital admission, while rebleeding before hospital admission (e.g. During transportation, inter-hospital and pre-imaging), referred to as Ultra-early rebleeding, might contribute to even higher morbidity and mortality rates, probably has not been included. (5)

The rate of ultra-early rebleeding has been found in the first 24 h following aSAH to be as high as 9–17%, with 40–87% of it occurring within the first 6 h. (5)

While many factors have been frequently found to be associated with an increased risk of rupture in many studies such as; longer time to treatment, poor Hunt Hess grade on admission, presence of intracerebral or intraventricular hematomas, larger aneurysm size, multiple aneurysms, hyperglycemia and hypertension (systole >160 mmHg), the precise mechanism and exact process underlying the eventual rebleeding remain poorly understood.\(^{6}\)

Aneurysm wall irregularities, lobulations, daughter sacs, and aspect ratios have been associated with higher rupture risk and may likely apply to re-rupture as well,\(^{7}\) but the relationship with rebleeding necessitates further investigations. However, aneurysm rebleeding following presentation with aSAH has shown to be independently associated with the TT genotype of the EDN1 G/T SNP.

Moreover, many recent studies have addressed coagulation and fibrinolysis after aSAH, suggesting disequilibrium between coagulation cascades and fibrinolysis in the aneurysmal microenvironment.\(^{8}\)

These data could indicate that rebleeding is a consequence of reduced clot stability in conjunction with increased fibrinolysis.

Since 1967, many studies have been conducted to evaluate the efficacy and safety of Antifibrinolytics (AF) such as tranexamic acid (TA) and ε-aminocaproic acid (EACA) as a preoperative treatment for aSAH. While the very early trial was using large doses (up to 30gm) daily for weeks, (9) more recent studies utilize the short-term use (maximum 72 hours) of smaller doses. (10)

Unfortunately, the results of many of the individual randomized studies show a lot of contradicts. A Cochrane Review in 2013 analyzed ten trials involving 1904 participants. AF therapy significantly reduced the risk of rebleeding (RR 0.65, 95% CI 0.44 to 0.97; 78 per 1000 people), but also significantly increased cerebral ischemia rates (RR 1.41, 95% CI 1.04 to 1.91; 83 per 1000 people). (11)

On the contrary, a recent meta-analysis of 17 relevant studies involving a total of 2,872 patients concluded that the short-term use of AF associated with medical prevention of ischemic deficit decreases the rate of rebleeding and does not increase the risk of cerebral infarction.\(^{(12)}\)

In addition, most reports that studied the short-term treatment with antifibrinolytic agents showed either reduces or no effect on the rate of rebleeding without or with insignificant increase in ischemic complications.\(^{(13)}\)

But, what is optimum drug? What is the proper time to initiate treatment? What is the optimum dose and course duration of the drug? And whether ultra-early and short term TXA treatment leads to a better functional outcome?

What is really needed, is a randomized, prospective, controlled trial to provide reliable answers to these unanswered questions. The Ultra-Early Tranexamic Acid After Subarachnoid Hemorrhage [ULTRA] trial is an ongoing trial, currently enrolling patients, and the final results are expected by January 2020.

No doubt that, the purpose of securing the aneurysm after aSAH is to prevent rebleeding. Up till now, securing the leaking aneurysm as soon as feasible, via either the open or the endovascular methods is the only definitive way to prevent aneurysmal rebleeding. However, during the initial first few hours after the primary bleed, the risk of rebleeding is highest, well out of reach of even the most ambitious treatment protocol for securing the aneurysm.

There is a general agreement that, the optimum strategy to get the maximum benefit from AF agents to prevent the aneurysmal rebleeding, is to give it as early as possible and to accelerate the definitive procedure of aneurysm treatment to minimize or even avoid the adverse effects of antifibrinolytics long-term administration.
Summary Points

- Cerebral aneurysm rebleeding is usually associated with poor functional outcome and high mortality rate.
- Securing the bleeding aneurysm is the only definitive way to prevent the overall risk of rebleeding.
- Risk factors and predictors of rebleeding are not well defined.
- Antifibrinolytic therapy can provide a promising tool to prevent the ultra-early aneurysmal rebleeding during the preoperative period.
- Further researches are needed to improve our understanding of the rebleeding phenomenon to be able to provide better preventive and management procedures.