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Mini Review

Rebleeding in Aneurysmal Subarachnoid Haemorrhage: Epidemiology, Risk Factors, Pathophysiology, Diagnosis and Preventive Treatment

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Abstract

Aim: To summarize briefly the principal aspect of rebleeding and to discuss the preventive treatment.

Methods: A literature search was performed to investigate Epidemiology, Risk factors, pathophysiology, Diagnosis and preventive treatment of rebleeding after aneurysmal Subarachnoid Haemorrhage (aSAH).

Results: The review of the literature revealed that rebleeding is a devastating complication with high incidence in the first hours and days. There are factors associated with increase of this complication, poor clinical condition, large aneurysm, and hemostatic parameters were some of them. Early aneurysm repair and short course of antifibrinolitic treatment have been showed favorable results.

Conclusion: Some factors are related with rebleeding, but are not clear the causal effect of them. The early surgery (clipping or endovascular) and short course antifibrinolitic therapy had been the most useful treatment to prevent aneurysmatic rebleeding. However, new researches are necessary to evaluate the best way of neurosurgical procedures to aneurysm secure and efficacy of short course of antifibrinolitic therapy.

Keywords: Aneurysm; Aneurysmal subarachnoid haemorrhage; Rebleeding; Mortality; Incidence; Stroke

Introduction

Aneurysmal ruptured is the main cause of non-traumatic Subarachnoid Haemorrhage, represents about 80 - 85% and is also know that saccular or berry aneurysm are common acquired lesions that occur in 1-2% of the population [1]. The rupture of an intracranial aneurysm (ICA) is a devastating event, and is still associated to a relatively poor outcome. Aneurysmal Subarachnoid Haemorrhage (aSAH) is one of the most deadly and debilitating type of stroke conservatively represents around 3% of all strokes [2]. Case fatality for aSAH ranges from 32% to 67%of cases, with one third of deaths occurring within 30 days of the event [3].

Unquestionably, there are several factors involved when talking about aSAH as the final outcome. However, rebleeding has a particular relevance, because it is a severe and devastating complication, with a fatality rate of 35% in hospitality environment [4]. The aims of this review were to expose briefly the principal aspect of rebleeding and to discuss the preventive treatment.

Sources and Selection Criteria

This review was based on a comprehensive literature review and prioritized well conducted studies of high impact and clinical relevance to the topic. Data sources included PubMed, HINARI, Clinical key, Scielo as well as reference lists from included articles. Searches were limited to English and Spanish languages articles available for review from January 1980 through March 2015. Our search terms included aneurysm, aneurysmal Subarachnoid Haemorrhage, Rebleeding, prevalence, incidence, stroke and mortality. The MeSH terms were included. The data were supplemented with expert interpretation of the results and summary of the cumulative data.

Epidemiology

Rebleeding rate varies according different researches. Some investigations showed that 8%–23% of rebleeding episodes occurred within the first six hours after the primary bleeding [5]. In 2007, Tanno et al. [6] reported overall rebleeding occurred in 88 out of 181 patients within 6 hours (48.6%). Also, Cha et al. [7] found that majority of rebleeding occurred within 2 hours (74.3%) after stroke onset. Accordingly, these findings suggest aneurysmal rebleeding occurs more frequently in the early period after the initial SAH, but, risk remains high in posterior stages. Other author´s reports show that the 37% of rebleeding happened among 3 to 7days after the first bleed, and a second peak was observed during the 11th to 12th day [8]. Kassell, in 1983, found that the peak of rebleeding was at first day of the onset symptoms or between 6th to 11th days [9].

From our point of view, underestimation of incidence exists. Rebleeding in early pre-hospital stage and in patients with late diagnosis of aSAH are examples of susceptible group. Delay in admission into high volume hospital (more 35 aSAH cases per year) is a serious problem in developing and developed countries.

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Risk Factors

Since the past century, numerous studies have identified some factors related to Rebleeding. Larsen et al. [5] summary all of them:

- Poor clinical condition (High Hunt-Hess and World Federation of Neurologic Surgeons grade, Low Glasgow Coma Scale score) on arrival
- Patient with more severe SAH has a larger amount of blood in the subarachnoid space (intracerebral hematoma, intraventricular hematoma, subdural hematoma)
- Systolic arterial blood pressure >160 mmHg
- Hyperglycemia in hospital admission
- Sentinel headache
- Aneurysm factors (size, location, total number)
- Angiography < 6 hours after initial SAH
- Hemostatic parameters (platelet hypoaggregability, High thrombin-antithrombin complex)

Factors not associate with Rebleeding:

- Demographic (age and sex)
- Aneurysm factors (Size and location)
- Larger amount of blood in the subarachnoid space (intracerebral hematoma, intraventricular hematoma, distribution of blood on initial CT scans)
- Hemostatic parameters
- High systolic blood pressure
- High Hunt-Hess grade.

As the authors exposed, disagreement persist about factors related to Rebleeding after aSAH, divergences reflects variation in study design and definition of study variable. Also there should be mentioned the small and specific criteria for selecting sample in that studies.

In fact, risk factors of Rebleeding after aSAH need to be researched more carefully, especially to identify modified factors in pre-hospital stage, because there will be available new therapeutic options to prevent this fatal complication.

However, the best current evidence suggests some factors related to aneurysm rebleeding including longer time to aneurysm treatment, worse neurological status on admission, initial loss of consciousness, previous sentinel headaches (severe headache lasting >1 hour that do not lead to the diagnosis of aSAH), larger aneurysm size, and possibly systolic blood pressure >160 mmHg [10]. One recent meta-analysis concluded that risk factors associated to rebleeding compromised elevated systolic pressures, poor Hunt-Hess grades, intracerebral or intraventricular hematomas, aneurysms >10 mm in size, and aneurysms in the posterior circulation [11].

Pathophysiology

Mechanism that produced rebleeding remains still uncertain. Several theories have been proposed. Most theories come from experimental investigations and they are the basis of treatment strategies. Transmural pressure, system coagulation and fibrinolysis are the most important elements.

Transmural pressure is equivalent to the difference between intra-aneurysmal pressure and Cerebrospinal Fluid (CSF) pressure against wall artery. Any increase on arterial pressure or decrease in cerebrospinal fluid pressure leads to an increase of the transmural pressure and consequently to an aneurysmal re-rupture. According to this theory, the leverage between intra and external pressure in wall artery is necessary to contribute with the integrity of the initial clot after the aneurysmal rupture.

High blood pressure rise intra-aneurysmal pressure, consecutively transmural pressure and they increase the risk of rebleeding. Those are the reason why Guidelines of Management of aSAH recommended reasonable decrease systolic blood pressure to <160 mm Hg. Although, the magnitude of blood pressure control to reduce the risk of rebleeding, has not been well stablished yet [10].

Although, recent studies try to demonstrated the CSF drainage by external catheter increase rebleeding rates (according decrease CSF pressure and increase of transmural pressure), has not been found any evidence yet that preoperative ventriculostomy performed after aSAH is associated with an increased risk of aneurysm rebleeding when early aneurysm surgery is performed [12,13].

Many coagulation and fibrinolysis factors have been proposed to play a relevant role in CSF and plasma after aSAH. Some of them are trying to link it to rebleeding. Thrombin-antithrombin complex, Plasminogen activator inhibitor 1, Plasmin-antiplasmin complex, D-dimer, reduced platelet aggregability are some examples [14].

Diagnosis

Diagnosis of rebleeding includes clinical manifestations and neuroimagen test. Clinical spectrum varies from a mild increase of headache to coma. Most patients refer an abrupt increase of headache and loss of consciousness, however. In another cases the loss of consciousness after a seizure or appearance or/and an increase focal sign may be related to a presence of rebleeding too.

Neuroimagen test is confirmed in suspected case. CT should be realized in all patients with clinical change and comparison with admission CT study to confirm the growth of haemorrhage in subarachnoid space. Occasionally it isn´t easy, because onset of symptoms and complication happen in pre-hospital stage, when neuroimagen test has not been done and/or patients has not received a specialized medical attention. Some cases of rebleeding are suspected, but the diagnosis is never confirmed. From the author´s point of view, some reference from the literature describe in a detailed way to diagnose this complication, almost all classical texts report a brief description [15,16]. Protocols to optimize periods of treatment are recommended, but it isn´t always possible in developing and developed countries, especially in the first group.

Preventive Treatment

Neurosurgical treatment

The most effective strategies to prevent rebleeding after aSAH

are to secure of the aneurysm as soon as possible and short course of antifibrinolitic therapy. A major determinant factor of rebleeding is whether the aneurysm is completely excluded from the circulation via or microsurgical or endovascular treatment [17]. A large debate has been sustained in the last years about which are the most convenient technique treatment. Only one multicenter randomized trial has been conducted to compare endovascular procedures and microsurgical clipping. ISAT study evaluated 2143 patients with aSAH across 42 neurosurgical centers [18]. Outcomes after one year follow up, showed a diminished death (24% *vs.* 31%), and disability (16% *vs.* 22%) in the group treated with endovascular procedures with higher technical complication (8% *vs.* 19%), and time needed to secure de aneurysm in patients treated with microsurgical clipping than endovascular procedures [19,20]. However, microsurgical clipping technique was more effectiveness in decrease late rebleeding (0.9% *vs.* 2.9%) and completed obliterate aneurysm (81% *vs.* 58%) than endovascular technique [18]. Despite a high efficiency of endovascular coil, some authors suggest long term following because durability remains a significant concern [21]. The ISAT´s results received some critiques and some authors considered that there was not exists great differences between the groups of the research, but it is the only randomized trial executed until now.

Finally, guidelines recommended determination of aneurysm treatment, as judged by both experienced cerebrovascular surgeons and endovascular specialists, should be a multidisciplinary decision based on characteristics of the patient and the aneurysm (Class I; Level of Evidence C). Microsurgical clipping may receive increased consideration in patients presenting with large (>50mL) intraparenchymal hematomas and middle cerebral artery aneurysms. Endovascular coiling may receive increased consideration in the elderly (>70years of age), in those presenting with poor-grade (World Federation of Neurological Surgeons classification IV/V) aSAH, and in those with aneurysms of the basilar apex (Class IIb; Level of Evidence C) [10]. New techniques have been researched, stent, glue and aneurysmal wrapping are some of them.

Antifibrinolitic therapy

Previous trials to determine value of antifibrinolitic therapy to reduce incidence of preoperative rebleeding was analyzed in systematic review published in 2003. Nine studies used Tranexamic Acid 4-9g/daily or Epsilon Aminocaproic Acid 24g/daily found a really important decrease of rebleeding, but not benefit in final outcome. In conclusion, it was abandoned because the results found an increase cerebral ischemia, poor outcome and death when antifibrinolitic therapy was administered [22]. However, subsequently studies to evaluate the use of Epsilon Aminocaproic Acid (EACA) and Tranexamic Acid (TXA) to prevent rebleeding concluded the effectives in reduced the incidence of this complication when were applied for a short time at the first 72 hours. Randomized multicenter trial showed TXA reduced rebleeding incidence 2.4% vs. 10.8% control group ($p<0.01$) and a 19% reduction of poor outcome with a 4% increment of good outcome [23]. By the other site, prospective observational study found EACA diminish rebleeding rate from 11.4% to 2.7% with a 10% improvement in good outcomes [24].

Based in this results the use of TXA or EACA is reasonable in patients with risk of rebleeding without contraindication (Class II, level of evidence B), but either EACA or TXA aren´t approved by the US Food and Drug Administration for prevention of aneurysm rebleeding [10].

Hypertension

Systolic blood pressure higher than 160mmHg has been related with increase of rebleeding. It could be assumed that during the very early phase of SAH, the fibrin net covering the rupture point is so fragile that changes in the arterial blood pressure might increase the transmural pressure beyond the compliance of the hemostatic clot and result in rebleeding [5,14]. Studies to evaluated the best range of blood pressure according outcome lack. The scholars recommend reasonable decrease systolic blood pressure lower than 160mmHg. Nicardipine doses 5mg/hour, with increase 2,5mg/h every 15 minutes. Maxim doses 15mg/h and labetalol doses 10–20 mg IV, repeat at 2 min, if necessary. If refractory hypertension you can use 40–80 mg every 10 min up to 300 mg. It´s important to mentione that hypotension could be diminish cerebral perfusion pressure and may lead the cerebral ischemia [25-27].

Conclusion

Rebleeding is a devastating complication after aSAH, with a higher rate of mortality. Incidence is more frequent in the first hours and days, but keeps upper during two weeks. Certain risk factors have been related to rebleeding. Patients with poor clinical condition at hospital admission, large aneurysm, and hemostatic parameters were some of them. But unquestionably, rebleeding is a complex and multifactorial condition involving several factors, reason why the exact mechanisms leading to rebleed continues poor understood. Aneurysm repair as soon as possible helps to diminish incidence and mortality due to rebleeding, and short course of antifibrinolitic therapy in patients with probably late aneurysm treatment have been showed favorable results too. However, new researches are necessary to evaluate the best way of neurosurgical procedures to aneurysm secure and efficacy of short course of antifibrinolitic therapy.

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