



● REVIEW

The “Brain Stress Timing” phenomenon and other misinterpretations of randomized clinical trial on aneurysmal subarachnoid hemorrhage

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Abstract

Clipping and coiling are currently the two alternatives in treatment of ruptured cerebral aneurysms. In spite of some meritorious analysis, further discussion is helpful to understand the actual state of art. Retreatment and rebleeding rates clearly favors clipping, although short-term functional outcome seems to be beneficial for clipping, while this different is not such if we perform the comparison at a longer follow up. Long-term follow ups and cost analysis are mandatory to have a clear view of the current picture in treatment of subarachnoid hemorrhage. Treatment strategy should be made by a multi-disciplinary team in accredited centers with proficient experience in both techniques.

Key Words: *SAH; subarachnoid hemorrhage; coiling; clipping; ruptured; aneurysm; timing; intracranial*

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Background

Aneurysmal subarachnoid hemorrhage (aSAH) is one of the most devastating neurological entities, counting a mortality rate up to 50% and morbidity that raises to a half of the survivors sustaining irreversible brain damage (Sarti et al., 1991). Aneurysm exclusion becomes mandatory in this scenario, in order to manage most of the potential neurological complications. The decision of microsurgical clipping versus coiling emerge, basically, as the two main options in the treatment of ruptured intracranial aneurysms (RIA). The decision of treating such lesions by whether endovascular or microsurgical techniques turns out as an undoubtable source of controversy. Clipping has been challenged by the presumably less invasive and less morbid endovascular alternative in the treatment of subarachnoid hemorrhage after cerebral aneurysm rupture.

Recent epidemiological studies have claimed that patients with ruptured and unruptured cerebral aneurysms treated with clipping are more often discharged to long-term facilities, suggesting that endovascular coiling is a much safer alternative with faster recovery times (Brinjikji et al., 2011). The largest study so far, the International Subarachnoid Aneurysm Trial (ISAT) study (Molyneux et al., 2002) including 2143 patients, was favorable for coiling in almost all outcome measures, such as Glasgow Outcome Scale and modified Rankin Scale. This study was stopped prematurely since the preliminary results favored to coiling at 1 year-follow-up. These findings have generalized the neurosurgical practice in aSAH in some parts of the globe, in spite of the fact that several flaws have been raised as concerns. Subsequent analysis in this and other randomized

controlled trial revealed that the superiority of coiling over clipping in terms of survival and rate of independency in not such when the outcome is evaluated after certain period of time that varies depends on the study between 3 and 5 years (Bakker et al., 2010; Spetzler et al., 2015).

Search Strategy and Selection Criteria

An electronic search of Medline and SCOPUS databases for randomized controlled trials (RCT) comparing different alternatives of treatment in ruptured cerebral aneurysms and subarachnoid hemorrhage from 1981 to 2018 was performed using the following conditions: SAH (MeSH Terms) OR Subarachnoid Hemorrhage (MeSH Terms) AND (Treatment (MeSH Terms) OR Clipping (MeSH Terms) OR Coiling (MeSH Terms)). The results were further screened by title and abstract to those compare at least two types of treatment. Meth-analysis including at least two RCTs were also considered. Non-RCTs and simple reviews were excluded. Up to date four large RCTs have been published.

Discussion

We hypothesize that, without regard to the potential adverse effects of additional procedures, there is a time in which exists an impairment of the metabolic state and homeostasis, directly or indirectly provoked by surgical trauma, that induces a reversible depression-like state that is thought to be the substrate behind this observation. We have coined the term “Brain Stress Timing” to define this phenomenon, since it is the stressful event of the operative procedure the responsible of this delay in the recovery for a definitive neurological outcome.

Besides some technical mistakes during the follow up and the *post-hoc* analysis (outcome follow-up assessment), we feel that it is reasonable to insist in some pitfalls during the design and data interpretation of ISAT study results that might lead to mistaken decisions. Only 20% patients were included in the randomization, which add a non-dismissible source of selection biases. Likewise, more than 90% patients included the most technically simple aneurysm (anterior circulation and small aneurysms) or in good clinical grade. However, results were extrapolated to the entire cohort of aSAH and use by some to argue against the benefits of the surgical technique in the modern era, while it is well accepted that patients in poor clinical grade or with great intracerebral hematomas are subsidiary of microsurgical technique. In addition, certain types of aneurysms are underrepresented in the ISAT study. Middle cerebral artery (MCA) aneurysms possess a unique complex anatomy that may limit the efficacy of endovascular therapy: they tend to have broad necks, frequently encompassing branches that originate directly from the aneurysm and the dimensional disposition of trunks may be tricky to decipher angiographically. Many of these factors influenced eligibility in ISAT, which required therapeutic equipoise between clipping and coiling for inclusion. The relatively few patients with MCA aneurysms in the ISAT is an acknowledgment of these difficulties with endovascular therapy. A major advantage of surgery is the ability to survey the complex anatomy of the aneurysm neck, its superior, inferior, and sometimes middle trunks, and surrounding lenticulostriates. Insights gained from handling this anatomy are more informative than any angiographic images (Rodríguez-Hernández et al., 2013). In a recent review of endovascular results in more than 800 patients with MCA aneurysms (Rodríguez-Hernández et al., 2013), only half of them experienced complete occlusion, whereas complete occlusion rates were superior to 95% in nearly all studies for patients with MCA aneurysms treated with surgical clipping. Several studies have corroborated the superiority of clipping over coiling, in terms of functional outcome, in the treatment of ruptured MCA aneurysms (Rodríguez-Hernández et al., 2013). In subsequent analysis of the results of the ISAT study clipping resulted in better outcomes in elderly patients with MCA aneurysms (Ryttefors et al., 2007). These late findings from the ISAT attracted less attention than its initial publication, but are important reminders that the early advantages of endovascular therapy cannot be assumed to last or generalize to all aneurysms (Rodríguez-Hernández et al., 2013). Moreover, the rupture of MCA aneurysm has been associated with intracerebral hematoma. In spite of the fact that the presence of intracerebral hematoma has been described as a negative prognostic factor in patients with RIA, patients with temporal intracerebral hemorrhage generally tend to have a favorable outcome following evacuation of the

intracerebral hemorrhages, supporting the idea that the microsurgical treatment might be more beneficial in this cohort of patients (Shimoda et al., 1997).

What seems to be clear is that clipping yield more durable aneurysm occlusion and higher complete occlusion rates (Molyneux et al., 2002; Bakker et al., 2010; McDougall et al., 2012; Spetzler et al., 2015). Initial analysis of the ISAT study demonstrated that coiled aneurysms had an increased risk of rebleeding and retreatment was almost 7 times more likely using endovascular techniques (Molyneux et al., 2002). This finding is a constant among the others randomized controlled trial comparing coiling and clipping in aSAH (Koivisto et al., 2000; McDougall et al., 2012). So then, a question might arise in this scenario: could late rebleeding overturn the superiority of cranial aneurysm coil embolization over clip ligation seen in the ISAT? In fact, this was already answered in a late analysis derived from the ISAT showing that clipping protected better than coiling in young patients (< 40-year-old) with minimal or no differences in safety (Mitchell et al., 2008). The effective and durable aneurysm repair offered by mechanical closure of the neck gives surgery its most important advantage. So that, this effect results more remarkable in patients with longer survival expectancies (**Figure 1**).

Another important factor that was dismissed during ISAT study design is that neither experience, nor morbimortality of the centers included, were analyzed. It is recommended that surgical clipping should be performed in those centers with, at least, 30 aneurysms a year (Connolly et al., 2012). It is remarkably that a Finnish study did not find differences in clinical outcome at 1 year, but rate of rebleeding and suboptimal occlusion favored surgical clipping (Koivisto et al., 2000). Likewise, additional microsurgical techniques, including opening of the lamina terminalis appear to significantly reduce deleterious effects derived from hydrocephalus and intracranial hypertension. There is, indeed, a window of time in which results are skewed in benefit of endovascular coiling, but after that period, advantages of coiling over clipping in terms of survival and independency are vanished. During this “Brain Stress Time”, neurovascular tissues suffers an extra stress derived from open surgery, inducing temporary changes in cerebral homeostasis, edema, similar to that occurred during TBI or second impact syndrome, that go beyond the first few days after surgery and might affect the general picture of the clinical outcome at short follow-up. Experienced surgeons with outstanding performance of the microsurgical techniques, shorter operative times and development of minimally invasive microsurgical approaches may narrow this window and overcome the potential pitfalls of surgery even at an earlier phase.

Conclusion

Retreatment and rebleeding rates clearly favors microsurgical clipping and this differences seems to be influ-

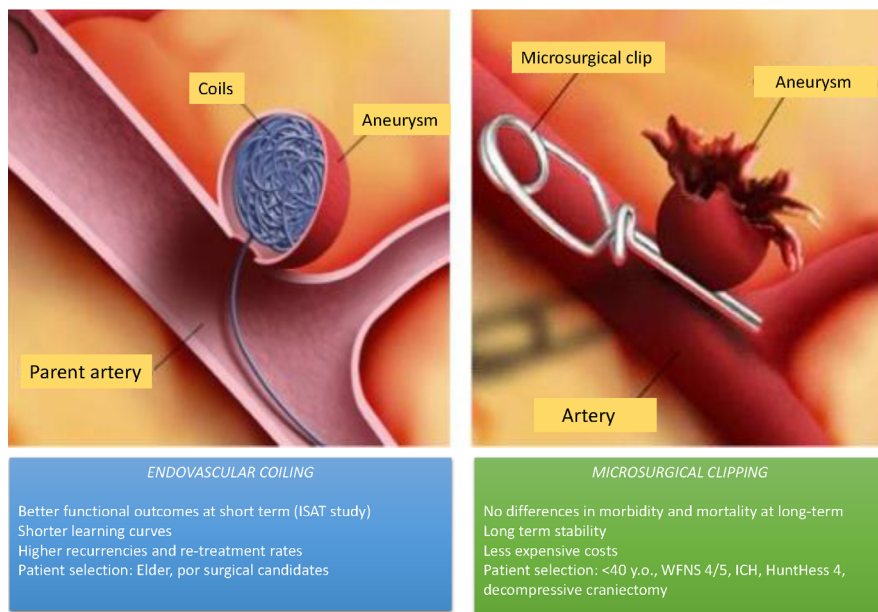


Figure 1 Alternatives in the treatment of ruptured cerebral aneurysms.
ISAT: International Subarachnoid Aneurysm Trial; y.o.: years old; WFNS: World Federation of Neurological Societies; ICH: intracerebral hemorrhage.

enced by longer follow-up times. Risks and higher costs derived from additional interventional procedures, including diagnostic angiograms, as its associated complications make coiling not such as attractive as previously though, particularly in certain regions, in whom proper follow-up and resources are not guaranteed. We sustain that treatment strategy should be made by a multi-disciplinary team in accredited centers with proficient experience in both techniques, considering the higher occlusion rate and longevity of the surgical treatment.

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