

# Considerations About Ultra-early Treatment of Ruptured Aneurysms

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When a patient with a ruptured aneurysm has been fortunate enough to reach a hospital alive, the main fear is that the aneurysm may re-bleed. Although initial medical treatment guidelines include measures to reduce the risk of re-bleeding, the only sure way to avoid such a catastrophe is to exclude the aneurysm itself from circulation, whether by surgical or endovascular means.

Since the inception of surgical treatment of aneurysms till the 1980s, exclusion of the aneurysm was postponed due to the limitations of surgical techniques, which were associated with unfavorable results while performed in an acute stage [1, 2]. At that time we were dealing with sub-optimal surgical exposure leading to forceful brain retraction and manipulation on a very swollen and tense brain. Hence surgery was often postponed, and it was not uncommon to witness patients dying from re-bleeding while waiting for surgery. This uncomfortable waiting period allowed us to quantify that risk, which was associated with a high mortality rate, as well as to determine the timing of re-bleeding and when this risk is the greatest [3]. The introduction of microsurgical techniques together with better peri-operative medical management of the effects of the initial hemorrhage and vasospasm explain the results of the international cooperative study published in 1990, which revealed that there was no difference in outcome between early (1–3 days post SAH) and late surgery (>10 days) [4, 5]. That is to say, thanks to these improvements, that early surgery is now feasible, and in fact this is now a common practice.

The experience gained over time has made it possible to secure the aneurysm earlier while limiting further damage to the brain. The advent of endovascular procedures has also helped to reach that goal. Yet despite earlier intervention, the risk of re-bleeding remains ominously significant, having been evaluated to be the most prevalent in the first 24 h [6–8].

Given all these improvements, presently, it would seem intuitive to occlude the aneurysm within 24 h (ultra-early aneurysm treatment). Indeed, some studies suggested that ultra-early aneurysm treatment might be associated with a better outcome [9–11]. Yet in this issue of *Neurocritical Care*, Oudshoorn et al., looked at two cohorts and concluded that aneurysm occlusion can be performed in daytime within 72 h after ictus, instead of on an emergency basis. In their observational study, the cohorts from the UMC Utrecht SAH database and from the randomized ISAT trial were categorized into aneurysm treatment <24 h and 24–72 h after ictus and analyzed for poor functional outcome. The data from each cohort were first analyzed separately and then pooled together. Aneurysm treatment <24 h did not result in better outcome than treatment 24–72 h after bleeding even in the worst-case scenario, when all the patients with re-bleeding >3 h after admission were recategorized into the group of 24–72 h [12].

This is not to say that we can postpone intervention to eliminate the aneurysm. These results in no way justify deliberate delay. This is a post-hoc analysis of two cohorts of patients admitted for aneurysmal SAH: the prospectively collected UMC Utrecht SAH database and the ISAT randomized trial. There are several aspects inherent in these two series that naturally bring about important bias to take into account. In both series, the patients were not randomized according to the timing of surgery, nor is it known how they were selected for their respective groups. Hence

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comparing them to determine a difference in the outcome based on the timing of surgery produces a biased selection. Despite the use of a regression model, there is a lack of ability to measure important confounders.

For example, one factor not taken into account is the cause of the clinical condition. It would not be surprising that in many centers, for patients in the same clinical grade upon admission, the timing of intervention may be influenced by the underlying cause of the said clinical grade, which may be different, for example hydrocephalus versus a hematoma. Yet, the different causes may be responsible for different outcomes.

It is often a natural tendency to treat more urgently those patients who are in a more severe state. Referring to the figures in Table 1, we see that there are a higher percentage of patients in high grade who were operated on in <24 h. This could have had a negative influence on outcome in this group of patients, yet the results showed that both groups had similar outcome, which would lead us to favor earlier intervention.

The ISAT, which was randomized to compare the efficacy of clipping vs coiling, included only patients who were suitable for both procedures. In addition to the design of the study, a large proportion of patients were excluded for various other reasons, thus creating a significant bias. Of the 9,559 patients assessed for eligibility, 78 % were excluded. Only 9 % of the patients refused to participate, and the remaining 69 % were excluded for reasons unknown [13]. We do not know how these excluded patients would have affected the results.

Recognizing the limitations of their study, the authors also rightly acknowledge that their results cannot be considered as definitive evidence to justify later intervention.

However, despite the aforementioned limitations of this study and yet keeping in mind the consequences of re-bleeding, in real life there are nonetheless circumstances where very early surgery is not feasible or even desirable, unless certain logistical modifications are implemented. It is generally accepted that there is a relation between outcome and the volume of cases in a particular center [14, 15]. For this reason, patients with ruptured aneurysms are ideally treated in tertiary centers. Although the transfer to a tertiary center will inevitably cause a delay, treatment in a specialized center, where options for both surgery and endovascular intervention exist, offer better results [15, 16]. The benefits from a tertiary center are not only dependent on the expertise of the treating physician, but also on that of the entire team as well as the environment. However, within the tertiary center itself, the most ideal conditions may not always be present at night or on weekends, when the supporting team may not be available, and for other logistical reasons. In addition there is the factor of fatigue; it is known that neurosurgeons and neuro-

interventionists work long hours and may not be at their optimal performance level. Even though there is conflicting literature regarding the link between fatigue and surgical error, it is known that fatigue may in fact bring about important impairment in basic and high-order cognitive function, which are necessary for these highly demanding and delicate procedures [17].

The authors deserve to be congratulated for bringing to light the fact that, in a large population, very early intervention is no guarantee for better outcome. Thanks to their study, they remind us that we must be very cautious in drawing any conclusions regarding the timing of occluding ruptured aneurysms. Although they admit that only a randomized trial could give more substantial evidence, they recognize that such a trial would be questionable. Even though they do not expand on the reasons for this questionability, it would be difficult to justify to a patient to deliberately delay definitive treatment of a ruptured aneurysm knowing that the risk of re-bleeding is most high in the first 24 h and not having concrete evidence that early intervention is harmful. Indeed, aneurysm occlusion within 24 h may facilitate the management of the processes induced by the aneurysm rupture, such as increased intracranial pressure, hydrocephalus, and delayed cerebral ischemia. Rather, there could be other future studies that would be more feasible, such as better identification of those aneurysms which are at very high risk of imminent rupture, based on imagery or biochemistry, and such as searching for medication capable of reducing the risk of early re-bleeding to allow a safer waiting time until definitive treatment is possible (e.g., antifibrinolytic).

In the mean time, for patients with a chance of a meaningful recovery, measures should be taken to ensure optimal conditions for the earliest intervention. For each patient, everyone involved at every level and stage, from initial evaluation to definitive treatment, must strive to reduce unnecessary delays caused by logistical, non-clinical obstacles. In addition, it would be advisable that each hospital has established measures to facilitate reaching this goal.

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