Letters to the Editor

NEUROSURGICAL FORUM

Timing of surgical aneurysmal exclusion in SAH

TO THE EDITOR: We read with great interest the article by Mahaney et al.2 (Mahaney KB, Todd MM, Torner JC: Variation of patient characteristics, management, and outcome with timing of surgery for aneurysmal subarachnoid hemorrhage. J Neurosurg 114:1045–1053, April 2011).

In this article, the authors reported the functional outcome of patients suffering from aneurysmal subarachnoid hemorrhage (SAH) regarding the timing of surgical exclusion of aneurysms. The data were extracted from a randomized controlled trial conducted for another purpose, and the study comprised 1000 patients.4

Mahaney and colleagues showed that functional outcomes were better if surgical exclusion was performed early (0–2 days after the initial hemorrhage) or late (7–14 days) rather than intermediately (3–6 days).

As we consider the issue of the timing of aneurysm exclusion in SAH of utmost importance, we carefully read this article. We were surprised at the total lack of data concerning preoperative rebleeding, which is a major and known factor of poor outcome, and its incidence is far from anecdotal.3

In this study, patients were in World Federation of Neurosurgical Societies (WFNS) Grades I–III at the time of surgery; these grades might have been different from those at the time of aneurysm rupture. These criteria might have automatically excluded patients with preoperative rebleeding, as rebleeding in most cases is associated with severe deterioration in neurological status.

Therefore, the conclusions of this study could contribute to a significant bias as the study does not include the eventuality of rebleeding as a prognostic factor. This bias may be significant; for example, in the late surgical exclusion group, if we consider the risk of early rebleeding, published in the International Cooperative Study on the Timing of Aneurysm Surgery, about 13% of these patients would have suffered from rebleeding.1 As these patients should not have a good functional outcome, the percentage of patients with a Glasgow Outcome Scale score of 1 in this group decreased from 67% to 54%. Thus, the results would be similar to those in the intermediate group, and probably really worse than those in the early group, as the risk of preoperative rebleeding in the early group is less important.

Therefore, the conclusions of this study are more limited than expected: with equal immediate preoperative clinical grades across all 3 groups, early and late surgical aneurysm exclusion are associated with better outcomes than intermediate exclusion (3–6 days).

We also do believe that early aneurysm exclusion in SAH is the best practice, as it decreases the risk of rebleeding and allows for aggressive therapy for vasospasm. This article provides a new argument: very early surgical exclusion almost by itself improves the functional outcome.

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DISCLOSURE
The authors report no conflict of interest.

References

Response
We appreciate Drs. Gaberel’s and Emery’s critique and commentary on our findings relating to timing of surgery in good-grade patients with aneurysmal SAH. The concern that rebleeding is an important factor affecting patient outcomes is appropriately highlighted.

The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) was designed as a clinical trial to test the hypothesis that hypothermia, as a form of neuroprotection during aneurysm surgery, would result in improved clinical outcomes by reducing secondary neurological injury in patients who preoperatively were in good clinical condition. Thus, by design, the study excluded both 1) patients who were in poor clinical condition as a result of the initial SAH and who did not improve to good condition prior to surgery and 2) patients who were admitted in good clinical condition but had neurological decline prior to surgery (including neurological decline from rebleeding). This does limit our conclusions regarding surgery beyond the early time period because of the exclusion of patients who
may have had neurological deterioration due to rebleeding. During IHAST, at the participating centers, 2856 patients underwent surgery to secure a ruptured intracranial aneurysm and 1183 of these patients met eligibility criteria for IHAST. A total of 1033 patients were enrolled and 1001 patients were randomized. The majority of patients who were excluded from IHAST were excluded either because of a poor WFNS grade on admission or because of intubation (which precluded a thorough baseline examination), and relatively few patients were admitted in good clinical condition and experienced deterioration prior to surgery. Thus, in the eligible patient population, rebleeding likely represented a small contribution to overall outcomes. This may also be due to the large number of patients who underwent early surgery (50% of patients in IHAST underwent surgery within 48 hours), effectively limiting risk of rebleeding.

In conclusion, we reiterate our recommendation that in patients presenting in good clinical condition with aneurysmal SAH, decisions regarding timing of surgery should be weighed carefully against the known risk of rebleeding.

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Fusion antibody Fc-endostatin

TO THE EDITOR: We are interested in the article by Grossman et al.1 (Grossman R, Tyler B, Hwang L, et al: Improvement in the standard treatment for experimental glioma by fusing antibody Fc domain to endostatin. Laboratory investigation. J Neurosurg 115:1139–1146, December 2011). Gliomas are highly angiogenic2,6 and refractory to conventional therapies.2–6 Studies on novel combination therapies are urgently needed. Grossman et al.1 performed a laboratory investigation to explore the effect of endostatin fused to antibody Fc domain (Fc-endostatin; mFc-endostatin for use in rodents) in combination with oral temozolomide (TMZ) on survival in a 9L gliosarcoma rat model. Their study demonstrated that either locally or systemically administered mFc-endostatin extended the survival of rats bearing orthotopic intracranial 9L gliosarcoma. Although the blood-brain barrier (BBB) is thought to restrict the delivery of drugs to gliomas, mFc-endostatin could exert its antiangiogenic effect against gliosarcoma even without passing through the BBB.

There are 2 flaws in their article. Firstly, in the Discussion, they stated that rats treated with mFc-endostatin did not show any remarkable local toxicity. In the Conclusions, they declared that the combination of subcutaneous mFc-endostatin with oral TMZ did not cause additional toxicity. Actually, the adverse effects of TMZ have been well documented, including nausea and vomiting.7 Theoretically, weight loss is a basic measurement of toxicity in an in vivo experiment. However, no experimental approach to assess in vitro or in vivo toxicity was addressed in the Methods of their article. Conclusions should be based on logical analyses of results obtained through adequate design of experimental methods. Secondly, in the Methods, control rats did not receive any treatment. This kind of study control is not stringent enough. Since Fc-endostatin has been modified through the fusion of endostatin to an antibody (IgG) Fc domain to overcome some deficiencies of bare endostatin, a better treatment control would be Fc-IgG control or denatured Fc-endostatin.

Despite these minor concerns, the authors’ study provided important evidence of improved survival in gliosarcoma. For future translational research into humans, further studies are warranted to improve gliosarcoma outcomes.

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Response

No response was received from the authors of the original article.

References


DISCLOSURE

The authors report no conflict of interest.