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.

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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 angiogenic^{2,6} 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 Theo-

retically, 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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DISCLOSURE

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Response

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

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Improving arteriovenous malformation research and care

TO THE EDITOR: In the November issue of the *Journal of Neurosurgery*, Elhammady and Heros² focused on their current management of unruptured cerebral arteriovenous malformations (AVMs) in the era after ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) had ended (Elhammady MS, Heros RC: Editorial. Management of incidental cerebral AVMs in the post-ARUBA era. *J Neurosurg* 121:1011–1014, November 2014). While recognizing their substantial expertise and major contributions to the field of vascular neurosurgery, we would like to go one step further and use this period of uncertainty created by ARUBA as an opportunity to improve evidence in the management of unruptured AVMs rather than continue on opinion and experience.

We are writing today with an urgent appeal to enter the post-ARUBA era. Now, while we are going through a questioning period, is the opportune time to dust ourselves off and embark on a new program combining research and practice to offer optimal care to our patients with AVM.⁶ The ARUBA study,⁴ which concluded that the medical management of unruptured AVMs is superior to any interventional treatment, has elicited from our community a multitude of editorials, critiques, baffled responses, and frustration.^{1–3,5,7} Some of ARUBA's shortcomings are the large number of nonrandomized but eligible patients, the definition of poor outcomes, the nonuniformity of treatment, and the short follow-up period. Given these weaknesses, many of us are reluctant to accept ARUBA's conclusions. The risk now is that we may come away from it not having learned any lesson and pursue some course of action without fully grasping the implications. Some may disregard the conclusions of the ARUBA study altogether and continue treating AVMs as they see fit. In contrast, others may embrace ARUBA's conclusions and stop treating unruptured AVMs entirely, period. As professionals concerned about the well-being of our patients, none of us can blindly ignore the fact that some patients will suffer in either case. This would be irresponsible. As controversial as this study may be, the next step seems clear: a new randomized study to justify our action or inaction before we establish a new course of action. Such a new study would allow the inclusion of all AVM patients, followed over a longer period of time, and would allow minor or predictable postoperative deficits to be considered as good outcomes given the possible devastating consequences of AVM rupture. This is the best way to minimize error and to have a chance to answer the crucial questions with which all AVM patients are confronted. We have been treating AVMs for decades, and we still do not know whether we should even treat them at all. The burden of proof rests on us. If we offer a curative treatment, it is our duty to prove that any risky preventive intervention will be beneficial. If we choose conservative management, there again we must base our decision on evidence.

For these reasons, we propose the TOBAS (Treatment of Brain AVMs) study. It is a pragmatic, prospective randomized study with an accompanying registry. Contrary

to ARUBA, which started off with the hypothesis that conservative management was best, the hypothesis of TOBAS favors curative treatment. There are 3 main objectives: 1) to allow clinicians to manage their patients within a research protocol, which is probably the best way to justify our action when faced with uncertainty and is probably also the best way to minimize potential error in our decision making; 2) to determine the role of curative treatment in unruptured AVMs; and 3) to stratify the risks associated with the various treatment modalities in unruptured and ruptured AVMs, including whether or not to pre-embolize, since the potential benefit of presurgical or preradiosurgical embolization remains contentious.

These goals are essential to increase our knowledge and improve care. As stated by Arthur L. Day and colleagues, "ARUBA is not the end of research in brain AVMs; it is just the end of the beginning of new research into their management."¹

We know that we can injure patients while treating an AVM, and ARUBA reaffirmed this. However, this does not mean that we should stop treating unruptured AVMs, as Elhammady and Heros have noted. It does mean that we cannot continue doing what we were doing without taking a closer look at what we are doing.

We invite physicians treating patients with AVMs to join TOBAS (ClinicalTrials.gov, trial registration no.: NCT02098252; tdarsaut@ualberta.ca or jraymond.nri@gmail.com).

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DISCLOSURE

The authors report no conflict of interest.

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Response

We appreciate Dr. Bojanowski and colleagues' expressed interest in our recent editorial. We certainly agree with their concerns that some may wrongly interpret the conclusions of the ARUBA study as indicating that no patient with an unruptured AVM should be treated. We also agree that it would be wrong to completely ignore the findings of the ARUBA study. At the very least we have learned from this study that any kind of intervention for unruptured AVMs can carry significant morbidity.

We agree with Bojanowski and colleagues that there is still some uncertainty about how and when to treat some unruptured cerebral AVMs and that continuing research is in order. However, we disagree with their statement that "we have been treating AVMs for decades, and we still do not know whether we should even treat them at all." We do believe that through accumulated experience, we have learned a great deal about treating AVMs and which AVMs should be treated. The lack of confirmation by a randomized study does not mean that what we have learned from personal experience and from a careful following of the literature is worth nothing. When faced with having to advise a patient, it would be unethical for us to recommend a course of action other than that which we think is best for that patient. As an extension of this, it would also be improper, in our opinion, to tell a patient that we do not know which course of action is better and therefore that we are willing to randomize him or her if indeed we believe that one course of action is better than another. This will make it hard for experienced clinicians to randomize a large number of patients into another study such as the TOBAS study proposed by the authors. It would be difficult for us to randomize patients with Spetzler-Martin (SM) Grades I and II AVMs since we firmly believe that the results of excision in this group of patients, in competent hands, are far superior to the lesion's natural history. Likewise, it would be very difficult to randomize unruptured SM Grade IV or

V malformations since we have learned that the morbidity of curative treatment of these lesions is too high to justify treatment given what we know about their natural history. We also believe that palliative treatment, such as partial embolization, for these lesions is ineffective. There may be an occasional Grade IV malformation, perhaps a very large lesion in the frontal or nondominant parietal lobe that does not directly involve eloquent regions of the brain, that we would randomize because we truly do not know if treatment, such as excision after embolization, is better than the natural history in these particular cases. I suspect we would randomize a number of Grade III malformations since we truly don't know if treatment is better than observation for many of these lesions. However, randomization would have to be specifically for the form of treatment that we believe would be best for that malformation. We would not, for example, randomize to radiosurgery a patient with a large Grade III malformation, nor would we want to randomize to excision a patient with a small deep malformation in an eloquent area of the brain that we believe would be best treated by radiosurgery.

Dr. Bojanowski and colleagues have been great contributors to the cerebrovascular field, and we are sure that if they lead the design of a new randomized study of AVM treatment, they would do so in a very thoughtful and most ethical way. We are just not very optimistic that a large enough number of patients can be recruited into such a study in a reasonable period of time.

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