Controversy: Clipping of a <7 mm Asymptomatic Aneurysm

Controversy: Clipping of Asymptomatic Intracranial Aneurysm That is <7 mm

Yes

Gary K. Steinberg, MD, PhD

The second (prospective) International Study of Unruptured Intracranial Aneurysms (ISUIA), published in 2003 in The Lancet, suggested that the risk of hemorrhage from an unruptured intracranial aneurysm <7 mm is extremely low, and that present microsurgical or endovascular treatment for patients harboring these lesions carries a far greater risk of incurring a neurologic deficit than the natural history. This has led to a much more conservative approach toward managing such patients. However, considerable controversy remains on whether or not to offer therapy (surgical or endovascular) to these patients.

We recall that the first (retrospective) ISUIA study, published in New England Journal of Medicine in 1998, demonstrated that asymptomatic intracranial aneurysms ≤10 mm had a very low rupture rate (0.05%/yr for group 1, no previous bleeding from another aneurysm; 0.5%/yr for group 2, previous bleeding from another aneurysm). The authors concluded that 10 mm should be the cutoff for considering treatment of these aneurysms, particularly in group 1 patients. This study also promoted a major change in clinical practice, so that many patients with aneurysms <10 mm were not treated. Was this a reasonable response? Probably not, especially in view of the more recent ISUIA data indicating that aneurysms that are 7 to 12 mm carry a considerable risk of bleeding. Should we significantly alter our practice on the basis of a single nonrandomized study, such as the 2003 ISUIA study?

A closer examination of the 2003 ISUIA study reveals that some aneurysms <7 mm have a significant risk of bleeding (Table). Five-year cumulative risks of hemorrhage were 2.5% for posterior communicating artery aneurysms in group 1; 1.5% for anterior communicating (AC), middle cerebral (MC), and internal carotid aneurysms in group 2; and 3.4% for posterior communicating artery aneurysms in group 2. All patients with these asymptomatic aneurysms should be considered for microsurgical or endovascular treatment. Group 1 patients with AC/MC/internal carotid aneurysms <7 mm had a 0% rupture risk. However, some concerns remain over these data. This study lacked randomization and contained selection bias for patients. Of 4060 patients enrolled, only 1692 patients were followed as part of the natural history, and 534 of these patients switched to being treated. Another 1917 patients received surgery, whereas 451 patients received endovascular therapy; the treating surgeon/interventionalist may have precluded patients from entering the natural history group who had a higher risk of bleeding based on aneurysm morphological characteristics or family history. Also, AC artery aneurysms were very underrepresented in the 2003 ISUIA study (only 10%), yet this location accounts for one fourth of all ruptured aneurysms in some large series. A meta-analysis of natural history studies that examined the risk of rupture in unruptured AC artery aneurysms showed a 2.5-fold greater rupture risk in these aneurysms than in other anterior circulation sites (2.2%/yr, range 1.6–5.8%/yr).

Furthermore, follow-up in the 2003 ISUIA study was relatively short with a mean of 4.1 years and <5-year follow-up in >50% of patients; the immediate risks of surgery might, therefore, be outweighed by the morbidity of bleeding over a longer period. In fact, ISUIA (2003) showed that patients <50 years old with asymptomatic anterior circulation aneurysms <25 mm had a surgical morbidity of only 5% to 6% (poor outcome being death; modified Rankin Score, 3–5; or impaired cognitive status).

Another issue is whether a 6-mm aneurysm is really physiologically, pathologically, or hemodynamically different from a 7-mm aneurysm, enough to make it less likely to rupture. Furthermore, is it truly possible to accurately differentiate a 6-mm aneurysm from a 7-mm aneurysm with any radiological imaging, including digital subtraction angiography? There is also the well-recognized paradox that many ruptured aneurysms are found to be <7 mm at the time of surgery or interventional treatment. Published series have shown mean and median ruptured aneurysm sizes of <7 mm, with 1 recent study of 613 ruptured aneurysms demonstrating a mean maximal aneurysm diameter of 6.5 mm and median of 5.7 mm. Moreover, 61% to 72% of ruptured aneurysms are ≤7 mm, and 40% to 50% of ruptured aneurysms are ≤5 mm. The following two explanations have been proposed for this discrepancy between sizes of ruptured aneurysms versus unruptured aneurysms that go on to rupture: (1) aneurysms decrease in size after they rupture; (2) aneurysms either rupture soon after they form, when they
are very small, or stabilize over a short period of time if they do not rupture, and the likelihood of rupturing is small if they stabilize at <7 mm. However, there is no evidence to support these hypotheses. Other natural history studies demonstrate a somewhat higher risk of hemorrhage from unruptured aneurysms compared with the 2003 ISUIA report. In a study of 142 Finnish patients, mostly with group 2 type unruptured aneurysms and a median follow-up of 19.7 years (0.8–39 years), the rupture rate for anterior circulation aneurysms (excluding posterior communicating aneurysms) was 1.1%/yr, 3.7-fold of the 2003 ISUIA rates. In the Unruptured Cerebral Aneurysm Study (UCAS) of Japan, recently published in New England Journal of Medicine and after 4195 aneurysms (96% group 1), >11 660 aneurysm-years demonstrated an annual rupture rate of 0.7% to 0.9%/yr for AC aneurysms <7 mm (compared with 0% in ISUIA for AC/MC/internal carotid group 1).

Most cerebrovascular surgeons have encountered patients with documented unruptured aneurysms <7 mm that have gone on to rupture, including those in group 1 and the AC/MC/IC internal carotid artery distribution who had a 0 risk of bleeding in the 2003 ISUIA study (Figure), also calling into question these results. Once an unruptured aneurysm bleeds, we have good data that the clinical outcome is dismal. In the 1998 ISUIA report, 32 patients ruptured with 66% mortality (83% group 1; 55% group 2); in the 2003 ISUIA study, 51 patients bled with 65% mortality; and in the UCAS, of the 39 ruptured aneurysms, 35% of the patients died and 32% of the patients had moderate to severe disability (modified Rankin Score, 3–5). This significant morbidity and mortality must be considered when balancing the treatment risks for a particular patient.

Certain epidemiological and aneurysm morphological features may also increase the risk of hemorrhage from an unruptured aneurysm. The Familial Unruptured Aneurysm Study showed that, of 313 subjects with unruptured aneurysms and a family history of intracranial aneurysms, 2 subjects with 3-mm and 4-mm AC aneurysms bled at 17 and 16 months after enrollment, with an overall 1.2%/yr rupture rate, 17-fold greater than reported in ISUIA (0.069%/yr with a matched distribution of intracranial aneurysms size and location). This analysis even excluded 2 patients with known unruptured intracranial aneurysms who bled before enrollment (one patient with a 4-mm AC aneurysm and the other with an 8-mm MC artery aneurysm and 5 mm posterior communicating artery aneurysms), as well as 1 patient who was enrolled and bled before the MR angiography was completed, who was shown to have a 4-mm MC aneurysm on angiography. Other studies also have shown that familial intracranial aneurysms have a greater risk of growth and rupture compared with sporadic aneurysms.

Evidence also suggests that unruptured aneurysms that are multilobulated have a daughter sac or are irregular in shape may be more prone to bleeding. Furthermore, unruptured aneurysms <7 mm that show growth on sequential radiological imaging may be at increased risk of rupturing, even before they reach a diameter of 7 mm. Inoue followed 18 patients with asymptomatic aneurysms who showed increasing aneurysm size on MR angiography (16 had aneurysms <7 mm). Of 18 patients, 4 ruptured within 1 to 23 months of follow-up MR angiography (18.5%/yr); all 4 had aneurysms <7 mm initially, including 1 patient with a 3-mm aneurysm that enlarged to 6.1 mm at 6 months and ruptured 1 month later. Chmayssani recently reviewed all publications that followed asymptomatic unruptured aneurysms ≤7 mm with 2 time points of size measurements (n=64; 63 were ≤7 mm). Thirty-three of these aneurysms ruptured and 27 showed enlargement before rupture, although 6 aneurysms bled without growing. Fourteen of these patients still had aneurysms <7 mm before rupture.

**Table. 5-Year Cumulative Rupture Rates, According to Size and Location of Unruptured Aneurysm**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>7–12 mm</th>
<th>13–24 mm</th>
<th>≥25 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavernous carotid artery (n=210)</td>
<td>0</td>
<td>0</td>
<td>3.0%</td>
<td>6.4%</td>
</tr>
<tr>
<td>AC/MC/IC (n=1037)</td>
<td>0</td>
<td>1.5%</td>
<td>2.6%</td>
<td>14.5%</td>
</tr>
<tr>
<td>Post-P comm (n=445)</td>
<td>2.5%</td>
<td>3.4%</td>
<td>14.5%</td>
<td>18.4%</td>
</tr>
</tbody>
</table>

AC indicates anterior communicating or anterior cerebral artery; IC, internal carotid artery (not cavernous carotid artery); MC, middle cerebral artery; and post-P comm, verteobasilar, posterior cerebral arterial system, or the posterior communicating artery.

This suggests that small aneurysms are prone to growth and rupture, rupture is more likely with aneurysm growth, but rupture of aneurysms initially <7 mm nonetheless occurred without aneurysm enlargement.

Finally, psychological factors are extremely important. Some patients are unwilling to live with the knowledge that they have an intracranial aneurysm with a risk of bleeding, despite being informed of a low risk of rupture. These patients may choose to accept the immediate risks of treatment to eliminate the delayed risk of hemorrhage with accompanying morbidity and mortality.

There is no doubt that smaller unruptured aneurysms have a lower risk of bleeding than do larger aneurysms. However, setting an absolute threshold of 7-mm diameter as the criterion for treatment is somewhat arbitrary and not supported by level 1 evidence. Selected patients with asymptomatic aneurysms <7 mm should be considered for treatment, either with microsurgery or endovascular therapy. These include patients with a previous subarachnoid hemorrhage from another aneurysm surgery or endovascular therapy. These individuals have aneurysm growth, certain aneurysm morphological characteristics, or psychological factors.

The recommendation for treatment of a patient with an asymptomatic intracranial aneurysm <7 mm should be individualized and based on the patient’s age, aneurysm location, aneurysm morphology, family history, medical comorbidity, psychological factors, and the risk of surgical or endovascular treatment for that aneurysm in the experience of the surgeon or interventional neuroradiologist.

Disclosures

None.

References


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