Management of Unruptured Brain Arteriovenous Malformations

Andrew F Ducruet, MD[1] and Robert M Friedlander, MD, MA[2]

1. Assistant Professor of Neurological Surgery;

2. Chairman and Walter E Dandy Professor of Neurological Surgery, Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, Philadelphia, US

Abstract

Brain arteriovenous malformations (bAVMs) portent a lifelong risk of hemorrhage but the treatment of these lesions may also be associated with significant morbidity. Two recent high-profile studies have suggested that patients undergoing treatment of bAVMs may suffer a worse outcome than patients managed conservatively. However, both of these studies suffer from significant limitations that limit the conclusions that can be drawn. Further work, including the establishment of a prospective registry, is necessary to definitively address this matter.

Keywords

Brain, arteriovenous, malformation, embolization, radiosurgery, resection, rupture

Disclosure: Andrew F Ducruet, MD, and Robert M Friedlander, MD, MA, have no conflicts of interests to declare. No funding was received for the publication of this article.

Received: September 15, 2014 **Accepted**: September 19, 2014 **Citation**: *US Neurology*, 2014;10(2):120–1 *DOI: 10.17925/USN.2014.10.02.120*

Correspondence: Robert M Friedlander, MD, MA, UPMC Presbyterian Hospital, 200 Lothrop Street, Suite B-400, Pittsburgh, PA 15213, USA. E: friedlanderr@upmc.edu

Brain arteriovenous malformations (bAVMs) are rare congenital lesions that confer a lifelong risk for hemorrhage. Treatment options for these lesions include microsurgical resection, embolization, and radiosurgery, alone or in combination. The goal of bAVM intervention is to eliminate the risk for future hemorrhage, which must mean complete obliteration of the lesion. However, treatment also poses a risk for morbidity and morbidity.

Two recent high-profile studies compared outcomes between patients with bAVMs treated with multimodality therapy with those managed conservatively.[1,2] Although both studies on the surface demonstrate worse outcome following intervention, they both have significant limitations, which preclude the conclusion that conservative management is superior to intervention in patients with bAVMs.

The primary results of the Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA) trial were recently published.[1] This multicentered international randomized trial compared interventional treatment to medical management for unruptured bAVMs. The primary endpoint of the study was symptomatic stroke or death, with a secondary outcome of death and disability measured by the modified Rankin scale (mRS). The trial was initially designed to include 800 patients, however, the target sample size was later reduced to 400 and the trial was halted after only 223 subjects were randomized. Of the 109 patients in the medical group, 10.1 % experienced the primary endpoint compared with 30.7 % in the interventional group (30.7 %). A significantly lower proportion of patients in the medical group (15 %) also demonstrated an mRS ≥2 versus 46 % in the interventional group.

Interpretation of these results is complicated by several limitations in trial design and execution. First, relatively slow patient enrollment engendered a significant selection bias. Of the 66 centers listed as participating, only 39 ultimately enrolled patients. Because of the low enrollment for each center, including some centers with large bAVM practices, many patients were treated outside the trial. A careful review of screening logs is thus required to understand how the patients that were treated outside the trial differed from those that were enrolled. It is likely that bAVMs with a perceived low treatment risk would be preferentially treated and ones with more benign natural history may have been randomized. These two would result in a preferential bias of randomizing bAVMs with perceived higher treatment risk as well as ones with a more benign natural history. Second, centers that treat as few as 10 bAVMs per year among all practitioners were allowed to participate in the trial without further rigorous accreditation. This is a critical limitation, as the relationship between volume and outcome has been repeatedly and convincingly demonstrated in cerebrovascular surgery.[3] Perhaps because of a relative lack of experience at the enrolling centers, no clear standardization in intervention was seen. In fact, only five patients underwent surgery alone, which is generally regarded as the gold standard treatment for low-grade bAVMs—perhaps because many centers may not have had access to a neurosurgeon to resect these lesions. A high number of patients were treated by standalone embolization (30 patients), which has been shown to yield a low rate of complete occlusion and potentially a high rate of complications. Finally, and perhaps most importantly, the trial was interrupted after only a short follow-up interval (mean of 33 months). Given the annual 2.2 % hemorrhage rate in the medical group, coupled with an average age of patients of 44 years in the interventional group, a

study design incorporating much longer follow-up would be essential to adequately compare outcomes between groups.

In the second study, Al-Shahi Salman et al. prospectively followed up to 204 patients with unruptured bAVMs over a period of 12 years. One hundred and three of these patients underwent intervention. Treated patients were likely to be younger, have smaller AVMs, and to have presented with seizure. During a mean follow-up of 6.9 years, the rate of progression to the primary outcome (death or sustained morbidity of any cause) was lower with conservative management during the first 4 years of follow-up (36 versus 39). Thereafter, rates were similar. The rate of secondary outcome (nonfatal stroke or death due to bAVM, associated aneurysm, or intervention) was also lower with conservative management during 12 years of follow-up (14 versus 38). The authors conclude that conservative management of bAVM was associated with better clinical outcomes for up to 12 years.

This study also suffers from several weaknesses that limit conclusions that can be drawn from the data. First, this was a nonrandomized study, and thus there are inherent differences between cohorts. Next, the authors report a complication rate of 27.1 % in the intervention group. This is strikingly high relative to the rate of 5.7 % calculated in a recent meta-analysis of 13,698 bAVM patients.[4] Additionally, the authors report a bAVM obliteration rate of only 66 %, which must be judged against a surgical obliteration rate of 96 % in the meta-analysis. Finally, 20 of 31 deaths in the conservative group were classified as unrelated to the AVM, which represents a much higher rate than in the treated cohort (six of 10). Mortality from AVM rupture occurring in patients who did not make it to the hospital may clearly have been missed.

Given the significant limitations of both of these recently published studies, it is impossible to conclude that conservative management will result in better outcomes than intervention for the broad population of unruptured bAVMs. Furthermore, neither of these studies can be effectively extrapolated to centers that routinely employ surgical resection of low-grade bAVMs. Further work is therefore necessary, and the establishment of a multicenter, adjudicated registry of consecutive patients is warranted. ■

1. Mohr JP, Parides MK, Stapf C, et al., Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial, *Lancet*, 2014;383:614–21.
2. Al-Shahi Salman R, White PM, Counsell CE, et al.; Scottish Audit of Intracranial Vascular Malformations, Outcome after conservative management or intervention for unruptured brain arteriovenous malformations, *JAMA*, 2014;311:1661–9.
3. Zacharia BE, Bruce SS, Carpenter AM, et al., Variability in outcome after elective cerebral aneurysm repair in high-volume academic medical centers, *Stroke*, 2014;45:1447–52.
4. van Beijnum J, van der Worp HB, Buis DR, et al., Treatment of brain arteriovenous malformations: a systematic review and meta-analysis, *JAMA*, 2011;306:2011–9.