Austin Journal of Cerebrovascular Disease & Stroke

Austin Publishing Group

Open Access Full Text Article

Editorial

Treatment of Unruptured Arteriovenous Malformations: The End of Tame Editorials

Bradley A Gross*

Department of Neurological Surgery, Boston Children's Hospital and Harvard Medical School, US

***Corresponding author:** Bradley A Gross, Department of Neurological Surgery, Brigham and Women's Hospital and Harvard Medical School, 75 Francis St, Boston, MA 02115, US, Email: Bgross1@partners.org

Received: September 08, 2014; **Accepted:** September 10, 2014; **Published:** September 11, 2014

Keywords

AVM: Arteriovenous Malformation; Surgery; Microsurgery; Embolization

Editorial

In contrast to cerebral aneurysms, cerebral Arteriovenous Malformations (AVMs) are generally considered congenital lesions and are thus often discovered in a generally younger patient population [1-5]. Although many can be asymptomatic, each possesses a compounded risk of causing focal neurologic deficits, seizures and/or hemorrhage [1-5]. In addition, females face a potentially considerably increased risk of AVM hemorrhage during pregnancy, with a recent study suggesting an eight-fold increased risk of hemorrhage during this period [6]. In addition to these concrete risks and their associated morbidity, all patients must carry a daily psychological burden of knowing such devastating events can happen at any time. Any time they endure physical activity or any time in their life they have a headache, they must fear AVM rupture.

Although a seminal study of AVM natural history did not demonstrate a difference in the risk of AVM hemorrhage between ruptured and unruptured lesions [1], a litany of subsequent reports [2-5], including an updated analysis of the patient population in this original study [2], have clearly demonstrated an increased risk of hemorrhage for ruptured AVMs. One early study demonstrated a marked discrepancy in the annual rate of hemorrhage for unruptured and ruptured AVMs (2.2% and 17.8%, respectively) [7]. The very high rebleed rate for the latter group was likely a function of the very short follow-up period in this study (8 months), a peculiar, recurring approach that the senior author of the analysis has taken in approaching AVMs. A subsequent study by the same group, based on a median follow-up of 3 months, reported what was, and what remains, the lowest, non-reproduced rate of hemorrhage for unruptured AVMs (1.3%) [5].

Despite innumerable reports of the safety and low morbidity of surgery for well-selected AVMs [8-13], in light of his study results, the senior author of these brief follow-up "natural history" studies published a series of editorials describing treatment of unruptured AVMs as "experimental therapy [14,15]." Of course, all ruptured AVMs were once unruptured AVMs and the treatment of AVMs had been published for decades up to that point. Nevertheless, a randomized trial evaluating no treatment of a disease process has considerable allure given the tremendous potential cost savings a result in favor of such an approach provides. Thus, despite the senior author's published biases, A Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA) was funded as the first randomized control trial of AVM treatment ("intervention") versus no treatment ("conservative management") [16]. Over a similar time period the Scottish Intracranial Vascular malformations Study (SIVMS) was collecting observational data on Scottish residents aged 16 or older with AVMs [17]. Results from both ARUBA [16] and a post-hoc retrospective analysis of the SIVMS [17] were recently published, suggesting superior outcomes after no treatment for unruptured AVMs as compared to treatment. Although terms such as "conservative therapy" and "medical management" have been euphemistically employed for the no treatment arms, this manuscript will use the more precise term, "no treatment," as for other disease processes, "medical management" frequently differs from no treatment.

Both studies failed in addressing the impact of intervention for AVMs as a result of lumping peculiar treatment practices for AVMs (embolization alone) with a paucity of cases treated surgically. In addition, the authors of the SIVMS analysis utilized post-hoc outcome measures that misrepresented their data-it is remarkably clear that patients managed with intervention had better functional outcomes at 12 years if one reviews eFigure 4, buried in the online supplement [17]. Despite 12 year follow-up data, the authors arbitrarily utilized a 4 year cutoff point for their primary outcome measure. Of course, intervention will fare worse in the short term, and it is quite peculiar that despite having long-term follow-up data, the authors instead decided to stop their primary analysis short at 4 years.

Natural History

In the SIVMS study, the authors first misrepresent the natural history literature in their introduction, quoting a 1% annual hemorrhage rate for unruptured AVMs based on two cited studies [4,5]. In the first study by Halim et al., the annual hemorrhage rate for unruptured AVMs was in fact 2-3% depending on follow-up period [4]. The other study they cite was based on a median follow-up period only 3 months [5]. In a recent meta-analysis incorporating 3923 patients with AVMs, the annual rupture rate for unruptured AVMs was 2.2% (95% CI 1.7-2.7%) [3]. In ARUBA, the annual hemorrhage rate for unruptured AVMs was 2.6%, and the overall annual stroke rate was 3.9% [16].

Importantly, the natural history of unruptured AVMs is likely to vary with time and depend on multiple factors [2-5]. Multiple studies, corroborated via a recent meta-analysis, have shown associated aneurysms, exclusively deep venous drainage and deep location to be independent risk factors for AVM hemorrhage [2-5]. Furthermore,

Citation: Gross BA. Treatment of Unruptured Arteriovenous Malformations: The End of Tame Editorials. Austin J Cerebrovasc Dis & Stroke. 2014;1(4): 1020.

associated arterial aneurysms and venous outflow angioarchitecture are dynamic elements of an AVM, underscoring that the natural history of an AVM is not constant [2-5].

In ARUBA, participating physicians had the option of enrolling patients in the study or managing them as they see fit. Few surgeons would randomize a young patient with a low grade AVM, and it is likely that this "optional" approach introduced a considerable element of selection bias into the results. The few neurosurgeons that participated in the study likely randomized few patients, given that they knew their surgical outcomes were superior to the natural history. Specifically, although 226 patients were randomized, a substantial number of patients, 177, were selected for treatment and an additional 323 refused to participate in the study.

ARUBA Results

At just less than 3 years of follow-up (33 months), the risk of death or stroke in the "interventional" arm was 30.7% as compared to 10.1% for patients managed without treatment (RR 0.33, 95% CI 0.18-0.61). Presumably, this comparison ought to have been a comparison of the risk of periprocedural ischemic stroke in the treatment arm as compared to the risk of hemorrhage of unobliterated AVMs in the no treatment arm. Remarkably, this was hardly the case as there was an astonishing 33 hemorrhages in the treatment arm as compared to 8 in the no treatment arm. These hemorrhages accounted for the majority of the morbidity in the treatment arm of the study. In short, this result was likely a function of overzealous embolization employed in this study, an unusual approach to the management of generally low grade AVMs as hemorrhage after surgery is an exceedingly rare event and hemorrhage after SRS ought to mirror the natural history rate within the first 2-3 years of follow-up.

Importantly, the study lacks external validity given its short follow-up. Paradoxically, patients with less than a 10 year life expectancy were excluded from this study; however in reality, the study would only have validity for patients with less than a 3 year life expectancy. Early morbidity after intervention must be higher than that for no treatment—the question is not whether intervention is superior or inferior to no treatment but rather *when* it becomes superior.

SIVMS Results

The primary outcome in the SIVMS post-hoc analysis was death or sustained morbidity of any cause. To quote the abstract verbatim, "During a median follow-up of 6.9 years, the rate of progression to the primary outcome was lower with conservative management during the first 4 years of follow-up (36 vs 39 events) [17]." Why would the authors not simply compare the number of events between the groups over the entire follow-up? The decision to present the rate of progression to the primary outcome at 4 years seems to have been chosen in order to achieve statistical significance. It is obvious that outcomes are better at longer follow-up from intervention in this study after perusal of eFigure 4. The authors attempt to justify this as a result of death due to other causes and cite treatment effect as non significant, but this may not in fact be the case. There were 11 AVM-related deaths in the conservative arm as compared to 1 death attributed to intervention in the treatment arm. At 12 year follow-up, 50% of patients were OHS 0 (intact) in the treatment arm as compared to slightly over 10% in the conservative arm. In fact, after approximately 5 year follow-up, the percentage of patients at OHS 0 in the treatment arm remains steady at 40-50% while this percentage declines steadily in the conservative arm over this period from 40% to nearly 10%! This finding is nevertheless not discussed in this paper and is in fact the crux of AVM obliteration—a long term benefit/protection from neurological decline/hemorrhage.

Intervention

In both ARUBA and the SIVMS analysis, all forms of intervention were grouped together. Microsurgical excision, the time honored treatment for low Spetzler-Martin grade AVMs, was performed in the minority of cases in both studies; in ARUBA, it was performed alone in only 5 cases (4% of the time). This occurred despite the fact that 68% of AVMs were grade I or II in ARUBA (93% were grades I-III). In both studies, AVMs were described according to Spetzler-Martin grade—a *surgical* grading scale; however, paradoxically, surgery was performed in the minority of cases.

Of course, compared with no treatment, surgical excision will have greater complication rates in the very short term that are unlikely to further accrue given the resultant high rate of successful AVM obliteration. In one study of 220 patients with Spetzler-Martin grade I or II AVMs treated with surgery, the overall surgical morbidity and mortality rates were 0.9% and 0.5%, respectively [9]. All AVMs were obliterated and no postoperative hemorrhages occurred over 1143 patient-years of follow-up. This is a remarkable contrast to results from ARUBA. Similar results have been reproduced across several surgical series among experienced surgeons [8-13].

In the case of unruptured AVMs, benefit from stereotactic radiosurgery (SRS) can only be derived after extended follow-up. Over the first 2-3 years prior to AVM obliteration, patients undergoing SRS continue to face a risk of hemorrhage similar to patients managed conservatively that is further compounded by complications from the intervention (SRS). By definition, outcomes in the "treatment arm" must therefore be worse during this initial period. Nearly half of the patients in the interventional arm of ARUBA were treated with SRS or SRS and embolization; at only 33 month follow-up, results for this cohort may be quite predictable.

Furthermore, obliteration rates after SRS as compared to microsurgery are significantly lower. The authors of the SIVMS study themselves have published a meta-analysis in JAMA incorporating 13698 patients that showed obliteration rates of 96% after microsurgery, 38% after SRS and 13% after embolization [18]. The latter emphasizes the belief of many experienced practioners who manage AVMs that embolization for cure is, at best, an unsupported "experimental" approach. The inexplicably high rate of hemorrhage in the treatment arm in both the SIVMS analysis and ARUBA most likely represents post-embolization hemorrhages resulting from procedural complications or from the partially-obliterated AVM. The authors of both studies nevertheless decided to group all treatment modalities together, despite the well-described tremendous heterogeneity and variable efficacy of these modalities.

Focus on the Patient

The conclusions drawn from the SIVMS analysis [17] and ARUBA [16] are vexing to neurosurgeons that practice AVM microsurgery since

they utilize "interventional" outcomes from unaccepted treatment practices (embolization alone). Are patients with low Spetzler-Martin grade AVMs being treated with embolization and sustaining hemorrhagic complications and bleeding from partially treated lesions? In short, ARUBA was plagued by clinically-insignificant, short follow-up and a predominance of peculiar treatment practices for low grade AVMs [16]. The SIVMS analysis was post-hoc and self-servingly presented a 4 year follow-up analysis despite better results at longer follow-up for intervention [17]. Although the daily psychological burden of knowing that a devastating hemorrhage can occur at any moment cannot be quantified in the no treatment arm of either study, this euphemized approach is of no service to patients with easily treated, low grade unruptured AVMs.

References

1. Ondra SL, Troupp H, George ED, Schwab K. The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. J Neurosurg. 1990; 73: 387-391.
2. Hernesniemi JA, Dashti R, Juvela S, Väärt K, Niemelä M, Laakso A. Natural history of brain arteriovenous malformations: a long-term follow-up study of risk of hemorrhage in 238 patients. Neurosurgery. 2008; 63: 823-829.
3. Gross BA, Du R. Natural history of cerebral arteriovenous malformations: a meta-analysis. J Neurosurg. 2013; 118: 437-443.
4. Halim AX, Johnston SC, Singh V, McCulloch CE, Bennett JP, Achrol AS, et al. Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. Stroke. 2004; 35: 1697-1702.
5. Stapf C, Mast H, Sciacca RR, Choi JH, Khaw AV, Connolly ES, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. Neurology. 2006; 66: 1350-1355.
6. Gross BA, Du R. Hemorrhage from arteriovenous malformations during pregnancy. Neurosurgery. 2012; 71: 349-355.
7. Mast H, Young WL, Koennecke HC, Sciacca RR, Osipov A, Pile-Spellman J, et al. Risk of spontaneous haemorrhage after diagnosis of cerebral arteriovenous malformation. Lancet. 1997; 350: 1065-1068.
8. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg. 1986; 65: 476-483.
9. Morgan MK, Rochford AM, Tsahtsarlis A, Little N, Faulder KC. Surgical risks associated with the management of grade I and II brain arteriovenous malformations. Neurosurgery. 2004; 54: 832-839.
10. Pik JH, Morgan MK. Microsurgery for small arteriovenous malformations of the brain: results in 110 consecutive patients. Neurosurgery. 2000; 47: 571-575.
11. Pikus HJ, Beach ML, Harbaugh RE. Microsurgical treatment of arteriovenous malformations: analysis and comparison with stereotactic radiosurgery. J Neurosurg. 1998; 88: 641-646.
12. Schaller C, Schramm J. Microsurgical results for small arteriovenous malformations accessible for radiosurgical or embolization treatment. Neurosurgery. 1997; 40: 664-672.
13. Sisti MB, Kader A, Stein BM. Microsurgery for 67 intracranial arteriovenous malformations less than 3 cm in diameter. J Neurosurg. 1993; 79: 653-660.
14. Stapf C, Mohr JP. Unruptured brain arteriovenous malformations should be treated conservatively: yes. Stroke. 2007; 38: 3308-3309.
15. Stapf C, Mohr JP, Choi JH, Hartmann A, Mast H. Invasive treatment of unruptured brain arteriovenous malformations is experimental therapy. Curr Opin Neurol. 2006; 19: 63-68.
16. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. Lancet. 2014; 383: 614-621.
17. Al-Shahi Salman R, White PM, Counsell CE, du Plessis J, van Beijnum J, Josephson CB, et al. Outcome after conservative management or intervention for unruptured brain arteriovenous malformations. JAMA. 2014; 311: 1661-1669.
18. van Beijnum J, van der Worp HB, Buis DR, Al-Shahi Salman R, Kappelle LJ, Rinkel GJ, et al. Treatment of brain arteriovenous malformations: a systematic review and meta-analysis. JAMA. 2011; 306: 2011-2019.

Austin J Cerebrovasc Dis & Stroke - Volume 1 Issue 4 - 2014
ISSN : 2381-9103 | www.austinpublishinggroup.com

Citation: Gross BA. Treatment of Unruptured Arteriovenous Malformations: The End of Tame Editorials. Austin J Cerebrovasc Dis & Stroke. 2014;1(4): 1020.