Treatment and outcomes of ARUBA-eligible patients with unruptured brain arteriovenous malformations at a single institution

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Object. Management of unruptured arteriovenous malformations (AVMs) is controversial. In the first randomized trial of unruptured AVMs (A Randomized Trial of Unruptured Brain Arteriovenous Malformations [ARUBA]), medically managed patients had a significantly lower risk of death or stroke and had better outcomes. The University of California, San Francisco (UCSF) was one of the participating ARUBA sites. While 473 patients were screened for eligibility, only 4 patients were enrolled in ARUBA. The purpose of this study is to report the treatment and outcomes of all ARUBA-eligible patients at UCSF.

Methods. The authors compared the treatment and outcomes of ARUBA-eligible patients using prospectively collected data from the UCSF brain AVM registry. Similar to ARUBA, they compared the rate of stroke or death in observed and treated patients and used the modified Rankin Scale to grade outcomes.

Results. Of 74 patients, 61 received an intervention and 13 were observed. Most treated patients had resection with or without preoperative embolization (43 [70.5%] of 61 patients). One of the 13 observed patients died after AVM hemorrhage. Nine of the 61 treated patients had a stroke or died. There was no significant difference in the rate of stroke or death (HR 1.34, 95% CI 0.12–14.53, p = 0.81) or clinical impairment (Fisher’s exact test, p > 0.99) between observed and treated patients.

Conclusions. The risk of stroke or death and degree of clinical impairment among treated patients was lower than reported in ARUBA. The authors found no significant difference in outcomes between observed and treated ARUBA-eligible patients at UCSF. Results in ARUBA-eligible patients managed outside that trial led to an entirely different conclusion about AVM intervention, due to the primary role of surgery, judicious surgical selection with established outcome predictors, and technical expertise developed at high-volume AVM centers.

Key Words • arteriovenous malformation • ARUBA • observation • microsurgical resection

Hemorrhage is the most common presentation of brain arteriovenous malformations (AVMs), yet a large number of AVMs are now discovered incidentally. The management of unruptured AVMs is controversial, as the risk of treatment-associated morbidity and mortality must be weighed against the risk of spontaneous hemorrhage.21,22 While the overall risk of AVM hemorrhage is estimated at between 2%–4% per year, patients with unruptured AVMs may have a lower risk of spontaneous hemorrhage.1–3,6,7,16,19,23

Mohr et al. recently published the first randomized trial of unruptured AVMs (A Randomized Trial of Unruptured Brain Arteriovenous Malformations [ARUBA], NCT00389181, clinicaltrials.gov), which was designed to provide better understanding of the natural history of these lesions and risks associated with treatment.13 They compared 109 patients assigned to medical management alone (pharmacological therapy for existing medical disorders or any coexisting vascular risk factors) to 114 patients assigned to medical management with interventional therapy, consisting of embolization, radiosurgery, microsurgical resection, or a combination. After 33 months of follow-up, 30.7% of patients in the intervention arm had a stroke or died, compared with only 10.1% of patients in the medical management arm. In addition, 46.2% in the intervention arm were clinically impaired (defined as a modified Rankin Scale [mRS] score of 2 or higher), compared with 15.1% in the medical management arm. Thus, unruptured-VM patients in the medical management group had a significantly lower risk of death or stroke and had better outcomes than patients in the treatment group.

However, ARUBA faced many difficulties with patient recruitment and was stopped early by the Data Safety and Monitoring Board, which has led some to question the
generalizability of the trial results. Only 226 (13%) of 1740 screened patients were randomized; 323 patients refused to participate, while clinicians selected treatment outside of the randomization process for 177 patients. Additionally, although 76 (68%) of the 112 patients randomized to intervention had low-grade AVMs, only 18 patients had surgery, despite evidence from observational studies that microsurgical resection of low-grade AVMs is safe and curative. Instead, most AVMs were treated with embolization or radiosurgery, both of which have lower obliteration rates than microsurgical resection. Thus, the higher rate of stroke or death and clinical impairment in ARUBA’s interventional therapy arm reflects not only treatment-associated effects, but also complications from partially treated AVMs. Thus, ARUBA’s relatively short follow-up of 33 months favors medical management, since curative effects would take longer for the any-treatment group, and differences observed between the 2 arms might dissipate over time.

The purpose of this study is to report the treatment and outcomes of ARUBA-eligible patients at the University of California, San Francisco (UCSF), one of the participating ARUBA sites.

Methods

Patients

We used the same inclusion/exclusion criteria as in the ARUBA trial with some additional exclusions as described below. During ARUBA’s enrollment period, from April 4, 2007, to April 15, 2013, 473 patients with AVMs were screened for enrollment at UCSF. Patients aged 18 years or older with an unruptured AVM diagnosed by catheter angiography, MRI, MR angiography, or CT angiography were eligible. Patients with evidence of previous hemorrhage, prior treatment, or AVMs unsuitable for treatment were excluded. Patients with baseline clinical impairment (defined as an mRS score of 2 or higher) were also excluded. Four (4.6%) of 87 eligible patients were enrolled in ARUBA.

Of the 87 patients eligible for ARUBA during the enrollment period, 3 patients were treated elsewhere and were excluded from our analysis. Ten patients with less than 30 days’ follow-up were also excluded. Five of these patients underwent uncomplicated resections of their AVMs and were discharged home in good condition but did not return to UCSF for postoperative follow-up. Five patients did not return after their initial screening evaluation. The remaining 74 patients were included in our analysis.

All patients were enrolled prospectively in the registry of the UCSF Brain AVM (BAYM) Study Project. Patient baseline characteristics included age, sex, clinical presentation (seizure, headache, or other), and mRS score (0 or 1). Nidus size (diameter in cm), venous drainage (superficial only or any deep), and eloquence were determined from preoperative angiograms, CT scans, and MRI scans for each AVM. All AVMs were graded using the Spetzler-Martin scale and the Spetzler-Martin supplemented scale.

Patients undergoing interventions were treated with microsurgical resection alone, microsurgical resection with preoperative embolization, embolization alone, Gamma Knife radiosurgery, or a combination. All AVM resections were performed by a single senior neurosurgeon (M.T.L.). AVM obliteration was documented by catheter angiography.

To maintain consistency with ARUBA’s analysis, we analyzed a composite of stroke or death from any cause. We also used the mRS to grade outcomes. As in ARUBA, an mRS score of 2 or higher was defined as clinical impairment. A trained study coordinator, under the supervision of a neurologist, performed assessments at presentation, preoperatively, postoperatively at clinic visits, and annually up to 2 years postoperatively in treated patients. Observed patients were assessed at presentation and annually. Follow-up information was obtained during routine clinic visits or telephone interviews.

Statistics

We used Fisher’s exact tests for categorical variables and t-tests for continuous variables to evaluate differences in baseline characteristics between observed and treated patients, including sex, age, clinical presentation, mRS score, AVM location, eloquence, venous drainage, size, Spetzler-Martin scale score, and Spetzler-Martin supplemented scale score.

We compared the rate of stroke or death in observed and treated patients using Kaplan-Meier survival analysis and the log-rank test. Cox proportional-hazards regression models were performed to estimate hazard ratios, adjusting for Spetzler-Martin grade, location, venous drainage pattern, patient age, and time from diagnosis. We compared the proportion of patients with an mRS score of 2 or higher at last follow-up in the observed and treated groups with Fisher’s exact test.

All p values reported are 2-sided and regarded as statistically significant if p < 0.05. All statistical analyses were performed using Stata 13.1 software (StataCorp LP).

Results

There were no significant differences in baseline characteristics, including patient sex, clinical presentation, mRS score, AVM location, eloquence, venous drainage, size, or Spetzler-Martin grade (Table 1). However, observed patients were significantly older than treated patients (59 vs 41 years, p < 0.001). Observed patients in our cohort were also significantly older than patients randomized to medical management alone in ARUBA (59 vs 44 years, p < 0.001). There were no other significant differences between ARUBA-eligible patients in our cohort and randomized ARUBA patients, including sex, clinical presentation, mRS score, Spetzler-Martin grade, eloquence, and venous drainage pattern.

In our cohort, 61 patients underwent an intervention, while 13 patients were observed. Patients undergoing interventions were treated with resection alone in 20 of 61 cases, resection with preoperative embolization in 23 cases, Gamma Knife radiosurgery in 15 cases, embolization in 1 case, and a combination in 2 cases (Table 2).

Observed patients had a longer mean length of follow-up than treated patients (30 vs 21 months, p = 0.12).
Patients with Spetzler-Martin Grade I and II AVMs or Spetzler-Martin supplemented scale Grade 4 and 5 AVMs were more likely to be treated with radiosurgery or multimodality therapy. Only 3 of the 13 patients with Spetzler-Martin Grade IV or V AVMs were treated with resection. Two of the 6 patients with a Spetzler-Martin supplemented scale score higher than 7 underwent resection.

A total of 10 patients had a stroke or died during the follow-up period. One (7.7%) of the 13 observed patients had a stroke or died, compared with 9 (14.7%) of the 61 treated patients. Five (11.6%) of 43 surgical patients had a stroke or died compared with 4 (26.7%) of 15 patients treated with radiosurgery. There was no significant difference in the rate of stroke or death in observed and treated patients (Fig. 1; HR 1.34, 95% CI 0.12–14.53, p = 0.81).

There were 4 deaths in the cohort. One (7.7%) of the 13 observed patients died after AVM hemorrhage, whereas 3 (4.9%) of the 61 treated patients died. A patient treated with Gamma Knife radiosurgery died after AVM hemorrhage. Two patients died of unknown causes, including a patient treated with Gamma Knife radiosurgery and a patient with an AVM completely obliterated by resection.

There was no significant difference in functional outcome between observed and treated patients. Eight (13.8%) of 58 treated patients were clinically impaired at last follow-up with an mRS score of 2 or higher, compared with 1 (7.7%) of the 13 observed patients (p > 0.99) (Table 3). Six surgical patients were clinically impaired with an mRS score of 2 or higher, but only 2 (4.8%) of the 41 surgical patients were dead or dependent (mRS score of 3 or higher) compared with 1 (7.7%) of the 13 observed patients. Three (20%) of 15 radiosurgery patients were clinically impaired; 2 of these 3 patients were dead and 1 patient had an mRS score of 2.

Complete AVM obliteration was documented by catheter angiography in 93.0% of cases after resection. Four patients had incompletely resected AVMs. Complete AVM obliteration was documented in 4 (28.6%) of 14 patients treated with Gamma Knife radiosurgery.

Discussion

While our ARUBA-eligible patients are similar to the patients who were included in that trial, their treatment and outcomes are not. Most patients in our cohort underwent resection with or without preoperative embolization (70.5% [43 of 61], as compared with 18% in the ARUBA trial). Fewer patients were treated with Gamma Knife radiosurgery (15 [24.6%] of 61), embolization (1 [1.6%] of 61), or a combination (2 [3.3%] of 61). Thirteen patients were observed.
High-grade AVMs in surgically inaccessible locations were treated with Gamma Knife radiosurgery or a combination of Gamma Knife radiosurgery, embolization, and surgery. Whereas 86.7% of AVMs treated with Gamma Knife radiosurgery (13 of 15 lesions) were high-grade, 62.7% of microsurgically resected AVMs (27 of 43 lesions) were Grade I or II. Given its low cure rate compared with resection and radiosurgery, embolization alone was not offered as a primary therapy. One patient in this series underwent embolization as an adjunctive treatment in preparation for surgery, but then declined surgery after embolization.

Our ARUBA-eligible treated patients were less likely to have a stroke or die than ARUBA patients (14.8% vs 30.7%) and were less likely to be clinically impaired (13.8% vs 46.2%), likely reflecting differences in treatment. Few patients (18%) in ARUBA were treated with surgery, and instead, most were treated with embolization and/or radiosurgery. In contrast, most patients in our cohort (43 of 61 treated patients) had surgery, while patients with higher grade, surgically inaccessible AVMs (15 of 61 patients) received radiosurgery. Radiosurgery patients had the highest rate of stroke or death (26.7%) and clinical impairment (20%), while fewer surgical patients had a stroke or death (11.6%) or were clinically impaired (14.6%). The 1 patient who died after surgery had a completely resected AVM and died of unknown causes. There was no significant difference in the rate of stroke or death or clinical impairment between observed and treated patients, which is the critical finding of this analysis because of the 3-fold difference reported in the ARUBA trial. This important finding demonstrates that differences in overall management strategy and surgical expertise between our cohort and the ARUBA trial led to an entirely different conclusion about AVM intervention.

The main limitation of our study is the small sample size, particularly in the observed group. Thus, our study is underpowered to detect statistically significant differences between observed and treated patients. A strength of our study is the prospective assessment of ARUBA eligibility and outcomes done independently of treating physicians and the relatively large sample of treated patients from our referral institution that may be more generalizable to other US centers.

**Conclusions**

Treatment of unruptured AVMs remains controversial, despite evidence from ARUBA suggesting observed patients have better clinical outcomes. Few screened patients were randomized and few patients randomized to intervention had resection, which is widely considered the gold standard of treatment, particularly for patients with low-grade AVMs. Our treated ARUBA-eligible patients had better outcomes than those reported in ARUBA. We found no significant difference in the rate of stroke or death or degree of clinical impairment in observed and treated ARUBA-eligible patients at UCSF, although the wide 95% confidence intervals reflect the estimate uncertainty. The 3-fold increase in stroke and death observed in ARUBA patients was not observed in our cohort, leading to an entirely different conclusion about AVM intervention. This difference

**TABLE 3: Proportion of patients who had a stroke or died or had clinical impairment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Observation</th>
<th>Intervention*</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients in group</td>
<td>13 (7.7%)</td>
<td>61</td>
<td>0.68</td>
</tr>
<tr>
<td>no. of patients who had a stroke or died</td>
<td>1 (7.7%)</td>
<td>9 (14.8%)</td>
<td>0.99</td>
</tr>
<tr>
<td>no. of patients w/ mRS score ≥2</td>
<td>1 (7.7%)</td>
<td>8 (13.8%)</td>
<td></td>
</tr>
</tbody>
</table>

* The mRS scores at last follow-up were available for 58 of 61 treated patients.
† Fisher’s exact test.
was due to utilizing surgery as the primary therapy, select-
ing surgical patients judiciously with established outcome
predictors, and developing surgical expertise through high
AVM case volume. While there is a role for observation in
patients with unruptured AVMs, longer follow-up and out-
comes by treatment type may also reveal low-grade AVM
patients to benefit most from microsurgical resection.

Disclosure

The authors report no conflict of interest concerning the mate-
rials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript prepara-

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