Title

Targeted Embolization of Aneurysms Associated With Brain Arteriovenous Malformations at High Risk for Surgical Resection: A Case-Control Study.

Journal

Neurosurgery, 82(3)

ISSN

0148-396X

Authors

Alexander, Matthew D
Hippe, Daniel S
Cooke, Daniel L
et al.

Publication Date

2018-03-01

DOI

10.1093/neuros/nyx167

Peer reviewed

Targeted Embolization of Aneurysms Associated With Brain Arteriovenous Malformations at High Risk for Surgical Resection: A Case-Control Study

Matthew D. Alexander, MD[*]
Daniel S. Hippe, MS[‡]
Daniel L. Cooke, MD[*]
Danial K. Hallam, MD[‡]
Steven W. Hetts, MD[*]
Helen Kim, PhD[§]
Michael T. Lawton, MD[¶]
Laligam N. Sekhar, MD[‖]
Louis J. Kim, MD[‖]
Basavaraj V. Ghodke, MD[‡]

[*]University of California San Francisco, Department of Radiology and Biomedical Imaging, San Francisco, California; [‡]University Washington, Department of Radiology, Seattle, Washington; [§]University of California San Francisco, Department of Anesthesia and Perioperative Care, San Francisco, California; [¶]University of California San Francisco, Department of Neurological Surgery, San Francisco, California; [‖]University Washington, Department of Neurological Surgery, Seattle, Washington

Correspondence:
Matthew Alexander, MD,
505 Parnassus Ave,
San Francisco, CA 94143.
E-mail: matthew.alexander@ucsf.edu

Received, September 9, 2016.
Accepted, March 10, 2017.
Published Online, April 13, 2017.

BACKGROUND: High-risk components of brain arteriovenous malformations (BAVMs) can be targeted to reduce the risk of lesion rupture.
OBJECTIVE: To evaluate targeted embolization of aneurysms against other means of treatment with a case–control analysis; we previously investigated this approach associated with BAVMs.
METHODS: Retrospective analysis of patients with BAVMs was performed, identifying patients treated with intention to occlude only an aneurysm associated with a BAVM. For each targeted aneurysm embolization (TAE) patient identified, 4 control patients were randomly selected, controlling for rupture status, age, and Spetzler-Martin plus Lawton-Young supplemental score. Analysis was performed to compare rates of adverse events (hemorrhage, new seizure, and death) between the 2 groups.
RESULTS: Thirty-two patients met inclusion criteria, and 128 control patients were identified, out of 1103 patients treated during the study period. Thirty-four adverse events occurred (15 ruptures, 15 new seizures, and 11 deaths) during the follow-up period (mean 1157 d for the TAE cohort and 1036 d for the non-TAE cohort). Statistically lower associations were noted for the TAE group for any adverse event (hazard ratio 0.28, $P = .037$) and the composite outcome of hemorrhage or new seizure (hazard ratio 0.20, $P = .029$).
CONCLUSION: For BAVMs at high risk for surgical resection, TAE can be performed safely and effectively. Patients treated with TAE had better outcomes than matched patients undergoing other combinations of treatment. TAE can be considered for BAVMs with high operative risk prior to radiosurgery or when no other treatment options are available.

KEY WORDS: Arteriovenous malformation, Aneurysm embolization, Radiosurgery, Resection

Neurosurgery 82:343–349, 2018 DOI:10.1093/neuros/nyx167 www.neurosurgery-online.com

Intracranial hemorrhage (ICH) is the most dangerous manifestation of brain arteriovenous malformations (BAVMs) and is the primary driver of poor outcomes for patients with these lesions. BAVM treatment seeks to prevent hemorrhage by complete removal or obliteration of the nidus. Treatment should be considered if the expected risk BAVM rupture exceeds risks of treatment. Depending on lesion features, one or more treatment modalities may be most appropriate. Embolization, radiosurgery, excision, or a combination of these treatments can be offered. Microsurgery offers immediate and durable results, eliminating risk of ICH if complete resection is achieved. However, some BAVMs cannot be resected without significant morbidity. In such lesions, high-risk features like associated aneurysms can be treated selectively to reduce the risk of hemorrhage. Aneurysms were found in 36% of BAVMs in recently published large cohort studies.[1,2] Our group has previously evaluated targeted embolization of aneurysms associated with BAVMs without subsequent resection.[3] The current study involves case–control analysis to compare results of

ABBREVIATIONS: AE, adverse event; **BAVM,** brain arteriovenous malformations; **HR,** hazard ratio; **ICH,** intracranial hemorrhage; **LY,** Lawton-Young; **mRS,** Modified Rankin scale; **SM,** Spetzler-Martin; **TAE,** targeted aneurysm embolization

Supplemental digital content is available for this article at www.neurosurgery-online.com.

targeted aneurysm embolization (TAE) with other forms of treatment.

METHODS

Under protocols approved by institutional review boards, all patients or their representatives provided informed consent for treatment and future research participation. Retrospective analysis of procedure databases was performed at 2 academic medical centers with high-volume neurointerventional radiology services. Patients with BAVMs with associated flow-related feeding artery or intranidal aneurysms undergoing treatment between July 1996 and June 2015 were identified. Among these patients, those treated with TAE without intention for subsequent resection were selected for further analysis. Final decisions against operative management were made by microvascular neurosurgeons involved in the care of each patient. We defined TAE as embolization intended to occlude only the BAVM-associated aneurysm. Patients were excluded if treatment of an aneurysm involved more extensive embolization of a feeding artery or AVM nidus. For every patient undergoing TAE, 4 matched controls were randomly selected from the cohort of patients with BAVMs with associated aneurysms on the basis of rupture status, age, and Spetzler-Martin (SM) plus Lawton-Young (LY) supplemental score. Rupture status was perfectly matched in all sets, age was matched within 5 years, and SM plus LY supplemental score was matched within 2 points.

Retrospective review of medical records was performed to gather demographic and lesion characteristics. Procedure success was defined as complete occlusion of the aneurysm without associated nontarget embolization or other procedural complication. Any complications were noted, as were any symptoms they caused. Clinical follow-up data were reviewed to identify adverse events (AEs), defined as ICH during or after treatment, new onset of seizures, or death. Modified Rankin scale (mRS) values were imputed from medical records for the time points of presentation and 30 d, 90 d, and 1 yr after treatment, and at the point of last contact.

Continuous variables were summarized as mean ± standard deviation (SD), and categorical variables were summarized as count (percentage). Baseline characteristics were compared between treatment groups using conditional logistic regression to account for the matched design. mRS values, dichotomized as 0 to 2 (good status) and 3 to 6 (poor status), were assessed over time in both treatment groups using mixed-effect logistic regression models. mRS was assessed at presentation and after 30 d, 90 d, and 1 yr. The mixed-effect models included random intercepts for each matched set (1 per TAE and 4 matching controls) to account for the matched design and for each subject to account for the repeated measures per subject. The models also included fixed-effect adjustments for age and SM + LY supplemental score since these variables were not matched exactly. Fixed-effect terms for TAE, time, and their interaction were included in the models to test for trends over time and compare treatment groups using Wald tests.

Long-term endpoints—hemorrhage, seizure, death, and their composite—were assessed using Kaplan-Meier curves, and treatment groups were compared using mixed-effect Cox regression models. The mixed-effect Cox models included a random intercept for each matched set and fixed-effect adjustments for age and SM + LY supplemental score. Additional adjustments for mRS at presentation, single draining vein, and radiosurgery were explored, as these variables tended to differ between treatment groups (see Table 1). All statistical calculations were conducted with the statistical computing language R (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria). Throughout, 2-sided tests were used, with statistical significance defined as $P < .05$.

TABLE 1. Baseline Characteristics

	Treatment group		
	TAE	Non-TAE	
Variable	(n = 32)	(n = 128)	*P*-value*
Male	14 (43.8)	66 (51.6)	.43
Age, years	43.1 ± 23.1	43.0 ± 22.3	.87
IPH	17 (53.1)	71 (55.5)	.78
SAH/IVH	20 (62.5)	83 (64.8)	.77
Prior seizures	5 (15.6)	16 (12.5)	.58
Single draining vein	17 (53.1)	27 (21.1)	**.001**
Spetzler-Martin score	3.0 ± 1.1	2.9 ± 0.9	.36
Size score	1.5 ± 0.6	1.5 ± 0.6	.84
Eloquence	24 (75.0)	113 (88.3)	.062
Deep drainage	25 (78.1)	71 (55.5)	**.019**
Supplemental score	2.8 ± 1.0	2.7 ± 0.9	.22
Unruptured	5 (15.6)	20 (15.6)	>.99
Age score	2.3 ± 0.8	2.4 ± 0.8	>.99
Diffuseness	10 (31.2)	21 (16.4)	.061
SM + supplemental score	5.8 ± 1.5	5.6 ± 1.2	.19
mRS at presentation			**.008**
0-2	8 (25.0)	64 (50.0)	
3-5	24 (75.0)	64 (50.0)	
Treatment			
Radiosurgery	24 (75.0)	40 (31.2)	**<.001**
Surgical resection	0 (0.0)	85 (66.4)	
Embolization	32 (100.0)	78 (60.9)	
None[a]	0 (0.0)	3 (2.3)	

*Wald test from univariate conditional logistic regression model.
[a]Patient underwent angiography with intention to treat but treatment was found to not be possible.
Values are no. (%) or mean ± SD unless otherwise specified.

RESULTS

Thirty-two patients met inclusion criteria for TAE out of 1103 patients with BAVMs studied with diagnostic cerebral angiography during the study period at the 2 institutions. With 4 control patients identified for each patient undergoing TAE, 128 control patients were included. Table 1 summarizes the baseline characteristics of the 160 total patients. TAE patients were more likely to have a single draining vein (53% vs 21%, $P = .001$), deep drainage (78% vs 56%, $P = .02$), and higher mRS at presentation (mRS 3-5: 75% vs 50%, $P = .008$). In addition, the TAE group was more likely to undergo subsequent radiosurgery (75% vs 31%, $P < .001$). In the TAE group, 16 (50.0%) had intranidal aneurysms, while 75 (58.6%) lesions in the non-TAE group had intranidal aneurysms ($P = .380$). All matched controls underwent some combination of surgical resection, embolization, and radiosurgery except for 3. These 3 patients underwent

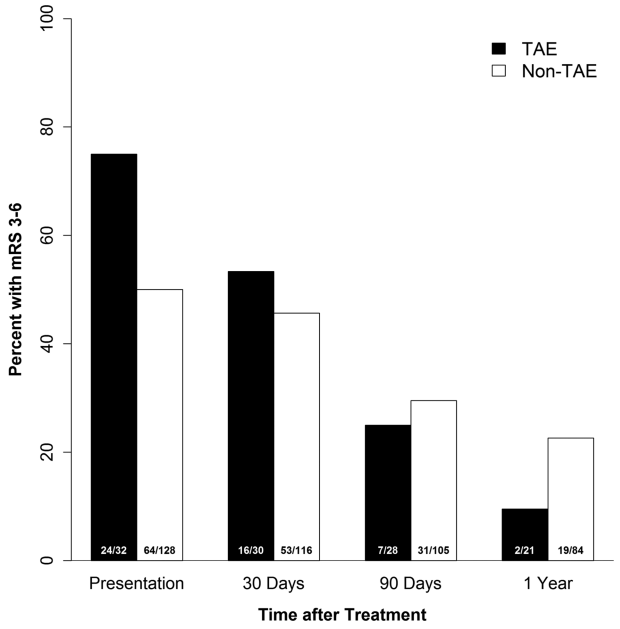

FIGURE 1. *Patients with disability or deceased (mRS>2) at various time points, separated into TAE and non-TAE groups.*

TABLE 2. Summary of Events

Event	Treatment group	
	TAE (n = 32)	Non-TAE (n = 128)
Hemorrhage	1 (3.1)	14 (10.9)
Seizures (any[a])	1 (3.1)	17 (13.3)
Seizures (new[a])	1 (3.1)	14 (10.9)
Death (any cause)	1 (3.1)	10 (7.8)
Adverse events (composite[b])	3 (9.4)	31 (24.2)

[a]New seizures only include seizures from initially asymptomatic patients and any seizures includes seizures in patients with seizures prior to treatment.
[b]Composite of hemorrhage, new seizures (excludes seizures in patients with seizures prior to treatment), and death.

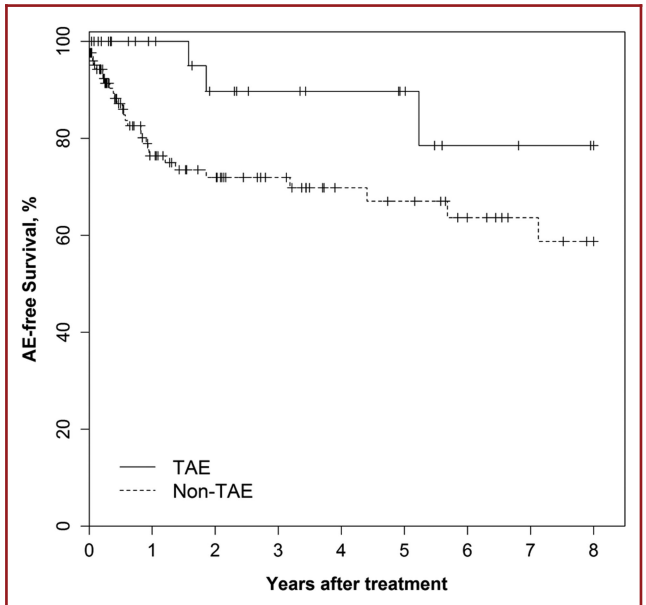

FIGURE 2. *Kaplan Meier survival curve demonstrating percentage of patients free of adverse events between TAE and non-TAE groups.*

angiography with the intention to treat, but treatment was subsequently deemed unsafe.

Short-term follow-up of mRS values over 1 yr after treatment is summarized in Figure 1. Both treatment groups showed significant improvements in mRS over time ($P < .001$ for trend in each group). The TAE group had a significantly faster rate of improvement than the non-TAE group ($P = .008$). The TAE group had worse mRS values at presentation and tended to have better mRS values at 1 yr, though this latter difference was not statistically significant (mRS 3-6: 9.5% vs 23%, $P = .36$).

The total clinical follow-up available for the 160 subjects ranged from 1 d to 15 yr, with a median follow-up of 1.6 yr and interquartile range of 4.1 mo to 4.7 yr. Thirty-four subjects experienced the composite AE endpoint, with the first event being hemorrhage in 15, new seizures in 14, and death in 5. Thirty-one AEs occurred in the non-TAE group and 3 occurred in the TAE group. AEs are summarized in Table 2.

One patient underwent TAE alone and died shortly thereafter of complications from the initial hemorrhage. Between 2 patients with AEs after undergoing TAE followed by radiosurgery, 1 had delayed rupture and another developed new seizures. Six patients had AEs following resection alone, including 2 deaths in the perioperative period, 1 delayed death, 1 hemorrhage, and 2 with new seizures. Three patients undergoing radiosurgery after subtotal resection had AEs, with 2 patients experiencing delayed rupture with and 1 patient with new seizures. One of the patients with re-rupture died. Ten patients had AEs after resection after preoperative embolization, with 7 patients developing new seizures, 2 hemorrhaging, 2 dying in the perioperative period, and 2 more dying in delayed fashion. Six patients treated with radiosurgery alone experienced AEs, with 5 hemorrhaging and 1 developing new seizures. Five additional patients experienced AEs after embolization then radiosurgery, with 3 hemorrhaging, 1 dying late after initial presentation, and 2 developing new seizures. 1 patient underwent embolization alone and died shortly thereafter before any additional treatment was undertaken. Details of AEs in these 34 patients are provided in the **Table**, **Supplemental Digital Content**.

Kaplan-Meier curves of the composite AE endpoint, hemorrhage, and new seizures are shown in Figures 2 and 3. In all cases, events accumulated relatively rapidly in the non-TAE group

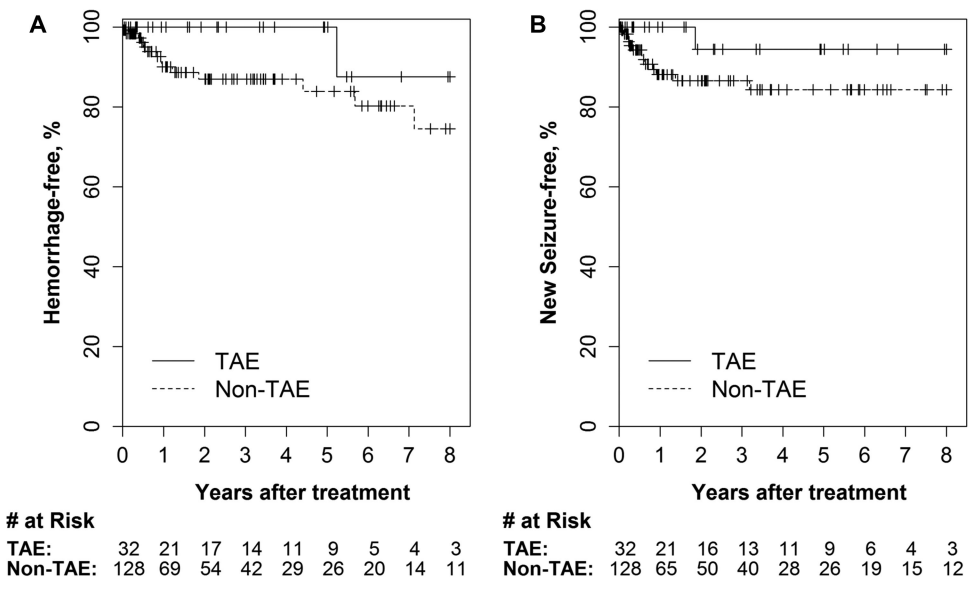

FIGURE 3. *Kaplan-Meier survival curves demonstrating percentage of patients free of* **A** *hemorrhage and* **B** *new seizures between TAE and non-TAE groups.*

TABLE 3. Associations Between TAE and Adverse Events (Based on Mixed-Effect Cox Model With Random Intercept Per Matched Set)

	No. of	Model 1			Model 2			Model 2		
Endpoint	Events	HR[a]	(95% CI)	*P*-value	HR[a]	(95% CI)	*P*-value	HR[a]	(95% CI)	*P*-value
Composite endpoints										
Adverse event[b]	34	0.28	(0.08, 0.93)	**.037**	0.21	(0.06, 0.77)	**.019**	0.21	(0.06, 0.79)	**.021**
Hemorrhage or new seizures	29	0.20	(0.05, 0.85)	**.029**	0.14	(0.03, 0.69)	**.015**	0.14	(0.03, 0.68)	**.015**
Individual endpoints										
Hemorrhage	15	0.23	(0.03, 1.74)	.15	0.15	(0.02, 1.38)	.093	0.12	(0.01, 1.06)	.057
New seizures[c]	15	0.20	(0.03, 1.54)	.12	0.18	(0.02, 1.75)	.14	0.2	(0.02, 2.00)	.17
Death (any cause)	11	0.243	(0.05, 3.46)	.43	0.39	(0.04, 3.39)	.39	0.48	(0.05, 4.51)	.52

[a]HR shows the relative risk of an adverse event for a patient treated with TAE compared with other treatments (HR < 1 indicates TAE is associated with lower risk of an adverse event).
[b]Adverse event is a composite of subsequent hemorrhage, new seizures, or death.
[c]Rupture status was removed from the model to allow the model fitting procedure to converge.
Model 1 = mixed-effect Cox model with random intercept per matched set and fixed-effect term for TAE, with adjustments for matching variables (age and SM + supplemental score); Model 2 = Model 1 + single draining vein and mRS at presentation; Model 3 = Model 2 + subsequent radiosurgery.

during the first year after treatment, with the event rate diminishing after the first year. No hemorrhages or new seizures were observed in the TAE group during the first year.

Multivariate mixed-effect Cox models were used to test whether TAE was associated with a lower rate of AEs (Figure 2, Table 3). TAE was associated with a 72% lower risk of the composite AE compared to the non-TAE group (hazard ratio [HR] = 0.28, 95% confidence interval: 0.08-0.93, $P = .037$), and TAE was associated with an 80% lower risk of hemorrhage or new seizures (HR = 0.20, 95% confidence interval: 0.05-0.85, $P = .029$). For the individual endpoints of hemorrhage and new seizures, TAE was associated with similar HRs as the composite endpoint (HR = 0.20-0.23), though these associations were not statistically significant, potentially due to the low number of events (Table 3). Further multivariate adjustments for mRS at presentation, single draining vein, and radiosurgery did not change conclusions (Table 3). Results were also little affected by excluding the 3 matched controls who underwent no treatment (data not shown).

DISCUSSION

BAVMs can lead to morbidity and mortality that is typically the result of rupture. While they can also cause seizures, the primary

reason to treat these lesions is to eliminate the nidus and risk of hemorrhage. Treatment can be performed with transcatheter embolization, surgical resection, radiosurgery, or a combination of these methods. Treatment is indicated when treatment risk is smaller than risk of hemorrhage. Various BAVMs features affect rupture risk, with respect to both natural history and treatment outcomes. The A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) trial sought to clarify when treatment is indicated, but it has raised many questions due to its design and interpretation of results.[4]

Natural history studies of BAVMs have reported various rates of hemorrhage.[5-11] The most complete studies are 2 recent meta-analyses.[7,11] Annual rupture rates of 2.3% and 3.0% were found among all BAVMs.[7,11] BAVMs that had previously ruptured had annual repeat rupture rates of 4.5% and 4.8%, compared to rates of 1.3% and 2.2% for unruptured lesions.[7,11] Among ruptured lesions, repeat hemorrhage rates are higher in the first year after hemorrhage, ranging from 6% to 15% annually.[5,6,8-11] In addition to prior hemorrhage, the presence of associated aneurysms affects risk of hemorrhage.[2,7,12-14] Gross and Du[7] reported an HR of 1.8 for the presence of aneurysms associated with BAVMs, and Kim et al[11] reported an HR of 1.58 for aneurysms with respect to repeat hemorrhage within 1 yr. BAVM rupture rates of 6.9% to 9.8% have been reported for lesions with associated aneurysms, compared to rates of 2.4% to 5.3% for BAVMs without aneurysms.[5,7,15-17]

A BAVM nidus must be completely obliterated to eliminate risk of hemorrhage. Such obliteration can be achieved by surgical resection, but surgery may be unsafe due to multiple factors.[18,19] Nidus obliteration can be achieved with stereotactic radiosurgery. This typically takes years to occur, and hemorrhage risk matches or may exceed the natural history risk during the latency period before the nidus is obliterated.[20,21] Furthermore, radiosurgery may lead to side effects such as radiation necrosis, hemorrhage, and neurological deficits. Such potential sequelae need to be weighed against the dose required to achieve nidus obliteration.[22] Transcatheter embolization can play an important role in BAVM treatment, although currently embolization is mostly utilized in the preoperative setting to reduce surgical morbidity.[23] Curative embolization can be achieved, but procedural morbidity has been reported at 2% to 20%, with mortality occurring in 1% to 2% of procedures, so most embolization must be adjunctive in combination with resection or radiosurgery.[24-31]

Even with multiple techniques that can be used to treat BAVMs, curative treatment remains unacceptably risky for certain lesions. Some argue that such lesions should undergo no treatment, while others believe that intervention can be performed safely enough to offer to patients.[4,23,32] Physicians offering treatment include those who tailor embolization to high-risk features.[26,32-38] The high-risk feature most appropriate for treatment is aneurysms associated with BAVMs. Two studies exist reporting retrospective analysis of targeted embolization for aneurysms associated with BAVMs, and these found lower rates of hemorrhage compared to expected rates based on natural history studies.[26,35] In these cases, technical success and complication rates were similar to those reported for AVM embolization procedures in general.[26,35]

To add to the previously reported results of endovascular treatments targeting the arterial pedicle supplying the high-risk feature, we previously reported our experience of 32 patients undergoing targeted embolization of only aneurysms associated with BAVMs.[3,26,32-36] Such an approach can secure the aneurysm without causing significant changes to flow dynamics of these high-risk lesions.[3] The current study further examines this cohort by performing case–control analysis. The procedural complication rate we reported for the TAE cohort was at the upper range of complication rates reported for BAVM embolization.[3] No symptomatic sequelae resulted from procedural complications, and technical success was achieved in all TAE procedures.[3] Furthermore, hemorrhage rates following TAE were far lower than those expected for comparable lesions based on natural history studies.[3] While our prior study's results are instructive, their widespread applicability is limited, particularly given the study's retrospective nature, nonuniform selection criteria, and inherent selection bias.

To address these limitations, the current study involves case–control analysis of the TAE cohort for more direct comparison to comparable lesions treated in other ways. Comparison cases were randomly selected while controlling for rupture status, age, and SM plus LY supplemental score. Additional demographic and lesion characteristics were very similar, as summarized in Table 1. Statistically significant differences were noted between the TAE and non-TAE group for 3 variables—number of draining veins, presence of deep drainage, and mRS at presentation. For all 3 variables, the TAE group was higher risk or had poorer initial functional status. Based on natural history studies, prognoses for the TAE and non-TAE groups can reasonably be expected to be similar or slightly worse for the TAE group. As would be expected based on this study's design, stereotactic radiosurgery was more commonly performed in the TAE group. This knowledge helps validate the outcomes results between the 2 groups, in which TAE was associated with lower rates of AEs despite arguably higher risk of rupture in the TAE cohort. Statistical significance was also found when a composite of hemorrhage and new seizures was considered. TAE was not significantly associated with any of the individual endpoints, though the magnitudes of the HRs for hemorrhage alone or new seizures alone were similar to those based on the composite event. This appeared to be driven by a weaker relationship between TAE and all-cause mortality, potentially because this endpoint is not as specific to the original arteriovenous malformation that was treated.

Limitations

While the current study addresses methodological shortcomings of our previously published analysis, some limitations persist. While mitigated by the case–control design, retrospective analysis remains a limitation, and difference in baseline

characteristics between the 2 cohorts may introduce bias. Specifically, perfect matching of SM and LY supplemental scores was not feasible, although mean scores between the 2 cohorts were very close. Imputing functional outcomes from the patient record could also introduce bias. Future prospective investigation is needed. Selection bias is inherent given study design based on nonrandomized inclusion criteria. Finally, understanding of the natural history of BAVMs remains limited, and more robust natural history data against which analyses of intervention can be compared would strengthen the study.

CONCLUSION

BAVM treatment seeks to eliminate or reduce risk of ICH. Treatment can be challenging, and determining the optimal therapy for a lesion can be problematic. TAE for aneurysms associated with BAVMs is both safe and effective for BAVMs for which surgical resection would be very morbid. For such high-risk lesions, TAE should be considered.

Disclosures

This work was supported, in part, by the National Institutes of Health grant R01 NS034949 to H. Kim. Dr Hippe receives grants from GE Healthcare, Philips Healthcare, and Toshiba America Medical Systems for statistical work on unrelated projects. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Bendjilali N, Nelson J, Weinsheimer S, et al. Common variants on 9p21.3 are associated with brain arteriovenous malformations with accompanying arterial aneurysms. *J Neurol Neurosurg Psychiatry*. 2014;85(11):1280-1283.
2. Stapf C, Mohr JP, Pile-Spellman J, et al. Concurrent arterial aneurysms in brain arteriovenous malformations with haemorrhagic presentation. *J Neurol Neurosurg Psychiatry*. 2002;73(3):294-298.
3. Alexander MD, Cooke DL, Hallam DK, Kim H, Hetts SW, Ghodke BV. Less can be more: targeted embolization of aneurysms associated with arteriovenous malformations unsuitable for surgical resection. *Interv Neuroradiol*. 2016;22(4):445-451.
4. 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(9917):614-621.
5. da Costa L, Wallace MC, Ter Brugge KG, O'Kelly C, Willinsky RA, Tymianski M. The natural history and predictive features of hemorrhage from brain arteriovenous malformations. *Stroke*. 2009;40(1):100-105.
6. Graf CJ, Perret GE, Torner JC. Bleeding from cerebral arteriovenous malformations as part of their natural history. *J Neurosurg*. 1983;58(3):331-337.
7. Gross BA, Du R. Natural history of cerebral arteriovenous malformations: a meta-analysis. *J Neurosurg*. 2013;118(2):437-443.
8. Hernesniemi JA, Dashti R, Juvela S, Vaart K, Niemela 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(5):823-829; discussion 829-831.
9. Itoyama Y, Uemura S, Ushio Y, et al. Natural course of unoperated intracranial arteriovenous malformations: study of 50 cases. *J Neurosurg*. 1989;71(6):805-809.
10. Yamada S, Takagi Y, Nozaki K, Kikuta K, Hashimoto N. Risk factors for subsequent hemorrhage in patients with cerebral arteriovenous malformations. *J Neurosurg*. 2007;107(5):965-972.
11. Kim H, Al-Shahi Salman R, McCulloch CE, Stapf C, Young WL, Coinvestigators M. Untreated brain arteriovenous malformation: patient-level meta-analysis of hemorrhage predictors. *Neurology*. 2014;83(7):590-597.
12. Stapf C, Mast H, Sciacca RR, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology*. 2006;66(9):1350-1355.
13. Stefani MA, Porter PJ, terBrugge KG, Montanera W, Willinsky RA, Wallace MC. Large and deep brain arteriovenous malformations are associated with risk of future hemorrhage. *Stroke*. 2002;33(5):1220-1224.
14. Turjman F, Massoud TF, Vinuela F, Sayre JW, Guglielmi G, Duckwiler G. Correlation of the angioarchitectural features of cerebral arteriovenous malformations with clinical presentation of hemorrhage. *Neurosurgery*. 1995;37(5):856-860; discussion 860-852.
15. Brown RD, Jr, Wiebers DO, Forbes GS. Unruptured intracranial aneurysms and arteriovenous malformations: frequency of intracranial hemorrhage and relationship of lesions. *J Neurosurg*. 1990;73(6):859-863.
16. Redekop G, TerBrugge K, Montanera W, Willinsky R. Arterial aneurysms associated with cerebral arteriovenous malformations: classification, incidence, and risk of hemorrhage. *J Neurosurg*. 1998;89(4):539-546.
17. Lv X, Wu Z, Jiang C, et al. Angioarchitectural characteristics of brain arteriovenous malformations with and without hemorrhage. *World Neurosurg*. 2011;76(1-2):95-99.
18. Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. *Neurosurgery*. 2010;66(4):702-713; discussion 713.
19. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg*. 1986;65(4):476-483.
20. Bollet MA, Anxionnat R, Buchheit I, et al. Efficacy and morbidity of arc-therapy radiosurgery for cerebral arteriovenous malformations: a comparison with the natural history. *Int J Radiat Oncol Biol Phys*. 2004;58(5):1353-1363.
21. Starke RM, Komotar RJ, Hwang BY, et al. A comprehensive review of radiosurgery for cerebral arteriovenous malformations: outcomes, predictive factors, and grading scales. *Stereotact Funct Neurosurg*. 2008;86(3):191-199.
22. Moosa S, Chen CJ, Ding D, et al. Volume-staged versus dose-staged radiosurgery outcomes for large intracranial arteriovenous malformations. *Neurosurg Focus*. 2014;37(3):E18.
23. Conger A, Kulwin C, Lawton MT, Cohen-Gadol AA. Endovascular and microsurgical treatment of cerebral arteriovenous malformations: current recommendations. *Surg Neurol Int*. 2015;6:39.
24. Jahan R, Murayama Y, Gobin YP, Duckwiler GR, Vinters HV, Vinuela F. Embolization of arteriovenous malformations with Onyx: clinicopathological experience in 23 patients. *Neurosurgery*. 2001;48(5):984-995; discussion 995-987.
25. Klurfan P, Gunnarsson T, Haw C, Ter Brugge KG. Endovascular treatment of brain arteriovenous malformations: the toronto experience. *Interv Neuroradiol*. 2005;11(suppl 1):51-56.
26. Meisel HJ, Mansmann U, Alvarez H, Rodesch G, Brock M, Lasjaunias P. Effect of partial targeted N-butyl-cyano-acrylate embolization in brain AVM. *Acta Neurochir*. 2002;144(9):879-887; discussion 888.
27. Saatci I, Geyik S, Yavuz K, Cekirge HS. Endovascular treatment of brain arteriovenous malformations with prolonged intranidal Onyx injection technique: long-term results in 350 consecutive patients with completed endovascular treatment course. *J Neurosurg*. 2011;115(1):78-88.
28. Taylor CL, Dutton K, Rappard G, et al. Complications of preoperative embolization of cerebral arteriovenous malformations. *J Neurosurg*. 2004;100(5):810-812.
29. 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(18):2011-2019.
30. van Rooij WJ, Jacobs S, Sluzewski M, van der Pol B, Beute GN, Sprengers ME. Curative embolization of brain arteriovenous malformations with onyx: patient selection, embolization technique, and results. *AJNR Am J Neuroradiol*. 2012;33(7):1299-1304.
31. Vinuela F, Duckwiler G, Jahan R, Murayama Y. Therapeutic management of cerebral arteriovenous malformations. Present role of interventional neuroradiology. *Interv Neuroradiol*. 2005;11(suppl 1):13-29.
32. Krings T, Hans FJ, Geibprasert S, Terbrugge K. Partial "targeted" embolisation of brain arteriovenous malformations. *Eur Radiol*. 2010;20(11):2723-2731.
33. Alexander MJ, Tolbert ME. Targeting cerebral arteriovenous malformations for minimally invasive therapy. *Neurosurgery*. 2006;59(5 suppl 3):S178-S183; discussion S173-S113.
34. Hademenos GJ, Massoud TF. Risk of intracranial arteriovenous malformation rupture due to venous drainage impairment. A theoretical analysis. *Stroke*. 1996;27(6):1072-1083.
35. Le Feuvre D, Taylor A. Target embolization of AVMs: identification of sites and results of treatment. *Interv Neuroradiol*. 2007;13(4):389-394.

36. Mansmann U, Meisel J, Brock M, Rodesch G, Alvarez H, Lasjaunias P. Factors associated with intracranial hemorrhage in cases of cerebral arteriovenous malformation. *Neurosurgery*. 2000;46(2):272-279; discussion 279-281.
37. Settecase F, Hetts SW, Nicholson AD, et al. Superselective intra-arterial ethanol sclerotherapy of feeding artery and nidal aneurysms in ruptured cerebral arteriovenous malformations. *AJNR Am J Neuroradiol*. 2016;37(4):692-697.
38. Alexander MD, Cooke DL, Nelson J, et al. Association between venous angioarchitectural features of sporadic brain arteriovenous malformations and intracranial hemorrhage. *AJNR Am J Neuroradiol.* 2015;36(5):949-952.

Supplemental digital content *is available for this article at www.neurosurgery-online.com.*

COMMENT

This paper presents a retrospective case-control comparison of patient with brain AVMs and those undergoing targeted embolization of AVM-associated aneurysms. The authors matched the cohort based on age and rupture. The paper analysis presents findings of lower rates of adverse events in the treated cohort and better rates of functional recovery. The targeted aneurysm embolization group encountered less short-term complications, implying that the upfront risk of treatment offsets the potential risk of subsequent morbidity.

Carlos David
Burlington, Massachusetts