Determinants of Staged Endovascular and Surgical Treatment Outcome of Brain Arteriovenous Malformations

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Background and Purpose—Therapy of brain arteriovenous malformations (AVMs) often requires the combination of different treatment modalities. Independently assessed data on neurologic outcome after multidisciplinary AVM therapy are scarce.

Methods—The 119 consecutive patients (49% women, mean age 34±13 years) with brain AVMs receiving endovascular embolization followed by surgical treatment were analyzed. Neurologic impairment was assessed prospectively by a neurologist using the modified Rankin Scale (mRS) before, during, and after completed AVM therapy. The association of demographic, clinical, and morphologic characteristics with new treatment-related neurologic deficits was calculated.

Results—The 119 patients were treated with 240 superselective embolizations (median, 2; range, 1 to 8) using n-butyl cyanoacrylate. Mean follow-up time after surgery was 9.6±13.2 months. On the Spetzler-Martin scale, 8% of the AVMs were grade 1, 27% grade 2, 40% grade 3, 22% grade 4, and 3% grade 5. Disabling treatment-related complications (mRS≥3) occurred in 5% (95% confidence interval [CI], 1% to 9%) of the patients. Nondisabling new deficits were observed in another 42% (95% CI, 33% to 51%). No patient died. Nonhemorrhagic AVM presentation (odds ratio [OR], 5.00; 95% CI, 1.75 to 14.29), deep venous drainage (OR, 3.09; 95% CI, 1.43 to 6.64), AVM location in an eloquent brain region (OR, 2.42; 95% CI, 1.10 to 5.33), and large AVM size (OR, 1.05; 95% CI, 1.01 to 1.09) were independently associated with new treatment-related deficits.

Conclusions—Our results suggest an increased treatment risk for patients with previously unbled AVMs from combined endovascular and surgical AVM therapy. Additional risk factors for treatment-related neurologic deficits may be large AVM size, deep venous drainage, and AVM location in eloquent brain regions. (Stroke. 2005;36:2431-2435.)

Key Words: AVM • brain arteriovenous malformation • embolization • outcome • surgery

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reatment decisions for patients with brain arteriovenous malformations (AVMs) are based on natural course risk estimates weighted against outcome data from invasive intervention.1-3 Depending on the size, location, and angioarchitecture of the AVM, complete obliteration of the malformation is frequently not achieved by endovascular treatment or surgical treatment alone and requires a combined therapeutic approach.5-7 In these cases, determinants of treatment risk derived from studies of single-modality treatment may not be applicable, eg, endovascular treatment of an AVM may have a positive or negative effect on the subsequent surgical risk,8,9 and patients with AVMs requiring combined treatment may face treatment risks different from those in whom AVM obliteration or removal can be achieved with embolization or surgery alone.10,11

Studies on AVM treatment outcome using independent neurologic data collection are scarce. The purpose of this single-center study was to prospectively and independently assess treatment outcome after combined embolization with subsequent surgical therapy of brain AVMs and to analyze determinants of treatment-related neurologic deficits.

Patients and Methods

The New York AVM Databank is an ongoing, prospective database collecting demographic, clinical, morphologic, and treatment data on consecutive patients admitted to the Columbia University College of Physicians and Surgeons with brain AVM proven by brain imaging and conventional cerebral angiography. Other types of intracranial fistulas (such as dural AV fistulas, vein of Galen type malformations) are not included. Patients enrolled are drawn from the New York metropolitan area as well as from distant referrals sites. The study was approved by the institutional ethics committee. Further

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details on the design and methods of the dataset have been described in prior publications.3,7

The 119 consecutive patients with brain AVMs receiving one or more endovascular treatments followed by surgical AVM resection between 1991 and 1999 were analyzed. Neurologic deficit, disability, and impairment were independently assessed by a study neurologist. Functional neurologic status was documented before and after completed embolization therapy and before and after surgical treatment using the modified Rankin Scale (mRS).12,13 Any worsening of the patients’ preembolization mRS score was coded as “new neurologic deficit.” This included worsening of patients with a preexisting neurologic deficit. New neurologic deficits were classified as “disabling” when mRS scores were ≥3. For patients with baseline mRS scores of 2 or worse, any score increase was classified as “disabling.”

For embolization, superselective microcatheter cannulation of arteries feeding the AVM and injection of N-butyl cyanoacrylate (NBCA) were used to occlude the fistulae. All embolizations were performed by the same senior neuroradiologist with longstanding expertise in the field using the same technique throughout the study period. Fifty-seven patients (48%) were embolized with one session each, 62 patients (52%) were treated multiple times (median, 2; range, 1 to 8 sessions). Median time between the embolizations was 42 days (interquartile range, 19.5 to 116 days). As a general rule, the a priori treatment plan for the studied patients required combined endovascular and surgical therapy. Embolization therefore was aimed at facilitating the subsequent operation without the primary goal of AVM occlusion by embolization alone.

After embolization, all patients underwent microsurgical AVM resection performed by one of 3 senior neurosurgeons of the institution’s faculty. Median time between last embolization and surgery was 14 days (range, 1 day to 14.8 months). AVM resection was performed once in 111 patients (93%), twice in 7 patients (6%), and 3 times in one patient (1%). Surgical outcome was assessed by a study neurologist postoperatively inhospital and then during long-term follow-up. Mean follow-up time after surgery was 9.6 months (±13.2 months).

Based on the morphologic AVM characteristics, the malformations were classified according to the 5-point Spetzler-Martin grading system with its 3 elements size (scored one for small size, 2 for medium size, and 3 for large size), drainage (scored one for AVM with any drainage into the internal, “deep” cerebral venous system), and location (scored one for AVM in functionally important, so-called “eloquent,” brain regions).14

Univariate logistic regression analyses were used to describe the effect of demographic factors, mode of initial AVM presentation, preembolization neurologic status, number of embolizations, and various morphologic parameters, including the Spetzler-Martin score and its components on neurologic worsening after completed treatment.

All variables with significant association in the univariate analyses (P<0.05) were entered into a multiple logistic regression model using backward elimination procedures to test their independent association with any treatment-related new neurologic deficits. The stepwise elimination process included variables with a significance level of P<0.05. The overall Spetzler-Martin score was not used in this analysis because its separate components were already included in the model.

All variables were tested for the association with outcome at long-term follow-up after surgery. Because of possible instability of neurologic deficits, intermittent neurologic assessments after embolization, immediately before surgery, and inhospital after surgery were not used for association analyses.

Results

Demographic, clinical, and morphologic data of the study sample are given in Table 1.

By baseline mRS score, 96% of the patients had no functionally relevant neurologic deficit (mRS=0 or 1), and 99% were nondisabled (mRS=2; Figure).

| TABLE 1. Demographic, Clinical, and Morphologic Characteristics of 119 Patients With Brain AVM Undergoing Staged Embolization and Surgical Therapy |
|---|---|
| Age (mean, SD, range) | 34 y, SD 13 y, range 6 to 68 y |
| Female gender | 58 (49%) |
| Initial presentation | |
| Intracranial hemorrhage | 41 (35%) |
| Seizure | 41 (35%) |
| Headache | 19 (16%) |
| Focal deficit | 8 (7%) |
| Other/asymptomatic | 10 (8%) |
| No. of embolizations | 240 (median 2, range 1 to 8) |
| Median time from first embolization to surgery | 32 days (semiquartile range 1 to 8) |
| Median time from last embolization to surgery | 14 days (semiquartile range 7 to 21 days) |
| Median follow-up time after surgery | 3.5 months (semiquartile range 6.7 mo) |
| Maximum AVM diameter (mean) | 35 mm (SD 13 mm, range 8 to 70 mm) |
| AVMs with deep arterial feeders | 23 (19%) |
| Borderzone AVM location | 63 (53%) |
| Infratentorial AVM location | 9 (8%) |
| Patients with concurrent arterial aneurysms | 21 (18%) |
| Spetzler-Martin score elements | |
| Small AVM (diameter <3 cm) | 32 (27%) |
| Medium AVM (3 to 6 cm) | 83 (70%) |
| Large AVM (>6 cm) | 4 (3%) |
| Deep venous drainage | 55 (46%) |
| Eloquent location | 72 (61%) |
| Spetzler-Martin score 1 | 10 (8%) |
| Spetzler-Martin score 2 | 32 (27%) |
| Spetzler-Martin score 3 | 48 (40%) |
| Spetzler-Martin score 4 | 26 (22%) |
| Spetzler-Martin score 5 | 3 (3%) |

*Defined as penetrating branches of the major intracranial arteries of the circle of Willis, the cerebellar, or of the choroidal arteries.†Arterial supply by branches of at least 2 of the major arteries of circle of Willis.$Includes aneurysms on feeding arteries, intranidal, and AVM-unrelated aneurysms.¶Includes location in the sensorimotor, visual, or language cortex, the basal ganglia, the internal capsule, the brainstem, the cerebellar peduncles, and the deep cerebellar nuclei. SD indicates standard deviation.

Postoperative angiographies were documented in 116 patients (98%). In 46 of them (39%), dysplastic vessels were present, and in 4 (4%), residual AVMs were documented, leading to a complete AVM obliteration rate of 96%. In one of the latter patients, complete AVM removal was considered too dangerous. He experienced a postoperative hemorrhage within 3 months of surgery, which left him with a mild neurologic deficit (mRS=1). A total of 50 patients (42%; 95% confidence interval [CI], 33% to 51%) showed treatment-related, new nondisabling
mRS scores of 119 patients (A) undergoing staged endovascular and surgical brain AVM treatment before, during, and after completed therapy. No patient died (mRS = 6). mRS distribution of patients with nonhemorrhagic initial AVM presentation (n=78) is shown in B. mRS = 0, no symptoms at all. mRS = 1, able to carry out all usual duties and activities. mRS = 2, unable to carry out all previous activities but able to look after own affairs. mRS = 3, requiring some help but able to walk without assistance. mRS = 4, unable to walk without assistance and unable to attend to bodily needs. mRS = 5, bedridden, incontinent, and requiring constant nursing care and attention.

neurologic deficits resulting from surgery in 32% (95% CI, 24% to 40%), from embolization in 6% (95% CI, 4% to 8%), and from both treatment types in 4% (95% CI, 1% to 8%). Another 6 patients (5%; 95% CI, 1% to 9%) had disabling deficits (3% from surgery and 2% from embolization). No patient died. There were no treatment-related improvements. After start of treatment, a total of 40 patients (34%; 95% CI, 26% to 43%) experienced a hemorrhage. It occurred within 1 week of embolization in one patient and within the first week after surgery in 6 patients. One of the latter patients experienced a permanent disabling deficit with severe hemiparesis (mRS = 5). In 7 patients, the hemorrhage occurred between the endovascular and surgical therapy, and in 19 patients, it was unrelated (>1 month) to therapy. Of the latter, 12 hemorrhages were noted within 3 months and a further 5 bleeds within the first year of treatment. In 7 patients, the time point of hemorrhage was unknown. The course of neurologic deficits defined by the mRS at multiple assessment points throughout the course of treatment is shown in Figure 1.

Overall, 63 patients (53%; 95% CI, 44% to 62%) experienced no change in neurologic status following treatment, and 91% (95% CI, 86% to 96%) were nondisabled (mRS = 2, Figure 1A) after completed therapy compared with 99% (95% CI, 97% to 100%) at initial presentation. Of the 63 patients who experienced no change in functional status, 17 (14%) had a pretreatment neurologic deficit that remained unchanged at long-term follow-up.

Among the 78 patients who, before the initiation of treatment, had not experienced an intracranial hemorrhage, 45 patients (58%; 95% CI, 49% to 67%) experienced new treatment-related deficits (of the 78 patients, 41% were mRS = 1, 10% mRS = 2, 3% mRS = 3, 0% mRS = 4, and 3% mRS = 5). Among the 41 patients who initially presented with intracranial hemorrhage, 11 patients (27%; 95% CI, 19% to 35%) experienced new treatment-related deficits (odds ratio [OR], 0.27; 95% CI, 0.12 to 0.61; P = 0.001).

The results of the univariate analyses are shown in Table 2. In the multivariate models, increasing AVM diameter, deep venous drainage, and eloquent AVM location were significantly associated with treatment complications (Table 3). There was a lower treatment risk for patients who initially presented with intracranial hemorrhage, or inversely, patients who had not bled before had a higher risk of new treatment-related deficits. For all other variables, no significant association was found. The low number of disabling treatment complications precluded a meaningful analysis.

Discussion

The rate of treatment-related permanent neurologic deficits and death from any method of AVM treatment culled from the literature ranges from 0% to 20% (mean 8%).7–18 Our data suggest an overall low risk of treatment-related disabling
Table 3. Multivariate Logistic Regression Model Testing the Independent Association of Demographic and Morphologic Parameters With Disabling and Nondisabling Neurologic Deficits Related to Staged Endovascular and Surgical AVM Treatment in 119 Patients at Long-Term Follow-Up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum AVM diameter*</td>
<td>1.05</td>
<td>1.01–1.09</td>
<td>0.01</td>
</tr>
<tr>
<td>Initial presentation with hemorrhage</td>
<td>0.27</td>
<td>0.11–0.69</td>
<td>0.006</td>
</tr>
<tr>
<td>Spetzler-Martin score elements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep venous drainage</td>
<td>3.24</td>
<td>1.35–7.80</td>
<td>0.009</td>
</tr>
<tr>
<td>Eloquent AVM location</td>
<td>2.42</td>
<td>1.02–5.73</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Per millimeter increase.

morbidity and mortality with independent neurologic evaluation. However, despite the low number of disabling complications, the overall rate of new neurologic deficits was 42% (95% CI, 33% to 51%), with the majority (32%) resulting from surgery. It was somewhat higher than could be expected from the data reported in the literature. In their series of patients managed with combined endovascular and surgical treatment, Vinuela et al detected a mild overall long-term morbidity of 6% with an additional moderate to severe morbidity and mortality rate of 13%.5 Morgan et al described a 33% total complication rate in their predominantly surgical series, in which 45 of 250 patients (18%) had preoperative embolization. Of their patients, 10% were left with a Rankin score of ≥3 and 22.8% with a Rankin score of one or 2. Previous work from our own database on single-modality treatment outcome showed a 14% (including 2% disabled, 1% dead) complication rate from embolization11 and a 38% (including 6% disabled, 0% dead) complication rate from surgery.10 Prospective and independent evaluation by a neurologist may reveal a larger number of less severe complications, as has also been shown in carotid surgery outcome studies, leading to a higher detection rate of nondisabling deficits.

In many prior publications, the patients’ baseline functional status is not provided, and information on change of functional status between embolization and surgery is also not provided. To distinguish between preexisting deficits and new treatment-related impairments, and to depict the clinical changes of the patients throughout the complete course of therapy, we added neurologic assessments at the time points shown in Figure 1. The low complication rate from embolization reported previously11 was confirmed without major changes in outcome until surgery. The distribution of mRS scores immediately after surgery reflects changes toward functional worsening that were also expected and previously reported partially reversible.5,10,22 However, the outcome measure used in our study, the mRS, with its low sensitivity to higher cortical function lesions, may underestimate important complications. In this light, treatment complications rated minor/nondisabling may still bear considerable weight in the risk balancing of AVM treatment decisions.

The low rate of disabling complications or death in our study precludes a meaningful analysis of their predictors. The detailed clinical analysis of the 6 patients with new disabling deficits, however, did not suggest a common cause for their deterioration under therapy.

In univariate analysis, more frequent embolizations, no neurologic deficit at baseline, nonhemorrhagic AVM presentation, large AVM diameter, the Spetzler-Martin score, and its elements “deep venous drainage” and “eloquent AVM location” were associated with long-term treatment-related neurologic deficits. Lacking independence, the significance was not sustained in multivariate analysis for some variables. Large AVMs likely need to be embolized more frequently, are more likely to be in eloquent brain regions, and are more likely to have deep venous drainage. Normal neurologic examination at baseline as a predictor of treatment-related deficits may reflect the higher likelihood of patients with no preexisting focal neurologic signs to reveal new symptoms, especially a better detection rate for mild deficits. A similar effect has been observed in exclusively endovascular AVM treatment,11 lending support to our observation in this study.

In our study, the Spetzler-Martin grading system and its elements “deep venous drainage” and “eloquent AVM location” were predictors of neurologic complication after treatment. The system was originally designed and validated to predict surgical treatment outcome.14,23 Given that the majority of neurologic outcome deterioration in our study followed during surgery, this confirms the validity of the grading system. In our results, maximal AVM diameter measured in millimeter increments seemed to have the stronger association with new deficits than the somewhat arbitrary, albeit easy-to-apply trichotomization used in the grading system.

Preoperative embolization has been routinely used in the treatment of brain AVMs.24–27 Although considered helpful by some authors, especially in large or deeply located AVMs,26 its usefulness is disputed by others, citing complication rates from embolization28 and worse outcomes in patients who had undergone preoperative embolization.19 Because all patients in our study received combined treatment, it remains unproven whether endovascular AVM treatment affects the complication risk from subsequent surgery, as suggested by others.19,29 Nonetheless, a prior analysis from our dataset did not suggest an adverse effect of endovascular therapy on AVM surgery outcome,10 and the low overall rate of 5% disabling complications in our series originated from endovascular treatment and surgical therapy in similar proportions.

Although independent associations between some of the tested variables and posttreatment neurologic deficits were shown, those found to be determinants were far from predicting all complications. Clinicians facing therapeutic decisions in AVM patients, including questions regarding treatment risks, are currently left with the rather simple notion that larger AVMs with deep drainage in difficult regions of the brain may bear a high treatment risk. Important morphologic characteristics like type and number of arterial AVM feeders and draining veins, the presence of venous aneurysms, and cortico-subcortical wedge-shaped morphology versus deep white matter location—to name a few—have so far not been rigorously tested in a population large enough to reliably identify them as poor outcome predictors.
Deep venous drainage and deep AVM location were previously reported as predictors of recurrent AVM hemorrhage. The similarity with predictors of poor treatment outcome increases the level of uncertainty for therapeutic recommendations. The higher treatment risk for unruptured AVMs suggested by this study further underscores the need for a randomized study on the risks and benefits of invasive treatment in unruptured AVMs.

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References
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