Title

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Journal

Neurosurgery, 88(5)

ISSN

0148-396X

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Publication Date

2021-05-01

DOI

10.1093/neuros/nyaa551

Peer reviewed

CNS Spotlight

Spetzler-Martin Grade III Arteriovenous Malformations: A Multicenter Propensity-Adjusted Analysis of the Effects of Preoperative Embolization

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Received, March 25, 2020.
Accepted, November 4, 2020.
Published Online, January 11, 2021.

BACKGROUND: Spetzler-Martin (SM) grade III arteriovenous malformations (AVMs) are at the boundary of safe operability, and preoperative embolization may reduce surgical risks.
OBJECTIVE: To evaluate the benefits of preoperative AVM embolization by comparing neurological outcomes in patients with grade III AVMs treated with or without preoperative embolization.
METHODS: All microsurgically treated grade III AVMs were identified from 2011 to 2018 at 2 medical centers. Neurological outcomes, measured as final modified Rankin Scale scores (mRS) and changes in mRS from preoperative baseline to last follow-up evaluation, were compared in patients with and without preoperative embolization.
RESULTS: Of the 102 patients with grade III AVMs who were treated microsurgically, 57 (56%) underwent preoperative embolization. Significant differences were found between the patients with and without embolization in AVM eloquence (74% vs 93%, $P = .02$), size $\geq$ 3 cm (47% vs 73%, $P = .01$), diffuseness (7% vs 22%, $P = .04$), and mean final mRS (1.1 vs 2.0, $P = .005$). Poor outcomes were more frequent in patients without embolization (38%) than with embolization (7%) (final mRS > 2; $P < .001$). Propensity-adjusted analysis revealed AVM resection without embolization was a risk factor for poor outcome (mRS score > 2; odds ratio, 4.2; 95% CI, 1.1-16; $P = .03$).
CONCLUSION: Nonembolization of SM grade III AVMs is associated with an increased risk of poor neurological outcomes after microsurgical resection. Preoperative embolization of intermediate-grade AVMs selected because of large AVM size, surgical inaccessibility of feeding arteries, and high flow should be employed more often than anticipated, even in the context of increasing microsurgical experience with AVMs.

KEY WORDS: Arteriovenous malformation, Embolization, Spetzler-Martin grade

Neurosurgery 88:996–1002, 2021 DOI:10.1093/neuros/nyaa551 www.neurosurgery-online.com

Brain arteriovenous malformations (AVMs) are associated with a high lifetime risk of significant morbidity from hemorrhage, and microsurgery offers a chance at curative resection.[1,2] Low-grade AVMs are typically treated with microsurgery alone without adjunctive therapy, but intermediate- and high-grade AVMs are a significant challenge to the neurosurgeon, and adjunctive therapy may be of benefit.[3] Preoperative embolization has been shown to reduce the risk of surgery by mitigating high-risk features such as blood flow through the nidus and AVM size. However, the effect of preoperative embolization on clinical outcomes remains controversial.[1,4-15]

Spetzler-Martin (SM) grade III AVMs are challenging lesions to resect because they straddle the limit of operability for many neurosurgeons.[16] SM grade III AVMs are a heterogeneous group of intermediate-grade lesions with variability in size, deep venous drainage, and eloquent location, which makes it difficult to develop a clear decision-making algorithm for preoperative embolization.[16-22] A small case series recently reported that preoperative

ABBREVIATIONS: AVM, arteriovenous malformation; **mRS,** modified Rankin Scale score; **SD,** standard deviation; **SM,** Spetzler-Martin; **STROBE,** Strengthening the Reporting of Observational Studies in Epidemiology

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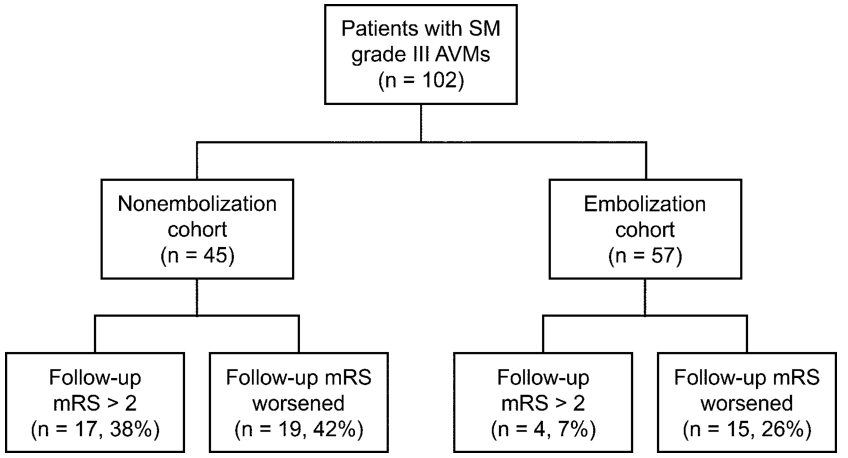

FIGURE. *Patient flowchart. AVM, arteriovenous malformation; mRS, modified Rankin scale score. Used with permission from Barrow Neurological Institute, Phoenix, Arizona.*

embolization facilitated microsurgical resection of these SM grade III AVMs and was associated with favorable patient outcomes.[19] Nonetheless, no papers to date have reported significant differences in outcomes between SM grade III AVMs treated with and without preoperative embolization, largely due to the small size of the surgical series. This study compares the neurological outcomes of patients with SM grade III AVMs treated with or without preoperative embolization in 2 major cerebrovascular centers to evaluate the effect of preoperative embolization on outcomes.

METHODS

All patients with SM grade III AVMs who underwent microsurgical resection at the University of California, San Francisco, from January 1, 2011, to July 31, 2017, and St. Joseph's Hospital and Medical Center in Phoenix, Arizona, from January 1, 2011, to December 31, 2018, were retrospectively analyzed. Patient data were collected from 2 prospectively maintained databases at the study institutions. The institutional review board at St. Joseph's Hospital and Medical Center in Phoenix, Arizona, approved the study protocol, and a multi-institutional data use agreement between the 2 institutions was established. A waiver for patient consent was granted due to the low risk the study presented to the patients. Patients' charts were retrospectively reviewed for absent data, including complications, treatments, neurological outcomes, and supplemental SM scores. The SM grade was verified by the authors of this study. This study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Surgical resections were performed by 2 neurosurgeons (R.F.S. and M.T.L.) and embolizations, by multiple interventionalists, with the majority performed by A.F.D. and F.C.A.

The patients were separated into 2 groups on the basis of whether they had undergone preoperative embolization (Figure). The primary outcome was neurological function at the last follow-up visit. A poor outcome was defined as a modified Rankin Scale score (mRS) >2. Secondary outcomes included mRS change from preoperative status and estimated blood loss during surgery. Preoperative mRS was measured immediately before resection.

Statistical analyses were performed with SPSS version 26 (IBM Corp., Armonk, New York) and included means and standard deviations (SDs), percentages, independent *t*-tests, and χ^2 analysis. Additionally, a propensity-matching analysis (for age, overall supplemental SM score, rupture status, diffuseness, deep venous drainage, size, eloquence, and nidus location) was performed to analyze the risk of a poor outcome (mRS > 2) when not undergoing preoperative embolization via multivariate logistic regression analysis. A *P*-value of <.05 was defined as statistically significant.

Preoperative angiography was performed in all patients. In 34 of these patients, adequate angiography was performed at the referring institution, and with embolization deemed unnecessary, angiography was not repeated at our institution. The remaining 68 patients underwent preoperative angiography at our institution, either with or without embolization. Intraoperative somatosensory evoked potentials were monitored routinely for these patients. Intraoperative angiography was rarely used, but intraoperative indocyanine green videoangiography was used as needed to assess residual shunt flow in veins upon completion of the resection. Postoperative digital subtraction angiography was performed in all patients.

RESULTS

A total of 102 patients were found to have SM grade III AVMs resected during the study period. Of these patients, 57 (56%) underwent preoperative embolization, whereas 45 did not. A higher number of patients were found to have eloquent AVMs in the nonembolization cohort (42/45, 93%), compared with the embolization cohort (42/57, 74%; $P = .02$). AVM sizes were smaller in the nonembolization group, in which 33 of 45 patients (73%) had an AVM < 3 cm in diameter compared with 27 of 57 patients (47%) in the embolization cohort ($P = .01$). A higher percentage of patients had diffuse AVMs

TABLE 1. Demographic and Clinical Characteristics of Patients With Spetzler-Martin Grade III Arteriovenous Malformations (AVMs) With and Without Preoperative Embolization[a]

Characteristic	Embolization cohort (n = 57)	Nonembolization cohort (n = 45)[c]	*P* value
Age, mean (SD), yr	31 (17)	38 (21)	.08
Male sex	29 (51)	23 (51)	.98
Age > 60 yr	5 (9)	8 (18)	.24
Race/ethnicity			.15
White	37 (65)	26 (58)	
Hispanic	4 (7)	11 (24)	
Black	5 (9)	3 (7)	
American Indian	1 (2)	0 (0)	
Asian	3 (5)	3 (50)	
Other	7 (12)	2 (4)	
AVM nidus location			.55
Frontal	14 (25)	7 (16)	
Parietal	3 (5)	6 (6)	
Temporal	10 (18)	7 (16)	
Occipital	8 (50)	8 (50)	
Deep (basal ganglia, internal capsule, corpus callosum, ventricle)	9 (16)	7 (16)	
Brainstem	3 (5)	5 (11)	
Cerebellum	10 (18)	5 (11)	
Supplemented Spetzler-Martin score			.79
4	8 (14)	7 (16)	
5	12 (21)	6 (13)	
6	24 (42)	21 (47)	
7	13 (23)	11 (24)	
Eloquence	42 (74)	42 (93)	.02
Motor eloquence	11 (19)	8 (18)	.84
Size			.01
<3 cm	27 (47)	33 (73)	
3-6 cm	30 (53)	11 (24)	
>6 cm	0 (0)	1 (2)	
Deep drainage	41 (72)	34 (76)	82
Rupture	25 (44)	26 (55)	.19
Diffuse	4 (7)	10 (22)	.04
Preoperative mRS, mean (SD)	1.2 (1.4)	1.4 (1.8)	.36
Preoperative mRS			.73
0	24 (42)	20 (44)	
1	17 (30)	9 (20)	
2	6 (11)	4 (9)	
3	3 (5)	2 (4)	
4	5 (9)	6 (13)	
5	2 (4)	4 (9)	
Estimated blood loss from resection, mean (SD), mL	402 (228)	398 (397)	.95
Surgical complications	14 (24)	9 (20)	.58
Severe surgical complications[b]	3 (5)	6 (13)	.17
Residual following resection	12 (21)	8 (18)	.68
Final follow-up mRS, mean (SD)	1.1 (1.3)	2.0 (1.7)	.005
Follow-up duration, mean (SD), d	355 (464)	318 (371)	.67

mRS = modified Rankin Scale score; SD = standard deviation.

[a]Data are presented as no. (%) unless otherwise indicated.

[b]Severe complications included hematoma, stroke, or new permanent neurological deficit following surgery.

[c]Two patients underwent preoperative angiography in preparation for embolization, but no arterial feeder was deemed appropriate for embolization.

TABLE 2. Details of Embolization Procedures[a] in Patients With Spetzler-Martin Grade III Arteriovenous Malformations

Characteristic	Patients (n = 57)*
Embolization material	
NBCA	24 (42)
Onyx	15 (26)
PVA	3 (5)
Onyx and NBCA	11 (19)
Coil and NBCA	1 (2)
PVA and NBCA	3 (5)
Multiple embolizations	16 (28)
Multiple pedicles embolized	25 (44)
Intranidal fistula	2 (4)
Intranidal aneurysm	6 (10)
Feeding artery aneurysm	11 (19)
Complications[b]	2 (4)
Time from embolization to surgery, mean (SD), d[c]	2.5 (5)

NBCA = *n*-butyl cyanoacrylate; PVA = polyvinyl alcohol.
*Data are presented as n (%) unless otherwise indicated.
[a]All embolizations were performed via a transarterial approach.
[b]Embolization complications included 1 intraparenchymal hemorrhage and 1 retained microcatheter.
[c]Range, 0 to 31 d.

in the nonembolization group (10/45, 22%) than in the embolization group (4/57, 7%; $P = .04$). No significant difference was found between the 2 groups regarding estimated blood loss during resection, age, location, supplemented SM score, rupture status, deep venous drainage, preoperative mRS, or follow-up days (Table 1). The mean follow-up mRS was higher in the nonembolization group (2.0 [SD 1.7]) than in the embolization group (1.1 [1.3]).

The most common embosylates administered were *n*-butyl cyanoacrylate (24/57, 42%), ethylene-vinyl alcohol copolymer (Onyx, Medtronic, plc, Dublin, Ireland) (15/57, 26%), or a combination of the 2 (11/57, 19%) (Table 2). Sixteen patients (28%) underwent staged embolizations, and 25 patients (44%) had multiple pedicles embolized. Nineteen patients (33%) were found to have high-risk features, including 2 (4%) with intranidal fistulas, 6 (10%) with intranidal aneurysms, and 11 (19%) with feeding artery aneurysms.

A significantly higher percentage of patients in the nonembolization group (17/45, 38%) than in the embolization group (4/57, 7%) had an mRS > 2 on follow-up neurological examination (odds ratio, 8; 95% CI, 2.5-26; $P < .001$) (Table 3). Additionally, 42% (19/45) of patients had a worsened neurological condition in the nonembolization cohort, whereas 26% (15/57) had a worsened neurological condition in the embolization cohort ($P = .10$).

A propensity-adjusted analysis was performed. Patients were matched for age, supplemented SM score, hemorrhage, diffuseness, deep venous drainage, size, eloquence, and nidus location to analyze risk factors for a poor neurological outcome (mRS > 2) using multivariate logistic regression analysis. This analysis showed that microsurgical resection without preoperative embolization was a significant risk factor for poor outcome (odds ratio, 4.2; 95% CI, 1.1-16; $P = .03$).

DISCUSSION

Key Results

SM grade III AVMs are intermediate-grade lesions at the limit of acceptable risk for microsurgical resection and are technically difficult to resect.[16] Studies have shown the usefulness of preoperative embolization of intermediate-grade lesions. Still, controversy exists as to whether preoperative embolization has a positive effect on neurological outcome.[18-21,23,24] In this study, microsurgical resection without preoperative embolization was associated with increased odds of a poor outcome. Differences between the 2 groups in age, eloquence, AVM size, and diffuseness prompted us to conduct matching via a propensity-adjusted analysis. Even after the propensity adjustment, microsurgical resection without preoperative embolization was a significant risk factor for a poor outcome. Other studies have also shown favorable outcomes with preoperative embolization of these AVMs, but none have demonstrated a statistically significant difference in neurological outcome.[19,24] Nonetheless, most previous studies have analyzed the differences between preoperative and postoperative mRS and found no statistically significant difference between patients with and without embolization.[23] Our results showed that 42% (19/45) of patients had a worsened neurological condition in the nonembolization cohort, whereas 26% (15/57) had a worsened neurological condition in the embolization cohort ($P = .10$).

Limitations

Although our patients were identified from a prospective database, our analysis of the data was performed retrospectively, with all of the limitations inherent to these studies. Additionally, experienced cerebrovascular and endovascular surgeons who are regarded as experts performed the majority of surgical procedures, which potentially limits the generalizability of the results.

Whether or not to embolize preoperatively was decided by the neurosurgeon in consultation with the endovascular team and was based primarily on large AVM size, the surgical accessibility of the feeding arteries, and their contribution to AVM flow. AVMs with deep feeders and high flow were selected for embolization, whereas AVMs with superficial feeders were not. Similarly, a cerebellar AVM with a proximal perinidal aneurysm would have been embolized to safely treat the aneurysm and occlude the deep AVM supply. Endovascular accessibility was also a factor. An AVM with en passage feeding arteries is difficult to embolize safely and effectively, as is an AVM with enlarged lenticulostriate arteries that supply a dominant hemisphere AVM. As much as

TABLE 3. Outcomes of Patients With Spetzler-Martin Grade III Arteriovenous Malformation Resection With and Without Preoperative Embolization

Characteristic	Embolization cohort (n = 57)	Nonembolization cohort (n = 45)	*P* value	Odds ratio (95% CI)
Follow-up mRS > 2	4 (7)	17 (38)	<.001	8 (2.5-26)
Follow-up mRS worsened	15 (26)	19 (42)	.10	2 (0.9-4.7)

mRS = modified Rankin Scale score.

the neurosurgeon would like some assistance in quieting these feeders, they would not have been embolized. In our experience, 2 patients (4%) underwent angiography with the intent to embolize preoperatively, but no suitable arterial feeder was found. These scenarios highlight the uniqueness of AVMs and the difficulty in constructing a universal decision-making algorithm. We had no such algorithm for preoperative embolization for patients in this study.

Interpretation

Embolization of these intermediate lesions is thought to facilitate resection in numerous ways, including reductions in intraoperative blood loss, occlusion of deeper, more difficult-to-reach arterial feeders, easier nidus dissection, and improved hemostasis.[19,25,26] The senior authors agree that embolization facilitated nidus dissection and quieted deep arterial feeders. The estimated blood loss did not significantly differ between the groups. This lack of statistical significance may be due to inaccuracy in the subjective estimation of intraoperative blood loss, which has been described previously in numerous microsurgical procedures.[27] Other reports have shown no difference in intraoperative blood loss between patients with preoperative embolized AVMs and those with nonembolized AVMs.[1] The difference in outcomes between the groups could be due to an association with severe surgical complications. Nine patients had severe complications that affected their outcomes, with all having a follow-up mRS > 2. Patients in the preoperative embolization group had fewer severe surgical complications (3 patients, 2 with new permanent neurological deficits, and 1 with a hemorrhage). In contrast, patients treated without preoperative embolization had more surgical complications (6 patients, 3 with new permanent neurological deficits, 2 with strokes, and 1 with a hemorrhage). The explanation could be significant differences in AVM diffuseness and size (more diffuseness and smaller size in the nonembolized AVMs) and nonsignificant differences in location (more brainstem AVMs).

In an earlier study of outcomes after microsurgical resection of 76 SM grade III AVMs, 79% of patients had good outcomes (mRS ≤ 2),[16] which matches the findings of the present study. In that earlier study, the proportion of patients with small SM grade III AVMS (S1V1E1) and neurological worsening according to the mRS score was 2.9%, which is lower than the 35% of patients with neurological worsening observed in this study. In the subgroup of patients with 60 small (<3 cm) SM grade III AVMs in the current study, the proportion of patients who underwent preoperative embolization and had neurological worsening was 23% (6/26 patients). In contrast, the proportion of those who did not undergo embolization and had neurological worsening was 44% (15/34 patients) ($P = .09$). Although the difference was not statistically significant, we believe that a benefit from embolization is possible in select cases. A larger study to determine and confirm such benefits is needed. Additionally, in the earlier study, embolization was performed in 75 of 76 patients (99%), which suggests a benefit from embolization. Although this comparison of the 2 studies suggests that the small SM grade III AVM subtype (S1V1E1) may be riskier to resect than previously thought, the duration of follow-up was shorter in the current study. The inverse correlation between the follow-up duration and outcome is well known.[16]

Earlier studies have demonstrated that preoperative AVM embolization can be performed safely.[1,19,24] In the current analysis, complications occurred in 2 embolization procedures (4%) (Table 2), including 1 intraparenchymal hemorrhage that required microsurgical intervention and 1 retained microcatheter following Onyx administration. Likewise, Luzzi et al[19] found 3 complications in 27 patients who underwent preoperative Onyx embolization for SM grade III lesions, 2 of which were due to catheter retainment. Other studies have reported higher incidences of complications from embolization, with associated increased morbidity.[28,29] Furthermore, multistage embolizations increase the overall complication risk, which may outweigh the benefit associated with embolization. Nonetheless, we found only 1 (2%) severe complication associated with embolization (Table 2). Similarly, in 77 patients with grade III AVMs who underwent preoperative embolization, Pandey et al[24] found a 1.6% risk of major complications from embolization.

Researchers have reported residual grade III AVMs in 3% to 14% of patients and surgical complications in 5% to 29% of patients,[3,16,24,30-32] which is comparable to that in our study. We found no significant differences in the rates of complications and residual AVMs between the embolization and nonembolization groups. Interestingly, Pandey et al[24] found that diameter ≥3 cm was a risk factor for surgical complications among patients with grade III AVMs We found more of these larger AVMs in the embolization cohort (30/57, 53%) than in the nonembolization cohort (12/45, 27%).

Generalizability

An AVM surgeon's use of embolization tends to decrease with increasing operative experience. Morgan's experience is the most dramatic example of this, with the complete abandonment of preoperative embolization in the later years of his AVM practice.[8,33] A decrease in the embolization of SM grade III AVMs in this study can be inferred from previous publications by the senior authors. It is likely that increased experience, advancements in technical skills, and greater confidence could make AVM surgeons less likely to incur the additional complication risks of preoperative embolization and to decide against it. Although this posture may be reasonable for low-grade AVMs, the results of the current study suggest that preoperative embolization of intermediate-grade AVMs should be employed more often than anticipated, even in the context of increasing microsurgical experience with AVMs.

CONCLUSION

SM grade III AVMs can be associated with significant morbidity following microsurgical resection. Preoperative embolization can be performed safely in most patients and is selected based on large AVM size, the surgical inaccessibility of the feeding arteries, and high flow. Nonembolization of SM grade III AVMs is associated with an increased risk of a poor neurological outcome following microsurgical resection. Preoperative embolization of intermediate-grade AVMs should be employed more frequently than anticipated, even in the context of increasing microsurgical experience with AVMs.

Funding

This study was funded by grant support: R01NS034949 (H.K.) and R01NS099268 (H.K., M.T.L.).

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this manuscript.

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Acknowledgments

The authors thank Ankush Bajaj for help with database organization and the Neuroscience Publications staff at Barrow Neurological Institute for help with manuscript preparation.