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Complications of Endovascular Treatments for Brain Arteriovenous Malformations: A Nationwide Surveillance

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ABSTRACT

BACKGROUND AND PURPOSE: Embolization is widely performed to treat brain arteriovenous malformations, but little has been reported on factors contributing to complications. We retrospectively reviewed a nationwide surveillance to identify risk factors contributing to complications and short-term clinical outcomes in the endovascular treatment of brain arteriovenous malformations.

MATERIALS AND METHODS: Data for endovascular treatment of brain arteriovenous malformations were extracted from the Japanese nationwide surveillance. Patient characteristics, brain arteriovenous malformation features, procedures, angiographic results, complications, and clinical outcomes at 30 days postprocedure were analyzed.

RESULTS: A total of 1042 endovascular procedures (788 patients; mean, 1.43 ± 0.85 procedures per patient) performed in 111 institutions from 2010 to 2014 were reviewed. Liquid materials were used in 976 procedures (93.7%): to perform presurgical embolization in 638 procedures (61.2%), preradiosurgical embolization in 160 (15.4%), and as sole endovascular treatment in 231 (22.2%). Complete or near-complete obliteration of brain arteriovenous malformations was obtained in 386 procedures (37.0%). Procedure-related complications occurred in 136 procedures (13.1%), including hemorrhagic complications in 59 (5.7%) and ischemic complications in 57 (5.5%). Univariate analysis identified deep venous drainage, associated aneurysms, infratentorial location, and preradiosurgical embolization as statistically significant risk factors for complications. Multivariate analysis showed that embolization of brain arteriovenous malformations in the infratentorial location was significantly associated with complications. Patients with complications due to endovascular procedures had worse clinical outcomes 30 days after the procedures than those without complications.

CONCLUSIONS: Complications arising after endovascular treatment of brain arteriovenous malformations are not negligible even though they may play a role in adjunctive therapy, especially in the management of infratentorial brain arteriovenous malformations.

ABBREVIATIONS: bAVM = brain arteriovenous malformation; JR-NET = Japanese Registry of Neuroendovascular Therapy

Brain arteriovenous malformations (bAVMs) are rare lesions characterized by the presence of a nidus containing abnormal tortuous vascular channels between feeding arteries and draining veins without an intervening capillary network.¹ AVMs most commonly result in hemorrhage, which carries a mortality rate of 10%~15% and a morbidity rate up to 50%.² The annual hemorrhage rate for AVMs is between 2% and 4% per year.³⁻⁶ The main

goal of therapy is complete AVM obliteration, which prevents future hemorrhage. Current treatment options include microsurgery, radiosurgery, embolization, or a combination of therapies.⁷

Endovascular embolization has typically been reserved as an adjunctive therapy in the management of bAVMs, either for preoperative devascularization or preradiosurgical volume reduction.⁸ In addition, palliative or target embolization may be used in high-risk components of bAVMs to stabilize symptomatic lesions.⁹ Recent technical advances, including flow-

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directed microcatheters and liquid embolic materials such as *n*-BCA and ethylene-vinyl alcohol copolymer (Onyx; Medtronic, Irvine, California), make it possible to treat bAVMs with embolization alone in selected cases.¹⁰⁻¹² With expanded capabilities, appropriate patient selection and risk estimation for the endovascular procedure for treatment of bAVMs becomes paramount. Nonetheless, studies of the complications of embolization using multicenter data collection have been scarce.

In this study, we retrospectively reviewed a nationwide surveillance to elucidate notable risk factors of procedure-related complications and short-term clinical outcomes after endovascular treatment of bAVMs.

MATERIALS AND METHODS

Data Extraction

The Japanese Registry of Neuroendovascular Therapy (JR-NET) is a nationwide retrospective registration study. Clinical and procedural data were enrolled through a Web site constructed by the Translation Research Informatics Center (Kobe, Japan) and anonymously reviewed by the principal investigators. The institutional review board at Kobe City Medical Center General Hospital approved the study protocol of JR-NET. Because of the retrospective observational nature of the study, written informed consent was not obtained from patients. Previous studies have been reported on data from JR-NET1 and JR-NET2, which were conducted from 2005 to 2006 and 2007 to 2009, respectively.^{13,14} A total of 40,169 endovascular procedures were reviewed in the JR-NET3 study from 2010 to 2014, including 1063 procedures (2.7% of all procedures) for bAVMs treated by embolization. After excluding incomplete or duplicate data, we analyzed 1042 procedures performed for bAVMs for which detailed data were available.

JR-NET studies were performed according to the principles of the Declaration of Helsinki.

Evaluation

The dataset of patients with bAVMs obtained from JR-NET3 included the following: basic information (patient age, sex, symptoms, mRS score before the procedure, and mRS 30 days after the procedure) and detailed information about the lesions (nidus location, maximal diameter, involvement of the eloquent brain area, associated aneurysms, and the features of the draining vein, including deep venous drainage, occlusion, stenosis, and varix). AVMs were also classified according to the Spetzler-Martin grading system.¹⁵ Procedural data were documented, including the number of participating physicians, the number of procedures, scheduled or emergency procedures, embolization strategy, sensory-evoked potential and/or motor-evoked potential monitoring, provocation test, type of microcatheter and embolic material used, the number of feeding vessels cannulated, embolization results, and complications. The embolization strategy was defined as curative, target, presurgical, or preradiosurgical. Procedure-related complications were classified as hemorrhagic (AVM rupture and vessel perforation), ischemic (vessel occlusion and distal embolism), or others. Clinical outcomes 30 days after endovascular procedures were dichotomized into favorable (mRS 0–2) or poor (mRS 3–6) for statistical analysis.

Statistical Analysis

Statistical analyses were performed using JMP software (Version 12; SAS Institute, Cary, North Carolina). Numeric data are expressed as mean $\pm$ SD. Group comparisons of mean and categorical data were performed using the Student *t* test and Pearson χ^2 test as appropriate. *P* values $< .05$ were considered statistically significant. A multivariate statistical analysis of factors related to the occurrence of complications was performed using a logistic regression model. Variables found to be significant in the univariate analysis were selected for testing in the final model.

RESULTS

Patient Characteristics

Table 1 summarizes the baseline characteristics of the study population. We reviewed 788 patients (471 males [59.8%]; age range, 0–90 years; mean, 41.3 years of age) with bAVMs who underwent a total of 1042 embolization procedures (1.43 ± 0.85 procedures per patient) in 111 institutions between January 2010 and December 2014. Clinical presentation was hemorrhage in 548 patients (69.5%), while 110 patients were asymptomatic. A Spetzler-Martin grade was determined for 752 of the treated AVMs (95.4%). There were 136 grade I (17.3%), 273 grade II (34.6%), 224 grade III (28.4%), 98 grade IV (12.4%), and 21 grade V (2.7%) lesions. AVMs were located in the cortical regions in 574 patients (72.8%), were deep-seated in 35 (4.4%), in the cerebellum in 126 (16.0%), and in the brain stem in 17 (2.2%). Associated aneurysms were found in 146 AVMs (18.5%), including flow-related arterial aneurysms in 92 AVMs (11.7%) and intranidal aneurysms in 45 (5.7%). Abnormalities of the drainage route were detected in 290 AVMs (36.4%), including occlusion of the draining vein in 12 (1.5%), stenosis in 92 (11.7%), and venous varix in 186 (23.6%).

Modalities of Treatment

Endovascular treatment for bAVMs included presurgical embolization in 638 procedures (61.2%), preradiosurgical embolization in 160 (15.4%), target embolization in 144 (13.8%), and curative embolization in 87 (8.3%). The purposes of the endovascular procedure were unknown in 13 (1.2%). Presurgical embolization was performed in patients with AVMs of Spetzler-Martin grade I in 107 (16.8%) procedures, grade II in 224 (35.1%), grade III in 165 (25.9%), grade IV in 91 (14.3%), and grade V in 50 (7.8%) (Online Table 1). Of all embolization procedures, 124 (11.9%) were performed as an emergency procedure. Provocation and evoked-potentials were monitored in 117 (11.2%) and 39 (3.7%) procedures, respectively. Coils were used in 165 embolization procedures (15.8%); *n*-BCA, in 627 (60.2%); and Onyx, in 432 (41.5%). An average of 3.3 embolization sessions per procedure was achieved. All procedures were performed via a transarterial approach.

Treatment Results

Technical success was achieved in 1023 procedures (98.2%). Curative embolization achieved complete obliteration of the nidus in 55.2% (48 procedures) and near-complete obliteration in 27.6% (24 procedures). Overall, endovascular procedures resulted in complete or near-complete obliteration of the AVM in 37.0% (386 procedures) and partial

Table 1: Summary of baseline characteristics

Characteristics	
No. of patients	788
Age (mean) (yr)	41.3 ± 19.9
Male (No.) (%)	471 (59.8%)
Clinical presentation (No.) (%)	
Hemorrhage	548 (69.5%)
NHND	130 (16.5%)
Asymptomatic	110 (14.0%)
Preprocedural mRS (No.) (%)	
0	562 (71.3%)
1	84 (10.7%)
2	44 (5.6%)
3	34 (4.3%)
4	27 (3.4%)
5	15 (1.9%)
Unknown	22
Spetzler-Martin grade (No.) (%)	
I	136 (17.3%)
II	273 (34.6%)
III	224 (28.4%)
IV	98 (12.4%)
V	21 (2.7%)
Unknown	36 (4.6%)
Size (No.) (%)	
<3 cm	443 (56.2%)
3–6 cm	278 (35.3%)
>6 cm	38 (3.8%)
Deep venous drainage (No.) (%)	438 (55.6%)
Eloquence (No.) (%)	318 (40.4%)
Location (No.) (%)	
Cortical	574 (72.8%)
Deep	35 (4.4%)
Cerebellum	126 (16.0%)
Brain stem	17 (2.2%)
Others	36 (4.6%)
Associated aneurysm (No.) (%)	146 (18.5%)
Flow-related	92 (11.7%)
Intranidal	45 (5.7%)
Unrelated	9 (1.1%)
Abnormality of drainage route (No.) (%)	
Occlusion	12 (1.5%)
Stenosis	92 (11.7%)
Varix	186 (23.6%)

Note:—NHND indicates nonhemorrhagic neurologic deficit.

obliteration in 60.3% (628 procedures). No morphologic changes were observed in the remaining 17 AVMs (1.6%) based on postoperative radiologic examinations.

Complications

Complications occurred in 136 embolization procedures (13.1%), with hemorrhage observed in 59 (5.7%) and ischemia in 57 (5.5%). Hemorrhagic complications included AVM rupture in 26 procedures (2.4%) and vessel perforation or rupture due to catheterization in 33 (3.2%). AVM rupture occurred intraoperatively in 8 procedures (30.8% of patients with AVM rupture), within 24 hours after endovascular procedures in 9 (34.6%), within 7 days in 5 (19.2%), and within 30 days in 4 (15.4%). Of the cases of AVM rupture, 12 patients (46.2% of patients with AVM rupture) underwent emergency open surgery for removal of a hematoma as well as ruptured AVMs after embolization. Procedures with AVM rupture were associated with severe persistent disability in 8 patients (30.8% of patients

with AVM rupture), mild persistent disability in 2 (7.7%), and transient neurologic deficits in 6 (23.1%). Death occurred in 2 patients (7.7%) with AVM rupture. There was no significant difference in patient characteristics, morphologic features of AVM, and the strategy, embolic materials, or results of the embolization between procedures with AVM rupture and those without.

Ischemic complications included normal artery occlusion in 34 procedures (59.6% of patients with ischemic complications), distal thrombotic embolism in 20 (35.1%), and arterial dissection due to catheterization in 3 (5.3%). Procedures with ischemic complications were associated with severe persistent disability in 9 patients (15.8% of patients with ischemic complications), mild persistent disability in 13 (22.8%), and transient neurologic deficits in 12 (21.1%).

Univariate analyses in regard to AVM features revealed that deep venous drainage ($P < .01$), infratentorial location including the cerebellum ($P < .01$) and/or brain stem ($P < .01$), and the presence of flow-related aneurysms ($P = .01$) were significantly correlated with procedure-related complications, while cortical location had a negative correlation with complications ($P < .01$, On-line Table 2). In relation to the type of endovascular procedure, preradiosurgical embolization was associated with procedure-related complications ($P < .05$, Table 2). Infratentorial location, including the cerebellum (OR, 2.38; 95% CI, 1.25–3.16) and brain stem (OR, 2.14; 95% CI, 1.48–10.13), remained significantly associated with procedure-related complications in a multivariate analysis ($P < .01$). AVM rupture (7/147, 4.8%) and ischemia (14/147, 9.5%) occurred more frequently in cerebellar AVMs than AVMs in other regions (16/895, 1.8%, $P < .05$, and 40/895, 4.5%, $P < .01$, respectively), while ischemic complications (6/20, 30%) occurred more frequently in brain stem AVMs than in other regions (48/1022, 4.7%, $P < .01$).

Clinical Outcomes

The 30-day morbidity and mortality rates were 291 (27.9%) and 8 (0.8%) of 1042 procedures, respectively. Two of the 8 deaths were accompanied by hemorrhagic complications (AVM rupture, $n = 2$). Endovascular procedures with complications were significantly associated with worse outcome compared with procedures without complications ($P < .05$, Table 3).

To determine the risk factors associated with the deterioration of mRS scores, we compared the procedures that led to worse mRS scores 30 days after the endovascular procedures and those in which mRS scores of patients improved or did not change (On-line Table 3). Univariate analyses revealed that older age ($P \leq .001$), hemorrhagic presentation ($P \leq .001$), nidus size ≤ 3 cm ($P = .001$), infratentorial nidus location ($P \leq .001$), presurgical embolization ($P = .021$), complete obliteration ($P = .003$), and procedure-related complications ($P \leq .001$) were significantly correlated with the deterioration of mRS scores 30 days after endovascular treatment. Older age ($P = .026$; OR, 0.99; 95% CI, 0.99–1.0), hemorrhagic presentation ($P \leq .001$; OR, 4.05; 95% CI, 2.91–5.73), presurgical embolization ($P = .002$; OR, 1.56; 95% CI, 1.17–2.09), complete obliteration ($P = .021$; OR, 1.71; 95% CI, 1.08–2.69), and procedure-related complications ($P \leq .001$; OR, 2.02; 95% CI, 1.36–3.02) remained significantly associated with the deterioration of mRS scores 30 days after endovascular treatment in a multivariate analysis.

Table 2: Endovascular procedures

	Total	Complication		P Value		OR (95% CI)
		Yes	No	Uni-	Multi-	
No. of procedures (%)	1042	136 (13.1%)	906 (86.9%)			
Emergency (No.) (%)	124	13 (9.6%)	111 (10.6%)	.366		
Provocation test (No.) (%)	117 (11.2%)	8 (5.9%)	109 (12.0%)	.059		
SEP and/or MEP monitoring (No.) (%)	39 (3.7%)	7 (5.1%)	32 (3.5%)	.561		
No. of treatments (No.) (%)						
Initial	778 (75.6%)	104 (76.5%)	684 (75.5%)	.48		
Second and more	254 (24.4%)	32 (23.5%)	222 (24.5%)	.48		
Strategy (No.) (%)						
Curative	87 (8.3%)	17 (12.5%)	70 (7.7%)	.061		
Target	144 (13.8%)	15 (11.0%)	129 (14.2%)	.312		
Presurgical	638 (61.2%)	74 (54.4%)	564 (62.3%)	.08		
Preradiosurgical	160 (15.4%)	29 (21.3%)	131 (14.5%)	.038	.074	1.13 (0.96–2.44)
No. of approaches (mean)		3.2 ± 1.2	3.3 ± 1.5	.28		
Embolic material (No.) (%)						
Coils	165 (15.8%)	16 (11.8%)	149 (15.3%)	.163		
n-BCA	627 (60.2%)	83 (61.0%)	544 (60.0%)	.827		
Onyx	432 (41.5%)	64 (47.1%)	368 (40.6%)	.073		
Results (No.) (%)						
Complete obliteration	101 (9.7%)	18 (13.2%)	83 (9.2%)	.134		
Nearly complete	285 (27.3%)	38 (27.9%)	247 (27.3%)	.869		
Partial	628 (60.3%)	76 (55.9%)	552 (60.9%)	.262		
Unchanged	17 (1.6%)	3 (2.2%)	14 (1.5%)	.571		

Note:—SEP indicates sensory-evoked potential; MEP, motor-evoked potential.

Table 3: mRS at 30 days after endovascular procedure

	Total	Complications		Univariate (P Value)
		Yes	No	
No. of Procedures (%)	1042	136 (13.1%)	906 (86.9%)	
mRS score (No.) (%)				
0–2	743 (71.3%)	87 (64.0%)	656 (72.4%)	.046
3–6	299 (28.7%)	49 (36.0%)	250 (27.6%)	.046

DISCUSSION

We reviewed 1042 AVM embolization procedures using data extracted from a nationwide surveillance (JR-NET3). Of all the cases reviewed, 13.1% experienced complications, including hemorrhage in 5.7% and ischemia in 5.5%, which are consistent with the reported rates of complications in 6.4%–21% of procedures.^{16–22} Multivariate analysis showed that embolization for infratentorial AVMs was significantly associated with complications. To our knowledge, this study includes the largest number of patients with bAVMs treated by endovascular procedures across multiple centers since the advent of current neuroendovascular techniques.

With the advances in neuroendovascular treatment throughout the past 2 decades, new techniques and devices have improved the possibility for successful embolization of bAVMs, alone or in combination with other therapeutic modalities.^{17,23,24} Despite the fairly large number of patients with bAVMs who are treated with embolization, published data on complications associated with embolization procedures are surprisingly scarce or only based on the experience of a single institution. Refinement of bAVM risk assessment for endovascular treatment is imperative in ensuring favorable outcome.²⁵

In the pre-Onyx era, endovascular treatment for bAVMs was deemed to carry a procedural risk related to the Spetzler-Martin grade, number of embolizations treated, and the patient characteristics (increased age and absence of pretreatment

neurologic deficits).^{26,27} After the introduction of Onyx for AVM embolizations, Bell et al²⁵ reported their experience of transarterial embolization in 126 patients with bAVMs and concluded that procedure-related complications did not correlate with the Spetzler-Martin

grade, but with a novel endovascular grading scale incorporating the number of feeding arteries, eloquence, and the presence of an arteriovenous fistula component. Pan et al¹⁹ categorized complications of AVM embolization using liquid materials into technique-related and non-technique-related. Technique-related complications, such as those induced by navigation or removal of the microcatheter and migration of embolic materials, can be overcome by further improvement in the endovascular procedures and devices. Complications unrelated to the endovascular technique are mainly associated with angioarchitectural characteristics of bAVMs, including eloquent cortical location or exclusive deep venous drainage.¹⁹ Baharvahdat et al¹⁶ analyzed 846 embolization procedures performed in their institution during a 10-year period and reported that hemorrhagic complications occurred in 11% of cases, including periprocedural arterial perforation (48%) and AVM rupture (52%). They also identified premature venous occlusion as an independent predictor of severe hemorrhagic complication. Reportedly higher volumes of embolic agent injected in a single session and deposition on the venous outflow before complete occlusion of the bAVM could account for severe hemorrhagic complications.^{18,28}

In the present study, although the volume of injected liquid agent was not evaluated, the use of Onyx was not associated with higher complication rates, probably because >60% of the

performed endovascular procedures were planned as presurgical embolizations followed by early surgical resection of the embolized AVMs and not as a curative embolization. By contrast, preradiosurgical embolization was significantly associated with procedure-related complications in univariate statistical analysis. This finding might be because preradiosurgical embolizations are mainly performed for bAVMs in locations not suitable for surgical removal, such as AVMs in the eloquent or deep-seated locations, both of which are reportedly associated with a higher risk of complications after embolization.¹⁹ The use of Onyx in such locations does not preclude complications in the preradiosurgical embolization (On-line Table 4). Considering that embolization before radiosurgery can decrease the rate of AVM obliteration, preradiosurgical AVM embolization should be decided prudently.²⁹

Patients with infratentorial AVMs have worse outcomes than those with supratentorial lesions.³⁰ They are more likely to present with hemorrhage, with annual rates of hemorrhage ranging from 4.4% to 11.6%, compared with all AVMs (2%–4%), and with an annual rehemorrhage rate of 34.4% for ruptured AVMs managed conservatively.³¹ Infratentorial AVMs are more frequently associated with feeding artery aneurysms than supratentorial AVMs (25% versus 5%).^{32–34} Associated aneurysms are the source of bleeding in 10.5% of cases of infratentorial AVMs, but in only 1.7% of cases of supratentorial AVMs.^{34,35} Hemorrhages occurring from infratentorial AVMs are more likely to be symptomatic, with a mortality rate of 60% due to their presence in the narrow confines of the posterior fossa and the proximity to highly eloquent structures.^{30,31,36}

These findings support an aggressive management for infratentorial AVMs both before and after rupture. However, infratentorial AVMs have also been reported to be difficult to treat with open surgery^{37,38} or stereotactic radiosurgery,^{39,40} and multimodal treatments including embolization have been recommended.⁴¹ The present study shows that embolization of infratentorial AVMs could also involve procedure-related complications with a significantly higher rate. Vessel tortuosity, a lower safety margin of eloquent areas, or frequent association with flow-related aneurysms might complicate embolization of infratentorial AVMs. A meticulous treatment plan is mandatory because procedure-related complications tend to be severe following the endovascular treatment of infratentorial AVMs.

The JR-NET study group previously reported the procedural complications of endovascular treatment for bAVMs (JR-NET1 and 2)¹⁴ after analyzing the data from 987 endovascular procedures for bAVMs performed from January 2005 and December 2009. We observed some differences in the results of bAVM embolizations between the present study and JR-NET1 and JR-NET2, possibly because of Onyx being approved for presurgical embolization in September 2009. As a result, Onyx was used as an embolic material in only 54 (5.5%) procedures assessed in JR-NET1 and JR-NET2, while 432 (41.5%) procedures in the present study were performed using Onyx.

The introduction of Onyx might lead to a higher rate of AVM occlusion and procedure-related complications, changing the risk factors for endovascular treatments of bAVMs. In the present study, we did not observe any significant change in the annual

rate of complete obliteration and procedure-related complications since Onyx has become widespread in the endovascular treatment of bAVMs in Japan (data not shown). Moreover, the recent advances in the field of embolization techniques such as transvenous embolization⁴² and the introduction of dual-lumen balloon microcatheters⁴³ or the detachable-tip microcatheters⁴⁴ for liquid embolic material are expected to improve the rate of nidus occlusion with fewer complications, though none are currently available in Japan.

This study has some limitations, including its retrospective nature and short-term follow-up period. The clinical outcomes for patients with bAVMs treated by an operation or radiosurgery after embolization were not available, so we could not determine the mRS scores 30 days after presurgical embolization to assess whether the outcomes or complications of open surgery led to any score change in these patients. Long-term outcomes, including recanalization and bleeding rates after curative embolization, were also not available. We extracted data from JR-NET3, which includes the data from 111 major neuro-interventional registered centers but may not represent the nationwide total. Future studies evaluating the long-term clinical outcomes, including recanalization and bleeding rates after embolizations, may be warranted, and further analysis could include a heterogeneous population of multiple medical centers in Japan as well as in other countries.

CONCLUSIONS

We observed that complications of endovascular treatment may result in worse outcomes in patients with bAVMs. Thus, interventionalists should be aware of potential complications, especially in the management of infratentorial AVMs.

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