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Original research

Onyx embolization for dural arteriovenous fistulas: a multi-institutional study

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ABSTRACT

Background Although the liquid embolic agent, Onyx, is often the preferred embolic treatment for cerebral dural arteriovenous fistulas (DAVFs), there have only been a limited number of single-center studies to evaluate its performance.

Objective To carry out a multicenter study to determine the predictors of complications, obliteration, and functional outcomes associated with primary Onyx embolization of DAVFs.

Methods From the Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR) database, we identified patients who were treated for DAVF with Onyx-only embolization as the primary treatment between 2000 and 2013. Obliteration rate after initial embolization was determined based on the final angiographic run. Factors predictive of complete obliteration, complications, and functional independence were evaluated with multivariate logistic regression models.

Results A total 146 patients with DAVFs were primarily embolized with Onyx. Mean follow-up was 29 months (range 0–129 months). Complete obliteration was achieved in 80 (55%) patients after initial embolization. Major cerebral complications occurred in six patients (4.1%). At last follow-up, 84% patients were functionally independent. Presence of flow symptoms, age over 65, presence of an occipital artery feeder, and preprocedural home anticoagulation use were predictive of non-obliteration. The transverse-sigmoid sinus junction location was associated with fewer complications, whereas the tentorial location was predictive of poor functional outcomes.

Conclusions In this multicenter study, we report satisfactory performance of Onyx as a primary DAVF embolic agent. The tentorium remains a more challenging location for DAVF embolization, whereas DAVFs located at the transverse-sigmoid sinus junction are associated with fewer complications.

INTRODUCTION

Dural arteriovenous fistulas (DAVFs) are abnormal connections between meningeal arteries and venous sinuses or subarachnoid veins contained within the dural leaflets. DAVFs comprise 10–15% of all intracranial vascular malformations,[1] with an incidence of 0.15–0.29 per 100 000 per year.[2–5] The DAVF classification scales described by Borden *et al*[6] and Cognard *et al*[7] use the venous draining patterns to predict the risk of intracranial hemorrhage (ICH) from DAVFs. High-grade DAVFs (Borden II and III, Cognard IIb–IV) have cortical venous drainage (CVD), which is associated with an annual bleeding risk of 8% and an annual mortality rate of 10%.[6–8] In contrast, low-grade DAVFs without CVD (Borden I and Cognard I and IIa) carry very low risks for ICH but may present with debilitating pulsatile tinnitus or ophthalmological complaints.[9 10] Treatment is indicated in high-grade DAVFs for risk reduction, and in low-grade DAVFs for symptom management.[9 10] In addition, among patients with high-grade DAVFs, those presenting with ICH or non-hemorrhagic neurological deficits (NHNDs) have even higher risks of future hemorrhage and require immediate treatment to minimize morbidity.[9 11]

Current DAVF treatment options include endovascular embolization, microsurgery, and stereotactic radiosurgery, of which endovascular embolization is the preferred modality.[5 12–15] Since its introduction, Onyx (ev3, Irvine, California, USA) has been considered the preferred embolic agent for DAVF due to better control. Yet there have been only a limited number of studies evaluating Onyx embolization of DAVFs. These prior studies are single center and often do not delineate between embolizations with Onyx exclusively and embolizations with Onyx in combination with other agents such

as coils or n-butyl cyanoacrylate (n-BCA).[5 10 13 15–18] In an effort to gain a better understanding of Onyx performance, the present study used the large, multicenter DAVF database compiled by the Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR) investigators to assess the obliteration rate, complications, and functional outcome of DAVF primary embolization with Onyx as sole agent, as well as the predictors for each endpoint.

METHODS

Ethics approval

The study was approved by the University of Miami institutional review boards under ID 20170149. Each center participating in the Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR) obtained individual institutional review board approval for this study. Consent was waived owing to the retrospective nature of the study.

Data collection

A database with selected variables was created and sent to participating centers. Each center retrospectively reviewed medical records of patients diagnosed with cerebral DAVF and entered deidentified data in the spreadsheet. Pooled data were screened for errors, and any uncertainties or ambiguities in the data were addressed by the contributing center. From this large database, the authors of the present study isolated for assessment the subset of patients who were treated for DAVF with Onyx-only embolization as primary treatment for DAVF between 2000 and 2013.

Collected data included patient demographics, comorbidities, clinical presentation, location of the DAVF, feeding arteries, drainage pattern, Borden/Cognard classification, endovascular treatment approach, angiographic result, procedure-related complications, and follow-up information. DAVF diagnoses were confirmed via DSA. The location of DAVF was defined as the first point of venous drainage. Angioarchitectural characteristics of DAVFs were used to determine Borden/Cognard classification. Favorable baseline functional status and good functional outcome are defined as modified Rankin Scale (mRS) core 0–2 at baseline and at latest follow-up, respectively.

Treatment and endpoints

All patients in this study were treated with primary Onyx embolization via a transarterial, transvenous, or combined transarterial/transvenous approach. Primary embolization is defined as embolization delivered as the first treatment intended to achieve obliteration. Patients were excluded from this study if Onyx was used in combination with other embolic agents, or if there was ambiguity about whether Onyx was the embolic agent used.

The primary endpoint of this study was obliteration after initial embolization as determined by the final angiographic run. Complete obliteration was defined as occlusion of the fistulous point and termination of early venous filling. Secondary endpoints were procedure-related complications and functional outcome at latest follow-up.

Statistical analysis

Statistical analysis was conducted using SAS 9.4. Continuous variables were reported as means and SD. Categorical variables were reported as frequencies and percentages. Univariate analysis was conducted to test covariates predictive for complete obliteration, complications, and functional independence. Student's t-test, with or without equal variance as necessary, was used for continuous variables. Chi-square or Fisher's exact test was used for categorical variables as appropriate. Factors predictive in univariate analysis ($p<0.150$) were entered into multivariate logistic regression models for complete obliteration, complications, and functional independence. Factors deemed clinically relevant were included in multivariate analysis even if not meeting preset significance level in univariate analysis. A p value of ≤ 0.05 was considered statistically significant.

RESULTS

Patient demographics and clinical presentation

A total of 146 patients receiving Onyx-only embolization as primary treatment for DAVF between 2000 and 2013 at 10 participating institutions were identified from the CONDOR database. Mean age was 60 (SD 15) and 59 patients (40.4%) were female. Common presentations included ICH (36.3%), NHND (28.1%), and flow symptoms (36.6%). Baseline mRS score was 0–2 in 123 patients (86.6%). Details of patient demographics, comorbidities, and presentations are included in table 1.

Fistula characteristics

The majority of the DAVFs in this study were in the transverse-sigmoid junction location (39.6%), convexity/superior sagittal sinus (18.1%), or tentorium (17.4%). The most common arterial feeders were middle meningeal artery (85.6%) and occipital artery (72.6%). CVD was present in 85.4% patients with 46.5% documented venous ectasia. The majority of the DAVFs were Borden grade III (71.2%); 28.8% were Cognard type III and 40.4% were Cognard type IV (table 1).

Obliteration

The majority of the DAVFs were embolized via a transarterial approach (93.2%), with complete obliteration achieved in 74/136 (54.4%) patients at the conclusion of the initial embolization. The transvenous approach was used in nine patients (6.2%), and six (66.7%) achieved complete obliteration after one embolization. One patient (0.7%) underwent embolization with a combined transarterial/transvenous approach. This patient had persistent venous drainage after embolization and was later treated with surgery successfully. Of note, patients who received onyx-only transvenous embolization comprised 5.3% (9 out of 170) of all patients who received transvenous endovascular treatment in the overall CONDOR database.

Overall, complete obliteration was achieved in 80 (54.8%) patients at the end of the initial embolization (table 1). CVD discontinuation or decreased venous filling in patients without CVD was achieved in 28 patients (19.2%). Thirty-eight (26.0%) patients had persistent venous drainage at the end of the initial embolization, and received re-treatment with more embolization sessions (34 patients), surgery (seven patients), or radiosurgery (seven patients). The average total number of embolization sessions was 1.4. Final obliteration rate was 68.5% after all treatment sessions including surgery and radiosurgery. Presence of flow symptoms, age over 65, occipital artery feeder, and preprocedural home anticoagulation were inverse predictors of obliteration (table 2). Three recurrences (3.8%) were discovered among the 80 patients with initial complete obliteration. All three were high-grade DAVFs (two Cognard type III and one Cognard type IV) located in the transverse-sigmoid junction and treated with a transarterial approach. All were successfully obliterated with a second embolization.

Complications

A total of 23 (16.1%) complications were seen, including two patients with ICH (1.4%), two ischemia (1.4%), three venous

Table 1 Patients and features of dural arteriovenous fistulas (DAVFs), DAVF treatment, outcome, and follow-up (n=146)

Age (mean±SD)	60±15
Female	59 (40.4)
Home antiplatelet use*	41 (28.9)
Home anticoagulation use*	14 (9.8)
HTN*	66 (46.2)
CHF*	7 (5.0)
Diabetes*	26 (18.1)
Smoking	42 (28.8)
Patient presentation	
Hemorrhage	53 (36.3)
NHND	41 (28.1)
Flow symptoms*	53 (36.6)
mRS score at baseline*	
0	61 (43.0)
1	46 (32.4)
2	16 (11.3)
3	10 (7.0)
4	5 (3.5)
5	4 (2.8)
Location*	
Anterior fossa	4 (2.8)
Convexity/SSS	26 (18.1)
Cavernous	5 (3.5)
Sylvian/middle fossa	3 (2.1)
Transverse-sigmoid junction	57 (39.6)
Foramen magnum	1 (0.7)
Torcular	8 (5.56)
Tentorial	25 (17.4)
Petrosal	3 (2.1)
Other	12 (8.3)
Feeding vessel	
Middle meningeal	125 (85.6)
Occipital artery	106 (72.6)
Ascending pharyngeal	34 (23.3)
Other ECA branches	59 (40.4)
ICA	5 (3.4)
Ethmoidal	5 (3.4)
Small ICA branches	51 (34.9)
Borden grade	
I	22 (15.1)
II	20 (13.7)
III	104 (71.2)
Cognard classification	
Type I	16 (11.0)
Type IIa	6 (4.1)
Type IIb	9 (6.2)
Type IIa+b	11 (7.5)
Type III	42 (28.8)
Type IV	59 (40.4)
Type V	3 (2.1)
Endovascular approach	
Transarterial	136 (93.2)
Transvenous	9 (6.2)
Both	1 (0.7)
Embolization result	
Complete obliteration	80 (54.8)
CVD discontinuation	11 (7.5)
Decreased venous filling	17 (11.6)
Persistent venous drainage	38 (26.0)
Complications*	
ICH	2 (1.4)
Ischemia	2 (1.4)
Venous infarct	3 (2.2)
Microcatheter retention	7 (5.0)
CN palsy	2 (1.4)
Dissection	1 (0.7)
Vessel perforation	1 (0.7)
Alopecia/burns	2 (1.4)
PE	1 (0.7)
Other complications	3 (2.3)
Total complications	23 (16.1)
Follow-up	
Length of follow-up (days), mean±SD	868 (913)
Recurrence after complete obliteration*	3 (3.8)
Re-treatment	41 (28.1)
mRS score at latest follow-up*	
0	65 (47.8)
1	36 (26.5)
2	13 (9.6)
3	10 (7.4)
4	4 (2.9)
5	4 (2.9)
6	4 (2.9)

Unless stated otherwise, data are presented as the number (%) of patients.
*Data only available for a portion of total patients (percentage of available patients shown).
CHF, congestive heart failure; CN, cranial nerve; CVD, cortical venous drainage; ECA, external carotid artery; HTN, hypertension; ICA, internal carotid artery; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; NHND, non-hemorrhagic neurological deficit; PE, pulmonary embolism; SSS, superior sagittal sinus.

infarct (2.2%), seven microcatheter retention (5.0%), two cranial nerve palsy (1.4%), one dissection (0.7%), one vessel perforation (0.7%), two alopecia/burns (1.4%), one pulmonary embolism (0.7%), and three with other complications (2.3%). There were no deaths attributed to procedural complications. The transverse-sigmoid junction location was associated with fewer complications (table 3).

Functional outcomes

Mean follow-up was 28.9 months (range 0–129.4 months). At the last follow-up, a good functional outcome (mRS score 0–2)

Table 2 Univariate and multivariate analyses for predictors of obliteration

	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Hemorrhage presentation	2.69	1.32 to 5.49	0.01	NS	NS	NS
NHND	1.42	0.68 to 2.96	0.35	NS	NS	NS
Flow symptoms	0.23	0.11 to 0.47	<0.0001	0.24	0.06 to 0.91	0.04
High Borden/Cognard classification	3.07	1.17 to 8.06	0.02	NS	NS	NS
Age >65 years	0.61	0.31 to 1.20	0.15	0.36	0.14 to 0.97	0.04
Female	0.77	0.39 to 1.49	0.43	NS	NS	NS
CHF	1.08	0.23 to 5.02	1.00	NS	NS	NS
HTN	2.13	1.08 to 4.19	0.03	NS	NS	NS
Smoking	1.14	0.55 to 2.35	0.72	NS	NS	NS
mRS score 0–2 at baseline	1.42	0.54 to 3.74	0.48	NS	NS	NS
Diabetes	1.71	0.70 to 4.13	0.23	NS	NS	NS
ICA feed	NA	NA	0.02	NS	NS	NS
Small ICA feed	0.43	0.21 to 0.86	0.02	NS	NS	NS
Ascending pharyngeal feed	0.49	0.22 to 1.06	0.07	NS	NS	NS
Occipital artery feed	0.41	0.19 to 0.90	0.02	0.34	0.12 to 0.96	0.04
Galen/straight sinus drainage	0.5	0.19 to 1.31	0.15	NS	NS	NS
Hypercoagulable state	0.39	0.09 to 1.62	0.30	NS	NS	NS
Home anticoagulation	0.29	0.09 to 0.97	0.04	0.15	0.03 to 0.86	0.03
Transvenous approach	1.25	0.34 to 4.65	1.00	NS	NS	NS

CHF, congestive heart failure; HTN, hypertension; ICA, internal carotid artery; NHND, non-hemorrhagic neurological deficit; NS, not significant in multivariate analysis.

was documented in 114/136 (83.8%) patients, while 22 (16.2%) had mRS score ≥3. Baseline mRS score 0–2 is predictive of good functional outcome, while tentorial location is predictive of poor functional outcome (table 4). Three DAVF-related deaths were reported. No incidences of delayed post-treatment ICH or NHND were seen.

DISCUSSION

In this study using the CONDOR DAVF database, we evaluated the obliteration rate, complications, and functional outcome of DAVF primary embolization using Onyx as sole embolic agent, and assessed the predictors for each endpoint.

Over time, the preferred primary treatment agent for DAVFs has evolved from detachable coils, to the adhesive liquid agent n-BCA (Codman Neuro, Raynham, Bristol County, Massachusetts, USA), and in recent years to the non-adhesive liquid agent ethylene vinyl alcohol (EVOH) copolymer, commercially available as Onyx. The main ingredient of Onyx is EVOH copolymer dissolved in dimethyl sulfoxide, with micronized tantalum powder for radiopacity. On contact with blood, the EVOH copolymer precipitates as dimethyl sulfoxide diffuses. Solidification begins on the surface, while the core remains liquid, resulting in a lava-like flow pattern.[19] This produces more controlled and prolonged casting, and allows for retrograde filling of multiple

Table 3 Univariate and multivariate analyses for predictors of complications

	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Hemorrhage presentation	0.31	0.10 to 0.95	0.03	0.25	0.06 to 1.09	0.07
NHND	1.53	0.59 to 3.96	0.38	NS	NS	NS
Flow symptoms	1.14	0.45 to 2.84	0.79	NS	NS	NS
High Borden/Cognard classification	1.25	0.34 to 4.64	1.00	NS	NS	NS
Age >65 years	1.53	0.62 to 3.75	0.35	NS	NS	NS
Female	1.11	0.45 to 2.74	0.81	NS	NS	NS
CHF	4.16	0.87 to 20.02	0.09	NS	NS	NS
HTN	0.93	0.38 to 2.29	0.87	NS	NS	NS
mRS 0–2 at baseline	1.80	0.39 to 8.40	0.74	NS	NS	NS
Transverse-sigmoid	0.49	0.18 to 1.34	0.16	0.319	0.10 to 1.01	0.05
Tentorial	0.67	0.18 to 2.45	0.77	NS	NS	NS
Transvenous approach	NA	NA	0.37	NS	NS	NS

CHF, congestive heart failure; HTN, hypertension; NHND, non-hemorrhagic neurological deficit.

Table 4 Univariate and multivariate analyses for predictors of functional independence

	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Hemorrhage presentation	0.62	0.25 to 1.57	0.32	NS	NS	NS
NHND	0.337	0.131 to 0.871	0.02	NS	NS	NS
Flow symptoms	4.36	1.21 to 15.66	0.02	NS	NS	NS
High Borden/Cognard classification	0.84	0.23 to 3.14	1.00	NS	NS	NS
Age >65 years	0.52	0.21 to 1.31	0.16	NS	NS	NS
Female	1.05	0.42 to 2.66	0.92	NS	NS	NS
CHF	0.24	0.05 to 1.14	0.09	NS	NS	NS
HTN	0.39	0.15 to 1.01	0.05	NS	NS	NS
Smoking	1.18	0.43 to 3.27	0.75	NS	NS	NS
mRS score 0–2 at baseline	14.58	4.61 to 46.16	<0.0001	17.15	3.71 to 79.37	0.00
Transverse-sigmoid	3.51	1.12 to 11.05	0.02	NS	NS	NS
Tentorial	0.27	0.10 to 0.74	0.01	0.12	0.02 to 0.70	0.02

CHF, congestive heart failure; HTN, hypertension; mRS, modified Rankin Scale; NHND, non-hemorrhagic neurological deficit.

arterial feeders from a single arterial injection.[13 17] The non-adhesive property of Onyx also makes it possible to temporarily pause injection to evaluate the progress of embolization.

The complete obliteration rate by primary embolization with onyx was 55% in our cohort (54% via transarterial approach and 67% via transvenous approach). In a previous single-center series of 75 patients, Moenninghoff *et al*[5] reported a comparable initial obliteration rate of 60%. In another study of 63 DAVFs, Rangel-Castilla *et al*[13] reported a higher obliteration rate of 83% after one embolization with Onyx, but the study included a lower percentage of high-grade DAVFs and fewer in challenging locations such as the tentorium compared with the present study. In addition, the our study included more DAVFs with occipital artery (OA) feeders and an overall older patient cohort, both of which were associated with non-obliteration by our analysis. For comparison, in the pre-Onyx era, initial DAVF occlusion rates after embolization with materials such as coils, polyvinyl alcohol (PVA), n-BCA, or combinations have been reported to be 53–60%.[14 20 21]

The presence of an OA feeder was a significant predictor for non-obliteration in our multivariate analysis. Owing to the tortuosity of the vessel and the small transosseous segments, the OA is often difficult to catheterize.[18] However, if alternative channels are not present, embolization via the distal OA may be necessary, requiring more proximal injections through small channels, which is less likely to achieve satisfactory penetration into the fistulous point. Concordantly, Moenninghoff *et al*[5] reported a lower Onyx obliteration rate in patients requiring combined OA and middle meningeal artery (MMA) embolization than those embolized via the MMA alone. There have also been reports of occipitovertebral anastomoses opening during embolization owing to increased intra-arterial pressure, with theoretical risk of embolic material passage and basilar stroke, although there was no incidence of this complication in our cohort.[12 22–24]

The presence of flow-related symptoms was also predictive of non-obliteration of the DAVF. The fistulous points of high-flow fistulas are often more difficult to visualize during embolization. In addition, while the slow solidifying nature of Onyx is generally favored, it is more difficult to achieve satisfactory embolization when injected under the impact of high flow. Therefore, high-flow DAVFs may require a rapidly solidifying agent such as n-BCA, which polymerizes immediately on contact with blood and forms adhesive bonds to the vessel wall.[14 16] Furthermore, even though angiographic cure is pursued when possible during embolization, the clinical treatment purpose for patients with flow symptoms without malignant presentation is symptom reduction. Therefore, intraprocedurally the operator might choose to be less aggressive in pursuing complete obliteration when balancing clinical need and technical feasibility, a consideration that could have contributed to the association between flow symptoms and non-obliteration in this study.

Other independent predictors for non-obliteration included age over 65 and home anticoagulation use. For elderly patients, the aggressiveness of treatment must be balanced with considerations of comorbidities and increased vessel tortuosity that is characteristic of this age group. Preprocedural home anticoagulation as a predictor for non-obliteration during primary embolization was a somewhat unexpected finding. Supratherapeutic anticoagulation may lead to decreased clotting around embolization material and thus decreased obliteration rates. Furthermore, comorbidities associated with hypercoagulability may lead to hemodynamic changes that alter the effects of embolization.

Major cerebral complications occurred in six patients (4.1%). The overall complication rate of this study was 16.1%. The transverse-sigmoid junction location was associated with a lower risk for complications. The most common complication occurring in this cohort was microcatheter retention (5%, with no significant clinical consequence). Microcatheter breakage or retention is a known risk of Onyx embolization, although the risk of catheter retention associated with Onyx is thought to be lower than with the adhesive agent n-BCA.[25] Detachable-tip microcatheters may be used to minimize the risk of catheter retention.[26]

At the latest follow-up, 84% of patients were functionally independent. Worse functional outcomes were observed in patients with DAVFs in the tentorial location. Tentorial DAVFs are rare fistulas with extensive vascular supplies from both the internal and external carotid arteries that tend to behave aggressively with a high risk for hemorrhage.[27 28] Owing to their distal location and internal carotid artery feeders, endovascular therapy is often challenging. Transcranial surgical treatment remains an option and there is no consensus on the optimal treatment modality for these complex fistulas. The present study continues to reflect the challenges in managing tentorial DAVFs. Previous studies have also reported other rare DAVFs that may not always be

amendable to endovascular embolization, including ethmoidal DAVFs and DAVFs with pial artery supply.[29 30]

Limitations

This study was limited by its retrospective nature and multicenter design with inevitable selection bias and technical variations. However, the large cohort and diversity of patient populations afforded us a vantage point to present the real-world experience of Onyx embolization of DAVFs. In addition, this study did not include any combined use of Onyx with other embolic agents. Although this required exclusion of patients treated with combination materials, the authors felt the strict selection criteria were necessary to objectively evaluate Onyx performance, and the knowledge gained from this study would better facilitate future practice in DAVF treatments.

CONCLUSION

In this multicenter study with the CONDOR DAVF database, we report satisfactory performance of Onyx in single-agent primary DAVF embolization. Presence of flow symptoms, age over 65, presence of an occipital artery feeder, and preprocedural home anticoagulation use were associated with non-obliteration. The tentorium remained a more challenging DAVF location, while those located at the transverse-sigmoid junction were associated with fewer complications.

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