



Clinical Article

Comparison of transarterial n-BCA and Onyx embolization of brain arteriovenous malformations: A single-center 18-year retrospective analysis

Faraz Behzadi¹, Daniel M Heiferman², Amy Wozniak³, Benjamin Africk⁴, Matthew Ballard¹, Joshua Chazaro¹, Brandon Zsigray⁵, Matthew Reynolds⁵, Douglas E Anderson⁵, Joseph C Serrone⁵

¹Stritch School of Medicine, Loyola University Chicago, Maywood, IL, USA

²Semmes-Murphey Clinic, Memphis, TN, USA

³Clinical Research Office, Stritch School of Medicine, Loyola University Medical Center, Maywood, IL, USA

⁴Department of Pediatric Neurology, Stanford University School of Medicine, Palo Alto, CA, USA

⁵Department of Neurological Surgery, Stritch School of Medicine, Loyola University Medical Center, Maywood, IL, USA

J Cerebrovasc Endovasc Neurosurg.
2022 June;24(2):144-153

Received: 14 December 2021

Revised: 11 February 2022

Accepted: 2 March 2022

Correspondence to
Joseph C Serrone

Department of Neurological Surgery, Stritch School of Medicine, Loyola University Medical Center, 2160 S 1st Ave Maywood, IL 60153, USA

Tel +1-708-216-8235

E-mail joseph.serrone@lumc.edu

ORCID <https://orcid.org/0000-0001-6517-1212>

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Objective: Brain arteriovenous malformations (AVM) are commonly treated with endovascular embolization. Due to the rapid evolution of endovascular technology and lack of consistent practice guidelines regarding AVM embolization, further study of AVM embolization outcomes is warranted.

Methods: We conducted a retrospective review of AVMs embolized at a single center from 2002-2019. Patient demographics, AVM characteristics, intention of embolization, and angiographic and clinical outcome after embolization were recorded. We compared the embolization results of those treated with n-butyl cyanoacrylate (n-BCA) and Onyx.

Results: Over an 18-year period at our institution, 30 (33%) of 92 AVMs were treated with embolization. n-BCA was used in 12 cases and Onyx in 18 cases. Eighty-seven pedicles were embolized over 47 embolization sessions. Fifty percent of AVMs treated with n-BCA underwent more than one embolization session compared to 22% when Onyx was used. The median total percent volume reduction in the n-BCA AVMs was 52% compared to 51% in Onyx AVMs. There were 2 periprocedural complications in the n-BCA cohort and none in the Onyx cohort.

Conclusions: In this small retrospective series, Onyx and n-BCA achieved similar occlusion results, although n-BCA required more sessions and pedicles embolized to do so.

Keywords Arteriovenous malformation, Embolization, n-butyl cyanoacrylate (n-BCA), Ethylene vinyl alcohol copolymer, Onyx

INTRODUCTION

Brain arteriovenous malformations (AVM) are connections between cerebral arteries and veins by way of an interposing nidus. AVMs may become symptomatic by hemorrhage, seizure, headache, or cause focal neurological deficits without evidence of hemorrhage. Treatment modalities for AVMs are aimed at their angiographic eradication. This is accomplished by sole implementation or a combination of microsurgery, radiation therapy, and embolization.²⁴⁾

Embolization involves endovascular administration of materials into feeding arteries, the nidus, and/or draining veins. The embolic material of choice has evolved from polyvinyl alcohol particles to cyanoacrylate liquid embolic agents including n-butyl cyanoacrylate (n-BCA), (Trufill, Johnson and Johnson, New Brunswick, NJ, USA) to ethylene vinyl alcohol copolymer liquid embolic (Onyx, Medtronic, Minneapolis, MN, USA).¹⁶⁾¹⁸⁾ The goal of embolization can be categorized as curative, adjuvant (pre-surgical, pre-radiosurgery), targeted (e.g. occluding a ruptured perinidal aneurysm), or palliative (e.g. reducing flow in patients with cerebral ischemia due to vascular steal).

Metrics for successful embolization vary based on the initial goal of embolization.²²⁾ For curative treatment, the metric is permanent angiographic eradication of the lesion. For adjuvant and palliative treatment, the most accepted metric is a percentage reduction of AVM volume.²⁵⁾ Contrarily, a successful targeted embolization may only occlude a perinidal aneurysm or ruptured portion of the nidus with less focus on reducing the volume of the nidus.²⁾

Due to the rarity of AVMs, heterogeneity in endovascular technique, and rapid evolution of endovascular technology, consistent practices regarding AVM embolization have been hard to define.⁴⁾⁶⁾¹¹⁾¹³⁾²²⁾²⁵⁾²⁶⁾ Retrospective analysis of AVM embolization results remains invaluable to our development of safe and effective embolization practices. In this study, we retrospectively evaluate the AVM embolization experience at a single center over 18 years with specific focus on the goals of

intervention, embolic agent used (n-BCA vs Onyx), and AVM volume reduction.

METHODS

The Loyola Health electronic health records were accessed to obtain adult patients who were diagnosed with brain AVMs from the date imaging was still available within our electronic medical records (2002-2019). Loyola University Medical Center electronic medical record was queried for ICD-9 (747.81) and ICD-10 (Q28.2 and Q28.3) codes corresponding to vascular malformations and CPT codes for AVM treatment (61680, 61682, 61684, 61686, 61690, and 61692). Individual patient charts were then reviewed to confirm an AVM diagnosis by angiographic or pathologic criteria. Patients with insufficient information in their medical record regarding their AVM diagnosis were excluded. Only patients who received an embolization treatment with reviewable angiograms were selected. Interventions were provided by 1 interventional neurologists, 3 interventional neuroradiologists, and 4 endovascular neurosurgeons over this time period. Over the 18-year period from 2002-2019, 92 AVMs were treated by surgery, radiosurgery, embolization, or a combination of these modalities at our institution. In this cohort, 30 AVM patients were treated with embolization as either a primary or adjunctive method and were included in the study.

Variables extracted from the medical record included patient demographics of age at diagnosis, sex, and race. Presentations were recorded as hemorrhage, headache, seizure, incidental, and other (including focal neurological deficit without hemorrhage). AVM characteristics included nidus appearance (diffuse versus compact), eloquence, deep venous drainage, size, location (cerebellar, deep cerebral, frontal, temporal, and parieto-occipital), nidal volume, AVM rupture status, eloquence, and Spetzler-Martin grade. Embolization variables including embolic agent, number of sessions, numbers of arterial pedicles treated, relative volume of AVM embolized ([pre-embolization AVM volume – post-emboliza-

tion AVM volume]/[pre-embolization AVM volume]), embolization 30-day complication outcomes, and status of cure were collected through a comprehensive chart review.³⁾ The volume of the AVM was calculated with (A+B+C)/2 methodology. The height and width of the AVM was taken from the anteroposterior (AP) angiogram and the depth was measured from the orthogonal lateral angiogram on the baseline and post-treatment studies.⁸⁾¹⁵⁾¹⁹⁾²¹⁾ Successful embolization was defined as ≥50% devascularization after the final embolization.¹⁶⁾ Complications were categorized into three groups of minor (transient or non-disabling fixed deficit), major (disabling non-fatal), and death. AVMs embolized for cure were only defined as cured if a delayed (>6 months) angiogram confirmed angiographic eradication.¹⁴⁾

The intention of treatment was categorized based on retrospective review on the interventionalists' clinical and procedural notes into 5 categories: curative, palliative, pre-radiotherapy, pre-surgical, or targeted. The latter 4 categories were then combined to make a non-curative embolization cohort. Embolization outcomes based on intention of treatment was evaluated.

Statistical analysis

Patient and AVM characteristics for normally distributed continuous variables are presented as means with standard deviations. Continuous variables that are not normally distributed are presented as medians and interquartile ranges. Categorical variables are presented as counts and proportions. Spearman rank correlation statistics were used to estimate the relationship between continuous variables of interest. Student t-tests were used to test the associations of continuous variables. Chi-square test or Fisher's exact test were used to test the associations of categorical variables. All analyses were performed with SAS 9.4 (Cary, NC, USA) and two-sided p-value <0.05 were deemed statistically significant.

RESULTS

Over an 18-year period, 30 AVMs were embolized

at our institution. Patient and AVM characteristics are listed in Table 1. The average age at diagnosis was 36±16

Table 1. Patient, AVM, and treatment demographics

All patients, n (%): N=30

	n-BCA group n=12	Onyx group n=18
Patient characteristics		
Age, yr		
Mean±SD	35±17	37±17
Sex		
Male	8 (67)	9 (50)
Race/ethnicity		
White	7 (58)	7 (39)
Presenting symptom		
Hemorrhage	2 (17)	4 (22)
Seizure	1 (9)	5 (28)
Headache	7 (58)	5 (28)
Neurological deficit	1 (9)	1 (6)
Other/ Incidental	1 (9)	3 (17)
AVM characteristics		
Diffuse nidus		
Yes	1 (9)	1 (6)
Eloquent area		
Yes	10 (83)	8 (44)
Deep venous drainage		
Yes	7 (58)	4 (22)
Nidal aneurysm		
Yes	3 (27)	3 (17)
Ruptured		
Yes	4 (67)	8 (44)
Size		
<3	6 (50)	8 (44)
3–6	6 (50)	8 (44)
>6	0 (0)	2 (11)
Location		
Cerebellar	1 (10)	2 (11)
Frontal	5 (50)	8 (44)
Temporal	1 (10)	2 (11)
Parieto-occipital	3 (30)	6 (33)
Spetzler-Martin grade		
Grade 1	0 (0)	6 (33)
Grade 2	4 (33)	5 (28)
Grade 3	5 (42)	4 (22)
Grade 4	3 (25)	1 (6)
Grade 5	0 (0)	2 (11)
Number of arterial feeders		
Median	2	2

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	n-BCA group n=12	Onyx group n=18
Treatment characteristics		
Modality of treatment		
Embolization alone	4 (33)	4 (22)
Embolization+surgery	4 (33)	8 (44)
Embolization+SRS	4 (33)	5 (28)
Embolization+surgery+SRS	0 (0)	1 (5.6)
Objective of embolization		
Curative	4 (33)	2 (11)
Non-curative: palliative	1 (8.3)	0 (0)
Non-curative: targeted	2 (17)	3 (17)
Non-curative: pre-surgery	3 (25)	9 (50)
Non-curative: pre-SRS	2 (17)	4 (22)

Note: Summary of the treatment modalities, AVM characteristics, and patient demographics of all 30 patients included in this study. AVM, arteriovenous malformations; n-BCA, n-butyl cyanoacrylate; SRS, stereotactic radiosurgery

years, and 17 patients (57%) were male. Fifteen (50%) of the AVMs were Spetzler Martin (SM) Grade 1-2, 9 (30%) were SM Grade 3, and 6 (20%) were SM Grade 4-5. The AVM locations was cerebellar (10%), frontal (43%), temporal (10%), and parieto-occipital (30%). AVMs presented with hemorrhage, seizure, headache, neurological deficit without hemorrhage, and other in 6 (20%), 6 (20%), 12 (40%), 2 (6.7%), and 4 (17%) cases, respectively.

These 30 patients underwent 47 embolization sessions (median 1, interquartile range (IQR) 1-2 sessions per patient) and had 87 pedicles embolized (median 2 IQR 1-2.3 pedicles per session and median 2 IQR 2-3 pedicles embolized per patient). The embolic agent used was n-BCA in 12 (40%) patients and 42 (48%) of the pedicles treated and Onyx in 18 (60%) patients and 45 (52%) of the pedicles treated. There were no complications associated with AVMs embolized with Onyx, and one minor complication (quadrantanopia) and one major complication (anterior choroidal artery stroke) were associated with the AVMs embolized with n-BCA. The overall complications rate was 6.7% per AVM, 4.3% per session, and 2.3% pedicle. Ultimately, 8 patients (27%) only had embolization, 12 patients (40%) had surgery in addition to embolization, 9 patients (30%) had radiosurgery in addition to embolization, and 1 patient (3%) had all three

modalities of treatment (Table 1). Clinical follow-up for these patients was 39 months±42 months. Angiographic follow-up for these patients was 19 months±26 months.

The median size of the AVMs treated with n-BCA was 3.5 mL (IQR 1.1-9.9 mL) compared to 4.4 mL (IQR 1.9-11 mL) in those that were embolized with Onyx. The median total percent volume reduction (percent devascularization) in the AVMs that were embolized with n-BCA was 52% (IQR 31-67%) compared to 51% (IQR 27-86%) in those that were embolized with Onyx (Table 2). Successful embolization (≥50% devascularization) occurred in 58% of n-BCA embolized versus 56% of Onyx embolized AVMs (Fig. 1). After the initial embolization, n-BCA AVMs had a median percent devascularization of 30% (IQR 0-52) compared to 43% (IQR 15-86) in the Onyx AVMs. The total number of pedicles embolized in the first embolization was 1.8 per patient in n-BCA AVMs compared to 2.2 per patient in the Onyx AVMs. Six (50%) of n-BCA embolized AVMs underwent more than one embolization session compared to 4 (22%) of the Onyx AVMs (Table 2).

The total number of sessions per person was 1.8±1.0 in n-BCA and 1.4±0.8 in Onyx. The total number of

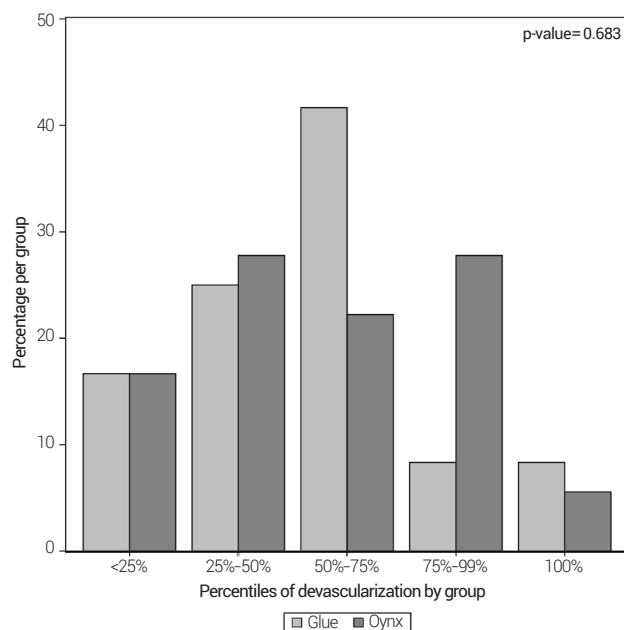


Fig. 1. Bar plot demonstrating the distribution of embolization sessions based on percent devascularization, in 25% increment bins, for n-BCA and Onyx groups. n-BCA, n-butyl cyanoacrylate

Table 2. Angiographic outcomes and embolization complications

All patients, n (%): N=30

Angiographic outcomes	n-BCA group n=12	Onyx group n=18
Initial volume, mL		
Median (Q1, Q3)	3.5 (1.1, 9.9)	4.3 (1.9, 11)
Total % devascularization		
Median (Q1, Q3)	52 (31, 67)	51 (27, 86)
<25%, n (%)	2 (17)	3 (17)
25-49%	3 (25)	5 (28)
50-75%	5 (42)	4 (22)
75-99%	1 (8)	5 (28)
>99%	1 (8)	1 (5)
Need for >1 embolization		
Yes, n (%)	6 (50)	4 (22)
Total number of sessions		
n	22	25
Number of sessions per person		
Mean±SD	1.8±1.0	1.4±0.8
Total number of pedicles		
n	42	45
Number of pedicles per person		
Mean±SD	3.5±1.9	2.6±2.0
Number of pedicles per session		
Mean±SD	2.1±0.9	1.9±1.1
% devascularization per pedicle		
Mean±SD	16±14	34±29
% devascularization by objective	Both groups: n=30 Mean±SD	
Curative (n=6)	61±34	
Non-Curative: Palliative (n=1)	79±N/A	
Non-Curative: Targeted (n=5)	48±19	
Non-Curative: Pre-surgery (n=12)	47±29	
Non-Curative: Pre-SRS (n=6)	54±36	
Complications, n (%)	n-BCA group n=12	Onyx group n=18
Minor	1 (8.3)	0 (0)
Major	1 (8.3)	0 (0)
Mortality	0 (0)	0 (0)
Total	2 (17)	0 (0)

Note: Summary of the embolization objectives, angiographic changes, and complication rates associated with embolization treatments. n-BCA, n-butyl cyanoacrylate; SRS, stereotactic radiosurgery

pedicles per session was 2.1±0.9 in n-BCA and 1.9±1.1 in Onyx. The percent devascularization per pedicle was 16% ±14 in n-BCA and 34% ±29 in Onyx with a p-value

of 0.032 (Fig. 2). Additionally, the correlation of percent devascularization with initial AVM volume and number of pedicles are presented in Fig. 3 and 4 respectively. Lastly, the percent devascularization based on the objec-

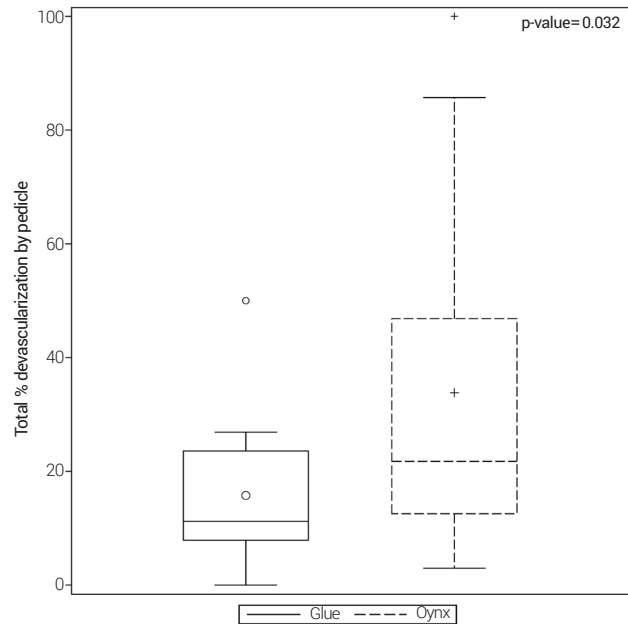


Fig. 2. Boxplot graph comparing the percent devascularization per pedicle between n-BCA and Onyx. n-BCA, n-butyl cyanoacrylate

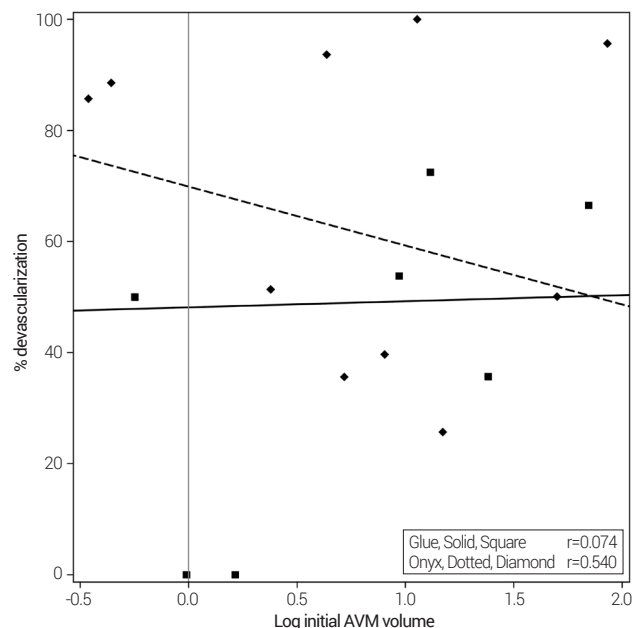


Fig. 3. Demonstrating the correlation of percent devascularization to the initial volume of the AVM in both the n-BCA and the Onyx groups. AVM, arteriovenous malformations; n-BCA, n-butyl cyanoacrylate

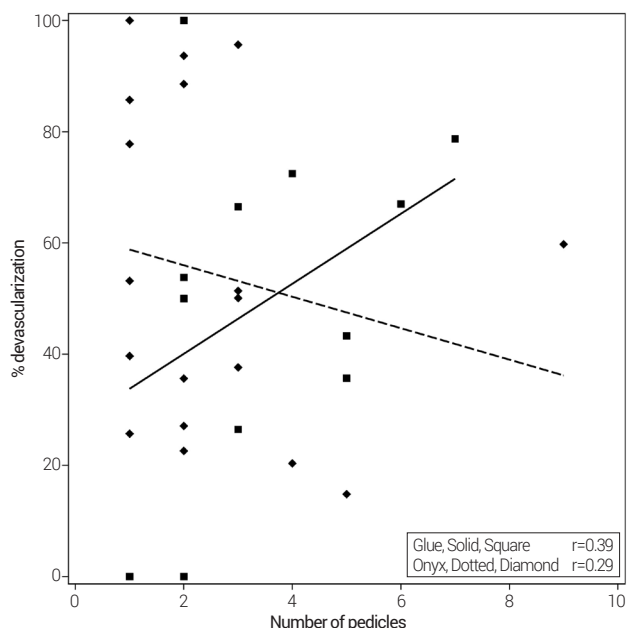


Fig. 4. Demonstrating the correlation of percent devascularization and the number of AVM pedicles embolized in the n-BCA and Onyx groups. AVM, arteriovenous malformations; n-BCA, n-butyl cyanoacrylate

tive of embolization was $61\% \pm 34$ in cure attempt, 79% in palliative, $54\% \pm 36$ in targeted, $47\% \pm 29$ in pre-surgery, and $48\% \pm 19$ in pre-radiosurgery (Table 2). This further summarizes into $61\% \pm 34$ in the cure attempt group versus $50\% \pm 28$ in the non-curative group.

DISCUSSION

This single center retrospective analysis of AVM embolization demonstrates similar final nidus reduction results whether using n-BCA or Onyx liquid embolic agents. However, more pedicles and more sessions were required to achieve similar embolization results with n-BCA. Additionally, it does appear that even though achieving the benchmark embolization result of 50% is the same for both groups, achieving a $>75\%$ embolization result may slightly favor Onyx. Most importantly, with the caveat of including patients over a 18-year period amongst 8 interventionalists, the use of both agents appears relatively safe and effective.

Trans-arterial embolization of AVMs warrants

continued study given the high complications seen in the ARUBA (a randomised trial of unruptured brain arteriovenous malformations) trial amongst AVMs receiving embolization. Of the 3 arms of intervention (microsurgery, stereotactic radiotherapy, and embolization), embolization was used the most commonly (62% of cases) and had the highest occurrence of a primary event (50% of cases).¹⁷⁾ During the ARUBA enrollment years, 2007-2013, all practitioners would have had substantial experience with n-BCA and/or Onyx. Little granular data is available from the trial about the embolizations, but overall, the results were dispiriting and suggests the field needs improvement.

Nidus reduction slightly favors Onyx

Onyx appears slightly superior at achieving nidus volume reduction compared to n-BCA. The industry supported randomized trial comparing Onyx to n-BCA defined the primary endpoint as achievement of 50% volumetric nidus reduction. This trial was not able to blind interventionalists since catheter selection and preparation requires knowledge of the agents and the visual and radiographic appearance are starkly different. With those caveats, Onyx achieved a 50% volume reduction in 96% cases compared to 85% of AVMs treated with n-BCA. These non-inferior results were achieved with a nearly identical number of sessions per AVM and pedicles per AVM.¹⁶⁾

In our study, a 50% volume reduction was less impressive, but similar between n-BCA and Onyx (58 and 56%, respectively), and a 75% volume reduction may favor Onyx (17% vs 33%) (Fig. 1). Most importantly, n-BCA required 32% more sessions and 37% more pedicles embolized to achieve these results. In a similar single center retrospective analysis, Crowley et al. found the same occlusion results comparing n-BCA to Onyx, but conversely found that more sessions were performed and more pedicles embolized in the Onyx group.⁵⁾ Sahlein et al. reported their exclusive n-BCA experience and described a more aggressive approach of embolizing 3.4 pedicles per session and 4.4 pedicles per AVM compared to our 1.9 and 2.9, respectively. This more aggressive

approach with n-BCA resulted in an 84% overall devascularization compared to our 52%.²²⁾ Lastly, in a large meta-analysis, Elsenousi et al. found that the angiographic results trended towards Onyx over n-BCA. It is likely that results with these agents will vary by operator.

Lower complications with less aggressive embolization

All complications were infrequent in our series, and this may be a function of the less aggressive nidal reduction during embolization. Our endovascular major complication rate of 3% is at the lower end of that reported in the literature (3.8-14%).⁹⁾¹⁰⁾ A cursory look at our data and the literature suggests that less aggressive embolization with less focus on trans-arterial curative intent may be a superior strategy (Fig. 5). This conservative embolization approach was recently endorsed by See et al. who observed a reduction in hemorrhagic complications with a flow reduction strategy minimizing nidal penetration with n-BCA.²³⁾ These authors have previously reported the usefulness of non-invasive analysis of the AVM flow volume in quantifying embolization results. This method of assessing embolization is perhaps more significant than angiographic volume reduction.¹⁾

A trend toward higher Onyx complications rates was seen in the Onyx trial with an adverse event in 9.3% of Onyx treatments compared to 4.8% with n-BCA. The meta-analysis by Elsenousi et al. also had a non-significant trend toward higher complications with Onyx.⁷⁾ The brain arteriovenous malformations embolization with Onyx (BRAVO) trial pursued very aggressive AVM Onyx embolization with >50% occlusion occurring in 85% of cases and cures occurring in 24% of cases, but incurred a treatment-related morbidity and mortality of 5 and 4%, respectively.²⁰⁾ Our data offers little on the comparison of complications between these 2 agents, but more suggestion that a less aggressive nidal occlusion may be preferential.

n-BCA vs Onyx is a matter of preference over evidence

There are numerous differences between these two agents. Most of the differences amount to a higher

convenience factor for Onyx since no mixing is required, it is better optically and radiographically visualized, and the injections are slower with less requirement for split second decision making. Whether there is true benefit of Onyx over n-BCA is not settled. Some techniques combine the agents such as the pressure cooker technique in which a coil and n-BCA plug is made to better penetrate Onyx into the nidus.⁴⁾ Selection of each agent based on the lesion angioarchitecture and operator experience is likely best practice. Further analysis of these liquid embolic agents and other emerging agents with the use of better balloons and detachable tip microcatheters will be of future interest.

Limitations

There are several limitations to our study. First, it is a retrospective analysis at a relatively low volume practice over 18 years amounting to only 1.7 embolized AVMs per year treated by 8 different practitioners. Although the care is diluted over time and practitioners, this may be a truer reflection of real-world AVM embolizations. Volumetric analysis was performed by an ABC/2 analysis which is a linear assessment based on assumptions of ellipsoidal nidal morphology. Our method was identical to that used by both the Onyx Trial Investigators and n-BCA Trial Investigators.¹⁶⁾¹⁸⁾ Although it is correlative to planimetric volume analysis, it has shown inaccuracies with absolute AVM nidal volume.¹⁵⁾²¹⁾ Since we did a relative comparison, this method is likely satisfactory although a planimetric or 3-dimensional assessment may be more accurate.¹²⁾ Variables that were not available but potentially relevant are the concentrations of Onyx and n-BCA. Also, since n-BCA was used in the early portion of this series (2002-2008) and Onyx in the later portion (2009-2019), other advances in imaging and endovascular devices would favor better results with Onyx. Lastly, the small sample size does limit our statistical analysis to discover small differences in the analyzed variables that may have been seen with a larger sample size.

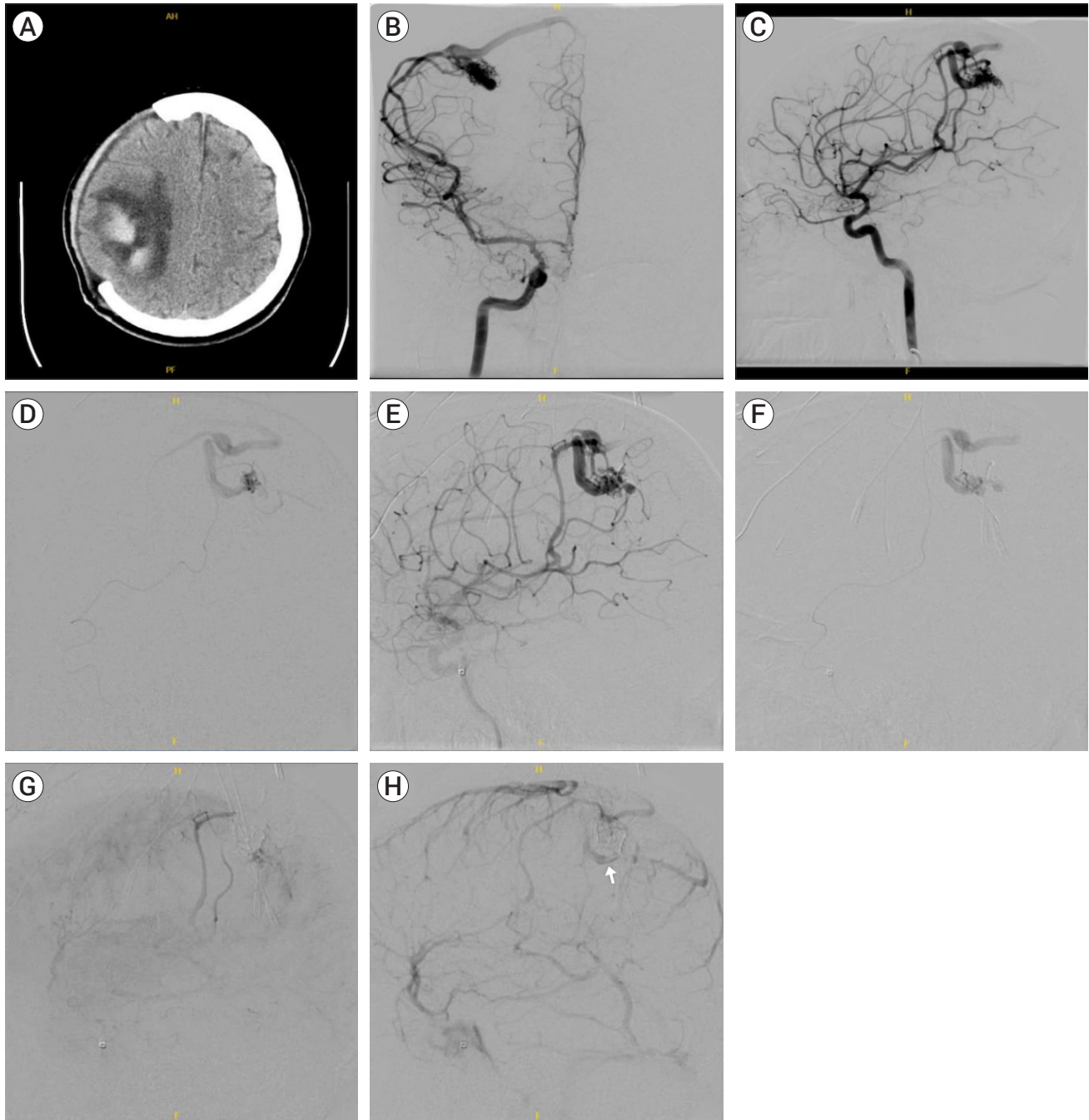


Fig. 5. Ruptured right parietal AVM, pre-surgical Onyx embolization. A ruptured right parietal AVM with intercranial hemorrhage and brain swelling requiring a decompressive hemicraniectomy (A). A pre-embolization right internal carotid artery angiogram with AP (B) and lateral (C) views show AVM dimensions of 1.9 cm×1.8 cm×1.1 cm with a calculated volume of 1.89 mL. Microcatheter angiography showing nidus and draining vein from the first MCA branch before onyx injection (D). Lateral right internal carotid angiogram after 1 MCA pedicle embolization showing 28% volume reduction (E). A second MCA feeding artery microcatheter angiogram with nidus and draining vein (F). The objective of this embolization was adjuvant pre-surgical. Final lateral right internal carotid artery angiogram shows a 94% volume embolization with delayed filling of the 2 embolized MCA pedicles (G) and delayed filling of the draining vein (white arrow) (H). AVM, arteriovenous malformations; AP, anteroposterior; MCA, middle cerebral artery

CONCLUSIONS

Continued analysis of AVM embolization experience is needed to identify risk factors for complications and improved embolization results. In this small retrospective series, Onyx and n-BCA achieved similar occlusion results although n-BCA required more session and pedicles embolized to do so. Both agents had low complications which may be related to less aggressive embolization strategies.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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