Seizures after Onyx Embolization for the Treatment of Cerebral Arteriovenous Malformation

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Summary

Onyx embolization of cerebral arteriovenous malformations (AVM) has become increasingly common. We explored the risk of seizures after Onyx use.

A retrospective review was conducted of 20 patients with supratentorial brain arteriovenous malformation (AVM) who received Onyx embolization between 2006 and 2009. Baseline demographics, clinical history, seizure history, AVM characteristics and treatment were compared between those who developed post-onyx seizure and those who did not. MRIs were reviewed for edema following Onyx treatment.

Of 20 patients who underwent Onyx embolization, the initial AVM presentation was hemorrhage in 40% (N=8). The median number of embolizations was two (range 1-4) and the median final obliteration amount was 90% (range 50-100%). A history of seizure was present in 50% (N=10) of patients pre-embolization and 12 (60%) patients received seizure medications (treatment or prophylaxis) prior to embolization. Seizur post-Onyx embolization occurred in 45% (N=9). The median time to seizur post-Onyx was seven days (range 0.3-210). Four patients (20%) with seizures post-Onyx had no seizure history. Two of these patients (10%) had no other identifiable cause for seizure other than recent Onyx embolization. Seizures in these two patients occurred within 24 hours of Onyx administration. Among patients with post-Onyx seizures, there was a trend toward larger AVM size (P=0.091) and lower percent obliteration (P=0.062). Peri-AVM edema was present in 75% of MRIs performed within one month of Onyx treatment and may represent a possible etiology for seizures.

New onset seizures post-Onyx embolization are not uncommon. Further study of seizure prevention is warranted.

Introduction

Brain arteriovenous malformations (AVM) commonly present with seizures in up to 40% of cases[1]. With more refined microsurgical techniques and multimodality treatments with endovascular embolization, increasing numbers of previously untreatable AVMs are being completely obliterated, significantly reducing the risk of new or recurrent hemorrhage. Seizures, however, continue to affect patients' quality of life, despite AVM obliteration. In those who present with seizures, up to 25% will continue to live with recurrent seizures, despite endovascular treatment with n-BCA[2]. In surgically treated AVMs, 6-57% can have new onset seizures and up to 17% may have recurrent disabling seizures. Up to 22% of patients whose AVMs are treated with radiosurgery continue to have disabling seizures after three years of follow-up [5]. Although the incidence and predictors of seizures have been studied among patients treated with standard embolic material, surgery or radiosurgery, the prevalence of new-

onset seizures among patients receiving Onyx (Ethylene-Vinyl Alcohol Copolymer, Micro Therapeutics, Inc., Irvine, CA, USA) has not been well described.

Materials and Methods

Study Population

A retrospective chart review of all patients with supratentorial AVMs treated with Onyx (ev3, Irvine, CA, USA) embolization between 1/1/2006 and 6/1/2009 was conducted at the Mount Sinai Medical Center. The inclusion criteria were defined as: ruptured or unruptured supratentorial intracranial AVM diagnosed by digital subtraction angiography and treated at any time with Onyx embolization, either as an adjunct to surgery or radiosurgery or as definitive or palliative treatment. We excluded dural arteriovenous fistulas and AVMs treated with any other embolic materials including N-butyl-2 cyanoacrylate (NBCA, Cordis Neurovascular, Inc.), infratentorial and spinal AVMs and AVMs of the external carotid artery circulation. We excluded patients who received other embolic materials, such as NBCA, to allow for examination of the effect of Onyx alone on seizure incidence. This study was approved by the Mount Sinai Medical Center (MSMC) institutional review board (IRB).

Medical and Endovascular Management

Angiography and embolization were performed by two neurointerventionalists. The neurointerventionalists, vascular neurosurgeons and radiosurgeon decided on the management approach based on the patient's clinical status, the AVM characteristics and the patients' wishes. Onyx embolization is performed as a preoperative adjunct to optimize surgical resection or to decrease the size of the AVM to <3 cm for radiosurgery. Only where possible, endovascular cure with Onyx is attempted.

All Onyx embolizations were performed under general anesthesia using isoflurane, desflurane or sevoflurane at half-MAC concentrations with supplemental use of narcotics (usually fentanyl) or propofol as needed. Patients who were not previously taking an antiepileptic drug (AED) as outpatients were administered 1 g of fosphenytoin and continued on prophylactic phenytoin 100 mg PO TID for seven days post-embolization. Patients with a history of hemorrhage routinely received AED prophylaxis prior to AVM repair. Patients were not loaded with AEDs if they were routinely receiving AEDs prior to embolization, but rather continued to receive their outpatient dosage of AED. Routine screening of AED levels prior to embolization was not performed. Additionally, dexamethasone (4-10 mg every 6 hours) was administered intravenously during the procedure and tapered post-procedure over two weeks.

Digital subtraction angiography was performed using a biplane angiographic unit (Philips, Andover, MA, USA). Catheterization was performed via a transfemoral approach with a standard coaxial technique. Super-selective Onyx embolization was carried out using either Onyx 18 or Onyx 34. All patients were monitored in the neuroscience ICU for 24 hours following embolization and received hourly neurological evaluations by the ICU nursing team. Patients with seizures were treated with lorazepam 2 mg IV bolus (to a maximum of 0.1 mg/kg) titrated to seizure abortion followed by titration of maintenance AEDs to achieve maximum therapeutic levels or addition of a second AED.

Clinical and Radiographic Measures

Baseline demographic information, including age and sex and presenting symptoms were recorded. Details of AVM treatment including embolization, surgery, radiosurgery and percent obliteration were documented. All patients who initially presented with or developed seizures had a detailed account recorded of seizure semiology, date of seizure onset, number and frequency of seizures before and after embolization, long-term AED use, AED type and dose, and length of AED use. Modified Rankin Scores were constructed from follow-up visits after embolization and/or surgical resection or radiosurgery. MRI was evaluated for the presence of edema defined as increased T2 or FLAIR signal in the peri-lesional white matter with mass effect, or gliosis defined as increased T2 or FLAIR signal with volume loss or atrophy.

Statistics

Continuous non-normally distributed variables were dichotomized at the median. The Mann-Whitney U nonparametric test (for con-

tinuous non-normally distributed variables) or the chi-squared test (for dichotomous variables) was used to assess the differences in demographics, clinical history, AVM morphological characteristics and treatment and modified Rankin Scores between patients who had post-onyx seizure and those who did not. Significance was set at $P<0.05$.

Results

From 1/2006 to 6/2009, 20 patients with supratentorial AVM were treated with Onyx embolization. The median age was 35 years (range 11-67), 40% (N=8) of patients had a history of hemorrhage (intracerebral, subarachnoid or both) and 50% (N=10) had a history of seizure

Table 1 **Detailed characteristics of patients with seizures post treatment, N = 9.**

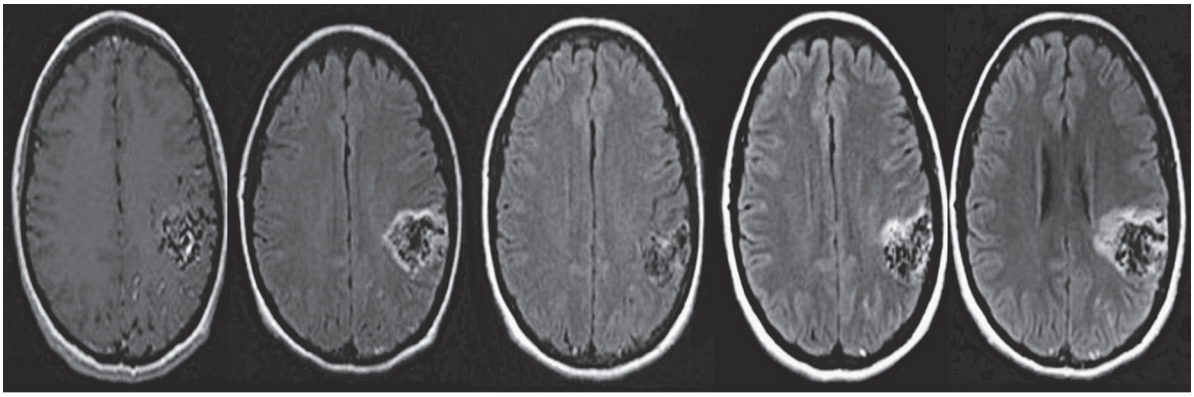
Age	Presenting symptoms	History of seizure	Pre-embo AED	AVM size (mm)	AVM location	Post-Onyx Seizure Semiology	Post-Onyx time of seizure onset	Total embos	% Obliterated with Onyx	Further Therapy
26	Complex Partial Seizure, Unruptured AVM	Yes	TEG	40	Right medial posterior frontal	Simple partial	<24 hours	2	85	
53	Complex partial seizure Unruptured AVM	Yes	LVT	25	Right temporal parietal	Simple partial	<24 hours	1	50	
21	GTC Seizure Unruptured AVM	Yes	PHT	25	Right medial frontal	Complex partial	2 months	2	80	
22	GTC Seizure Unruptured AVM	Yes	PHT	33	Left temporal	Complex partial	7 months after Onyx+ surgery	3	95	Surgery
40	Headache Unruptured AVM	No	None	35	Right frontal	Complex partial	<24 hours	3	95	
29	Headache Unruptured AVM	No	None	40	Left inferior parietal	GTC	<24 hours	4	90	
48	Simple partial seizure, ICH	Yes	PHT	60	Right medial temporal, basal ganglia, thalamic	Simple partial	6 months	1	5	
42	ICH and SAH	No	PHT	40	Left parietal	GTC	6 weeks after Onyx and ICH	3	90	Surgery
31	ICH	No	LVT	40	Left occipital-parietal	Simple partial	1 week after Onyx and radio-surgery	4	90	Radio surgery

AVM, arteriovenous malformation; AED, antiepileptic drug; embo, embolization; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; GTC, generalized tonic clonic seizure; TEG, tegretol; LVT, levetiracetam; PHT, phenytoin.

Table 2 **Patient and AVM characteristics among those with and without post-Onyx seizure, N = 20.**

	Entire Cohort	Post Onyx Seizure	No Post Onyx Seizure	P
Demographics				
Age (median, range)	35 (11-67)	40 (21-53)	34 (11-67)	0.790
Gender, male (N, %)	10 (50)	4 (44)	6 (55)	1.00
Clinical History				
Hemorrhage (N, %)	8 (40)	1 (22)	5 (46)	0.374
SAH (N, %)	2 (10)	1 (11)	1 (9)	1.00
ICH (N, %)	8 (40)	2 (22)	6 (55)	0.197
Neurological deficit pre-treatment (N, %)	6 (30)	2 (22)	4 (36)	0.642
Seizures (pre-treatment) (N, %)	10 (50)	5 (56)	5 (46)	1.00
Long term AED pre-treatment (N, %)	13 (65)	6 (67)	6 (55)	0.670
Type of AED Phenytoin	8 (40)			
Leviteracetam	4 (20)			
Oxcarbazepine/Carbamazepine	2 (10)			
Total number of AEDs pre-treatment (median, range)	1 (0-2)	1 (0-1)	1 (0-2)	0.481
On AED at time of embolization (N, %)	18 (90)	8 (89)	10 (91)	1.00
AVM baseline characteristics				
Spetzler Martin Grade (median, range)	3 (1-5)	3 (1-5)	2 (1-4)	0.519
Size, largest dimension (mm), (median, range)	35 (10-60)	40 (25-60)	28 (10-45)	0.091
Eloquent location (N, %)	12 (60)	6 (67)	6 (55)	1.00
Deep venous drainage (N, %)	8 (40)	2 (22)	6 (55)	0.170
Associated aneurysm (N, %)	7 (35)	3 (33)	4 (36)	0.764
AVM Treatment				
Total number of Onyx embolizations (median, range)	2 (1-4)	2.5 (1-4)	1.5 (1-4)	0.430
Number of vessels injected total (median, range)	2 (1-4)	3 (1-4)	1 (1-4)	0.112
% Obliteration after last Onyx embo (median, range)	90 (50-100)	80 (50-95)	99 (50-100)	0.062
Surgery post-Onyx (N, %)	4 (20)	3 (33)	1 (9)	1.00
Radiosurgery post-Onyx (N, %)	2 (10)	1 (11)	1 (9)	1.00

prior to treatment. Twelve patients (60%) were taking a median of one (range 0-2) AED for seizure treatment or prophylaxis (when hemorrhage was present) as an outpatient prior to Onyx embolization. The median number of seizures prior to Onyx treatment (among patients with a seizure history) was two (range 1-3). The most common AED to treat seizures pre-embolization was phenytoin (N=5), followed by leviteracetam (N=2), phenytoin plus leviteracetam (N=1), tegretol (N=1) and trileptal (N=1). There were no procedural episodes of hypoxia or hypotension requiring vasopressors during any Onyx embolization based on a review of the anesthesia records. During a median follow-up of 12 weeks (range 1-64), nine patients (45%) had a seizure following Onyx embolization. The median number of days to seizure post-Onyx was seven (range 0.3-210). Of the nine with post-Onyx seizures, five (25%) had a history of seizures and four (20%) had new onset seizures. Of those with new onset seizures after Onyx treatment one (5%) had a concurrent hemorrhage and one (5%) had received radiosurgery. Two patients (10%) had new onset seizures following Onyx administration with no other inciting factor for seizure. Of these two patients, one had a therapeutic total phenytoin level of 21.3 mcg/mL (therapeutic range 10-20 mcg/mL), while the other had a



Pre-Onyx embolization | 24 hours post-Onyx embolization | 5 months post-Onyx embolization | 24 hours post-repeat Onyx embolization | 7 days post-repeat Onyx embolization

Figure 1 MRI T2 FLAIR axial sequences of left parietal AVM demonstrating increased FLAIR signal around the nidus following the first and repeat Onyx embolization, as well interval resolution of flair signal 5 months after the first embolization. This patient developed seizures after both Onyx embolizations.

sub-therapeutic level of 7.4 mcg/mL at the time of seizure. Both of these patients had seizures immediately post-procedure (<24 hours). Though one patient was successfully treated with phenytoin and remained seizure-free, the other had recurrent complex partial seizures 30 days after the initial Onyx embolization. Detailed characteristics of the nine patients with post-Onyx seizures are listed in Table 1.

There were no significant differences in demographics, clinical history, AVM morphological characteristics or AVM treatments comparing patients who developed seizures post Onyx embolization to those who did not (Table 2). Among those with post-Onyx seizures there was a trend toward larger AVM size (40 versus 29 mm, P=0.091) and a lower median percentage of obliteration (80% versus 99%, P=0.062). We were unable to assess for a relationship between the dose of Onyx administered and post-Onyx seizures since these data were not collected.

MRI was obtained within one month of Onyx embolization and prior to any other treatment (i.e. surgery or radiosurgery) in nine patients following 12 Onyx treatments. Overall, peri-lesional edema was noted within one month after 9 (75%) Onyx treatments and gliosis was present in four (33%) patients. No patient had extravasation of Onyx into the subarachnoid space. Three of the nine patients (33%) with MRI documented edema developed seizures post-Onyx embolization. Of the two patients with new onset seizure with no other known etiology, one had an MRI revealing edema while the other patient had no MRI imaging. Compared to a baseline MRI, the edema in this case appeared within one day post-Onyx embolization, abated after five months and recurred one day after a repeat Onyx embolization procedure (Figure 1). There was no association between the amount of AVM obliteration that occurred during each treatment and the development of edema on MRI.

The median modified Rankin (mRS) score prior to Onyx treatment was one (range 0-3). After a median of 4.5 months of follow-up (range 1-12), the median mRS was one (0-2). There was no difference in post-Onyx mRS between those who had post-treatment seizure and those who did not (P=0.611).

Discussion

Complications of BAVM embolization with various embolic materials including Onyx have been described in the literature. These include hemorrhage, ischemic events, neurologic deficits and procedural complications. More recent articles report a permanent morbidity of 3.8-8.5% and mortality of 0-3.2% after embolization with Onyx [8-11]. To our knowledge, however, no studies specifically address new onset seizures after Onyx embolization.

In our series of 20 brain AVMs, nine of 20 (45%) patients developed seizures after Onyx embolization, of whom four patients (20%) had new onset seizures. Two of the four (10%) patients with de novo seizures had not known etiology for the seizure (i.e. hemorrhage, radiosurgery). Because all patients received prophylac-

tic AEDs prior to embolization, the rate of seizures in untreated patients following embolization may actually be higher. The literature for describing seizures after any type of AVM embolic material administration is limited. Hoh et al. reported a 5.7% incidence of new onset seizures in a series of nBCA treated AVMs [7]. In an earlier article by Fournier et al., using isobutyl 2-cyanoacrylate and nBCA, four patients (8.2%) treated for brain AVMs developed immediate new onset focal seizures, which were easily controlled. In this series, 43% of patients with seizures prior to treatment had reduced seizure frequency after embolization [12]. The seizure frequency we observed following Onyx administration was higher than that reported following nBCA embolization. However, post-procedure seizures may actually be underreported in the literature since it is unclear if transient neurologic deficits reported in some series, may in fact be seizure-related.

Among patients with a history of seizure prior to Onyx and seizures following treatment, it is unclear if post-embolization seizures represent seizure relapse or a new seizure focus. Two patients with a history of complex partial seizure had simple partial seizures after embolization, two patients with generalized tonic clonic seizures had complex partial seizures after embolization and one patient with simple partial seizures prior to embolization had similar simple partial seizures six months after embolization. Since we did not have EEG data before and after embolization to determine with certainty if the seizures were from the same focus, we cannot definitively determine if the seizures post-Onyx represented new seizures or recrudescence of old seizures. Though the semiology seemed to change in four patients, it is possible that the semiology described post-Onyx was a prelude to the typical semiology described by the patient pre-embolization. For example, most generalized tonic clonic seizures are actually preceded by a focal or complex partial seizure. The patient with simple partial seizures before and after embolization, however, did seem to have a consistent seizure type and likely had a relapse of seizure. Among those with seizure pre-embolization, 50% had seizures after embolization, despite AED treatment. Since we do not have data on anti-epileptic levels at the time of seizure and since some seizures were delayed several months post-embolization, it is possible that sub-therapeutic AED levels may have contributed to seizure recurrence. Based on our data, we cannot comment on the efficacy of AED prophylaxis in patients with no history of seizure.

Interestingly, the MRI findings in one of these patients demonstrated peri-lesional edema formation within 24 hours of two separate Onyx embolizations with intervening abatement. Though the edema response to Onyx is not unique among embolic agents, it may have contributed to the development of seizures in this cohort. Unfortunately, routine MRI pre and post-Onyx was not performed in the entire cohort, so it is impossible to prove a causal link between Onyx, peri-lesional edema and seizures. Indeed, it is possible that the edema seen on the MRI was a secondary effect of the seizure, rather than causal. However, Onyx has been demonstrated to trigger intra- and perivascular inflammation on histological analysis after embolization [6]. Natarajan et al. reviewed specimens from 22 surgically resected AVMs pretreated with Onyx and ten with nBCA and observed similar evidence of vascular and perivascular inflammation, but increased chronic foreign body giant cells (54.5%) and angionecrosis (59.1%) in the Onyx embolized specimens compared to 40% and 18.2% in nBCA treated AVMs13. Four days after embolization with Onyx and resection, Jahan et al. found histological evidence of chronic inflammatory changes in AVM tissue specimens [8]. Peri-lesional ischemia and thrombosis may also occur after Onyx administration. In a study of nBCA and Onyx-treated patients, Cronqvist analyzed MRIs with specific attention to DWI and perfusion images of AVMs after treatment and concluded that ischemic and perinidal venous thrombotic events appeared to be more frequent than previously understood [14]. Changes following Onyx embolization, such as edema or ischemia surrounding the AVM, could conceivably contribute to the development of seizures. Though post-Onyx seizures were common in our cohort, there were no differences in functional outcome between those who suffered seizures and those who did not.

The etiology of seizures in AVMs remains unclear. Various hypotheses exist including: neuronal cell loss, glial proliferation and abnormal glial physiology, altered neurotransmitter levels, free radical formation, aberrant second messenger physiology [15], previous hemorrhage resulting in gliosis or hemosiderin deposition in surrounding cortex as a seizure generator [16], perilesional neurochemical changes, or ischem-

ic changes and "steal" phenomenon from surrounding cortex [7]. Turjman et al. studied the angioarchitectural factors associated with seizure incidence of brain AVMs prior to treatment, and found that frontal cortical location, feeders from the middle cerebral artery, absence of aneurysms, cortical location of the feeding arteries and the presence of varices/varix in the venous drainage had a positive association with seizure incidence [17]. Hoh et al. studied clinical predictors of seizure incidence and seizure outcomes in patients with seizure history and brain AVMs and observed male sex, age of less than 65 years, AVM size of more than 3 cm, and temporal lobe AVM location to be statistically associated with pretreatment seizures [7]. It is possible that because of the excellent nidal penetration of Onyx, entry of embolization material in the veins might lead to edema and subsequent seizures. Because of our small sample size, we did not observe a relationship between percent obliteration, MRI edema and seizures. Conversely, there was a trend toward lower obliteration rates among patients who had post-Onyx seizures.

Though the main indication for AVM treatment is to prevent hemorrhage, seizure morbidity would ideally be ameliorated with treatment. Several authors have demonstrated that surgery and radiosurgery, though with widely varying results, can successfully achieve this; yet the mechanism is not understood [7]. Surgical resection of the mass itself, should theoretically eliminate the seizure generator, and yet de novo seizures occur in 8-57% of patients [7]. This is likely due to the epileptogenic focus, whether it is gliosis or hemosiderin left behind after surgery. Baumann et al. found that when the hemosiderin borders of a cavernous malformation resection were included, patients had better seizure outcomes [20]. It is proposed that radiation therapy induces thrombosis in the AVM, which can reduce "steal" phenomenon and seizure frequency [5]. Others propose that irradiation of the area surrounding the AVM inhibits seizure activity. Among AVMs treated with radiosurgery, however, 0-6.5% still develop de-novo post-treatment seizures. It remains unclear whether Onyx is associated with higher seizure risk than other embolic agents, surgery, radiosurgery or the natural history of an untreated AVM. Randomized trials, such as the international ARUBA (A Randomized trial of Unruptured Brain Arteriovenous malformations) trial may help answer this question.

Conclusions

This small case series of Onyx treated brain AVM demonstrates that seizure after Onyx treatment is not uncommon and new onset seizures may be due to Onyx administration. Though the mechanism is not clear, the development of edema and inflammation surrounding the nidus following Onyx administration may play a role. Further studies of peri-procedure anti-epileptic medications and close neurological observation following Onyx administration may be warranted.

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