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Treatment of pediatric intracranial vascular malformations using Onyx-18

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Object. Onyx-18 is a relatively new liquid embolic agent. The initial success with this polymer will result in increased utilization in children, but its use and safety in the pediatric population have not been firmly established.

Methods. Between December 2005 and January 2008, the cerebral vascular malformations in 6 children were embolized using Onyx-18. The ages of the patients ranged from 1 day to 12 years. Pathological types of the vascular malformations included 4 arteriovenous malformations and 2 vein of Galen malformations. Clinical presentations included intracranial hemorrhage in 2 patients, papilledema in 1 patient, and high-output heart failure in 3 patients.

Results. In 6 pediatric patients, 21 embolization procedures were performed utilizing a combination of Onyx-18, platinum coils, and Embosphere microspheres. The average estimated size reduction for the arteriovenous malformations was 60%. Total obliteration of a malformation was achieved in 1 patient. Two patients received adjuvant radiosurgery. Of the 2 vein of Galen malformations, one was completely embolized and the other had an ~ 50% reduction in flow. No open surgical intervention was used. Clinical follow-up ranged from 7 to 12 months. Angiographic follow-up data were obtained at 1, 6, and 7 months in 3 patients, whereas 1 patient awaits repeat angiography. Complications included a transient monoparesis with complete resolution in 1 patient. Two patients died within 24 hours of an embolization procedure due to intracranial hemorrhages.

Conclusions. Onyx-18 is a feasible embolization agent for use in intracranial vascular malformations in the pediatric population, but long-term follow-up data will be necessary to assess the continued efficacy and safety of this agent. *(DOI: 10.3171/PED/2008/2/9/171)*

Key Words • endovascular embolization • Onyx • vascular malformation • vein of Galen

Arteriovenous malformations most commonly present in patients between 20 and 40 years of age,[7] and children comprise 3 to 20% of all cases.[2] With an estimated risk of hemorrhage of 2–4% per year, AVMs cause 30–50% of all ICHs in the pediatric age group.[9] The estimated morbidity and mortality rate for each hemorrhagic event in children is 50% and 5–10%, respectively.[4,11] Symptomatic VOGMs also have an abysmal prognosis if left untreated. Although the natural history of VOGMs depends on the patient's age at presentation, once symptomatic, these malformations require treatment to prevent progressive heart failure, hydrocephalus, seizures, or further neurological deterioration.[6]

Abbreviations used in this paper: ACA = anterior cerebral artery; AChA = anterior choroidal artery; AVM = arteriovenous malformation; DMSO = dimethyl sulfoxide; EEG = electroencephalography; FIM = functional independence measure; GKS = Gamma knife surgery; ICH = intracranial hemorrhage; IVH = intraventricular hemorrhage; MCA = middle cerebral artery; mRS = modified Rankin Scale; PCA = posterior cerebral artery; PICA = posterior inferior cerebellar artery; SSEP = somatosensory evoked potential; VA = vertebral artery; VOGM = vein of Galen malformation.

With so much at stake and the continually escalating and cumulative risk of hemorrhage over a young person's lifetime, the general consensus is that pediatric AVMs and VOGMs should be aggressively treated. For AVMs, resection in appropriately selected pediatric patients has shown durable results, perhaps with better outcomes than in their adult counterparts.[2,8] However, Spetzler–Martin Grades III, IV, and V AVMs or those with a single, discrete feeding vessel may be amenable to treatment by alternative means with equivalent or reduced morbidity and mortality rates.

In the past 2 decades, radiosurgery and endovascular embolization have become accepted methods of treatment for some vascular malformations. In one of the largest reviews to date, Bristol and colleagues[1] described the treatment of 84 AVMs in 82 children. In this study, > 50% of the patients received adjuvant therapy with radiosurgery or endovascular embolization, with a trend toward a greater reliance on endovascular embolization. Endovascular embolization has now become the standard of care in the treatment of VOGMs.

Improvements in catheters and embolization devices have greatly expanded the utility of endovascular treatment. The

Onyx liquid embolic system (ev3, Inc.) is a cohesive polymer of ethylene vinyl alcohol and DMSO that was approved in 2005 by the US Food and Drug Administration for the presurgical embolization of brain AVMs in adults. We report the utility of this unique polymer in the treatment of pediatric vascular malformations.

Methods

The records of 6 children (age < 18 years) with intracranial vascular malformations who were treated endovascularly between December 2005 and January 2008 were retrospectively reviewed. All information obtained was subject to approval by the local institutional review board for this study. Treatment utilized Onyx-18 in conjunction with adjuvant therapies. The patients consisted of 3 girls and 3 boys, ranging in age from 1 day to 12 years old at the time of their first endovascular treatment. Patient ages and pathological characteristics are shown in Table 1.

The clinical presentations included isolated IVH, lobar ICH, high-output heart failure in 3 patients, and 1 incidental finding of papilledema after a child failed his school vision test. Clinical and functional assessments were made using the FIM instrument (Table 2) when applicable and the mRS adapted for use in infants and children as described by Sanchez-Mejia and associates[8] (Table 3).

All patients were treated at the same center and by the same endovascular neurosurgeon (M.H.). Procedures were intentionally staged to limit contrast-induced renal toxicity, with the intention of keeping the dye load below 5 ml/kg. We believe staging procedures also allow the brain to adapt to altered hemodynamics following vascular occlusion. All procedures were performed while patients were in a state of general anesthesia with the use of neurophysiological monitoring consisting of SSEPs and continuous EEG. Brainstem auditory evoked responses were monitored in selected cases involving the posterior circulation. Every effort was made to conduct a modified Wada test before embolization of an artery feeding eloquent cortex. Typically, 1 ml of lidocaine or 3 ml of methohexital sodium was injected into the vessel of interest. A senior staff neurophysiologist reviewed the continuous SSEPs, brainstem auditory evoked responses, and EEG monitoring during injection for any changes. No disturbances were noted in all vessels studied prior to embolization.

TABLE 2
The FIM instrument

Score	Independence Level
7	complete independence
6	independence w/ assistance device
5	modified dependence, supervision needed
4	modified dependence w/ 25% assistance
3	modified dependence w/ 50% assistance
2	complete dependence w/ 75% assistance
1	complete dependence w/ 100% assistance

Vascular access was achieved via the common femoral artery or vein. When an imminent follow-up arteriogram or intervention was anticipated, the sheath was left in place, secured to the skin, and continuously flushed with heparinized saline. When necessary, for repeated access of the same vessel in neonates, the general surgery team was consulted to obtain access via a peripheral surgical incision. Dimethyl sulfoxide–compatible microcatheters supported by platinum microwires were used in all cases. All references to Onyx in this study refer to Onyx-18, as opposed to the more viscous formulations that include Onyx-34 and HD 500. The limited follow-up period ranged from a few days to 1 year.

Results

The procedures are delineated in Table 1. These 6 children underwent a total of 21 endovascular procedures over a period ranging from 1 day to 1 year.

Case 1

The patient in Case 1 underwent 4 endovascular emboli-

TABLE 1
*Summary of pediatric patients with intracranial vascular malformations treated using Onyx-18**

Case No.	Age, Sex	Location	AVM Size (cm)	AVM Drainage	Clinical Presentation	Treatment	Angiographic Outcome (% residual)	Clinical/ Radiographic FU (mos)	mRS/ FIM Score
1	10 yrs, M	rt cerebellar	2.5	superficial	papilledema	1 endovascular embolization, 1 GKS	20		
		rt frontal	2.5	superficial	papilledema	2 endovascular embolizations, 1 GKS	40		
		lt frontoparietal	3	superficial	papilledema	1 endovascular embolization, 2 GKS	40	12/7	0/7
2	10 yrs, F	rt parietal	5.5	superficial	hemorrhage	4 endovascular embolizations, 1 GKS	60	7/1	0/7
3	5 days, F	lt hemisphere	>10	deep	high-output heart failure	5 endovascular embolizations	70	NA	6/NA
4	12 yrs, M	rt parietooccipital	3.5	deep	IVH	1 endovascular embolization	0	10/6	2/5
5	20 days, F	VOGM	NA	NA	high-output heart failure	6 endovascular embolizations	NA	12/0	0/NA
6	1 day, M	VOGM	NA	NA	high-output heart failure	1 endovascular embolization	NA	NA	6/NA

* FU = follow up; NA = not applicable.

TABLE 3
The mRS adapted for use in pediatric patients

Score	Description
0	normal
1	neurological deficit or symptoms noted on examination, but no impairment
2	neurological deficit that interferes w/ daily activities, but some functional use of involved limb
3	no functional use of a limb, but ability to resume baseline daily activities
4	no functional use of a limb & inability to resume baseline daily activities
5	severe neurological deficits & disability
6	death

zations followed by 4 staged GKS treatments to treat 3 separate AVMs. A 2.5-cm right cerebellar AVM with superficial venous drainage fed by the right superior cerebellar artery and right PICA was embolized. Both vessels were treated in a single setting using Onyx to achieve an ~ 80% reduction in nidus volume (Fig. 1). The patient received 1 GKS treatment.

A 2.5-cm right frontal AVM with superficial drainage fed by the pericallosal artery was embolized in 2 procedures over 48 hours. First, 2 branches of the right pericallosal artery were embolized using Onyx to achieve an ~ 30% obliteration. This AVM was retreated the next day. Two proximal ACA branches were embolized using Onyx and one branch was treated with 300–700-μm Embospheres (BioSphere Medical) followed by proximal vessel sacrifice with 2- and 3-mm Tornado embolization coils (Cook Medical, Inc.) to achieve a 60% nidus reduction. The patient received 1 GKS treatment.

The patient returned home and came back 1 month later for a 3-part staged embolization of a 3-cm left frontoparietal AVM with superficial drainage fed by the ACA and MCA. The first stage involved embolization of 3 distal left MCA feeding arteries with a combination of Embospheres, Onyx, 2-mm platinum fibered coils, and Tornado embolization coils. Forty-eight hours later the left A_3 feeding vessel was treated with 2 ml of Onyx. The third and final endovascular procedure took place 48 hours later and involved the embolization of another distal ACA feeder using Embospheres, 2-mm platinum fibered coils, and Tornado embolization coils to achieve a final nidal reduction of 60%. The patient ultimately returned home and received 2 staged GKS treatments over the ensuing 6 months.

Case 2

The patient in Case 2 underwent 4 endovascular embolizations over 14 days and 1 GKS treatment to treat a right parietal 5.5-cm AVM with superficial drainage. The first treatment involved embolization of 3 right M_4 feeders using 0.69, 0.71, and 0.6 ml of Onyx to obliterate ~ 20% of the AVM. Four days later, another 4 M_3/M_4 branches were sequentially embolized using Onyx. Stage III occurred 48 hours later, in which 2 pericallosal branches were embolized using Onyx. The final stage took place after another 7 days, when 3 more ACA branches and a newly recruited MCA branch were embolized with Onyx. Gamma knife surgery was performed 1 month later on the residual 60%.

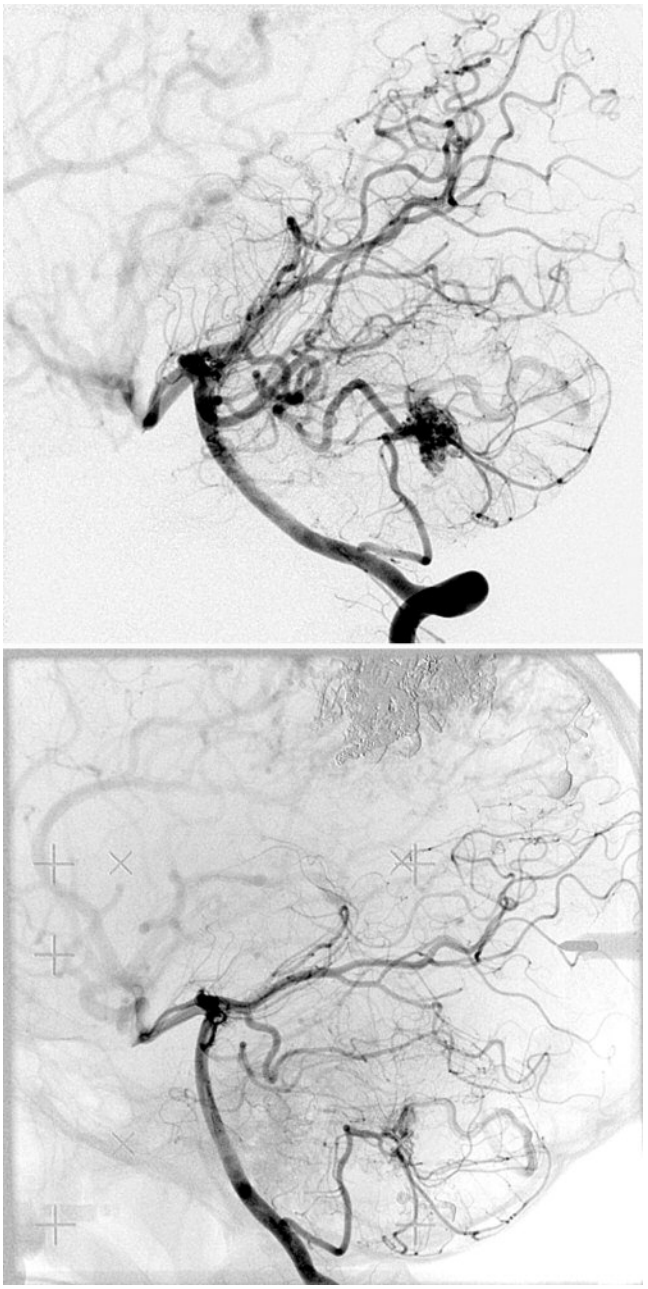

FIG. 1. Case 1. *Upper:* Right VA injection angiogram depicting a 2.5-cm cerebellar AVM with arterial feeders from the superior cerebellar artery and PICA. *Lower:* Right VA injection angiogram after Onyx embolization of both arterial feeders used to achieve an 80% reduction in nidus volume.

Case 3

The patient in Case 3 underwent 5 endovascular procedures over a period of 11 days to treat a left hemispheric AVM with an associated VOGM fed by the PCA, AchA, external carotid artery, ACA, and PICA. Palliative therapeutic embolization was recommended to ease the left heart strain. On Day 5 of the patient's life, a large muscular branch of the left subclavian artery was embolized with Tornado embolization coils. Four days later, the left inter-

nal maxillary artery and AChA were treated with 1.5 and 3 ml of Onyx, respectively. The following day, 3 platinum coils were placed in a direct fistula between the left ACA and a large venous varix to provide a lattice for 9 ml of Onyx. The fistula flow was significantly reduced. The next day, due to persistent life-threatening hemodynamics, the left paraclinoid internal carotid artery and left PICA were sacrificed using Onyx. Stage V took place 3 days later on Day 14 of life, and involved embolization of 2 P_3 branches with Onyx to achieve a final nidal reduction of 30%.

Case 4

The patient in Case 4, with a 3.5-cm right parietooccipital AVM with deep and superficial drainage, underwent a single embolization procedure. The AVM nidus was obliterated via a single feeding vessel from the posterior medial choroidal artery with 5 ml of Onyx-18 (Fig. 2). A 6-month follow-up arteriogram revealed no residual AVM.

Case 5

As previously reported,[3] the patient in Case 5 underwent 6 endovascular procedures over a period of 1 year to treat a VOGM fed by the bilateral PCAs and AChA with drainage from the falcine and straight sinuses (Fig. 3). Stage I involved placement of NXT Tetris platinum coils (ev3, Inc.) into the fistula via a dual transarterial and transvenous route. The distal left PCA was also sacrificed using coil placement. Stage II involved repeat embolization of 2 left PCA branches using NXT coils. Stage IV involved embolization of a venous varix fed by the right PCA with NXT coils. During Stage V, the right AChA was sacrificed using NXT coils. Flow through the fistula was significantly reduced, allowing the infant to regain normal hemodynamic parameters and return home. The patient returned 1 year later, requiring a sixth procedure to cure the malformation. The PCA was proximally embolized using Onyx. After transvenous access to the fistula was obtained, Onyx was injected into the previously placed coil mass to achieve complete eradication of flow through the fistula.

Case 6

The patient in Case 6, with a choroidal-type VOGM, underwent a single embolization procedure. After arterial roadmaps were obtained, transvenous coiling of the fistula was performed using 25 platinum coils followed by injection of Onyx to achieve an ~ 50% reduction of venous outflow.

Although the follow-up period was short in this study, the average AVM nidal reduction was 60% with no evidence of recanalization up to 7 months after the procedure.

Intraprocedural Complications

Intraprocedural complications occurred in 2 patients. In Case 1, while traversing a sharp turn in a distal M_3 branch, the catheter perforated the vessel wall as it was advanced over the guidewire. Although there was no change in neurophysiological monitoring, subarachnoid contrast extravasation was immediately visualized. Onyx was used to plug the perforation by pushing the polymer while simultaneously retracting the catheter back into the vessel, ensuring that the flow was stopped prior to the catheter tip re-

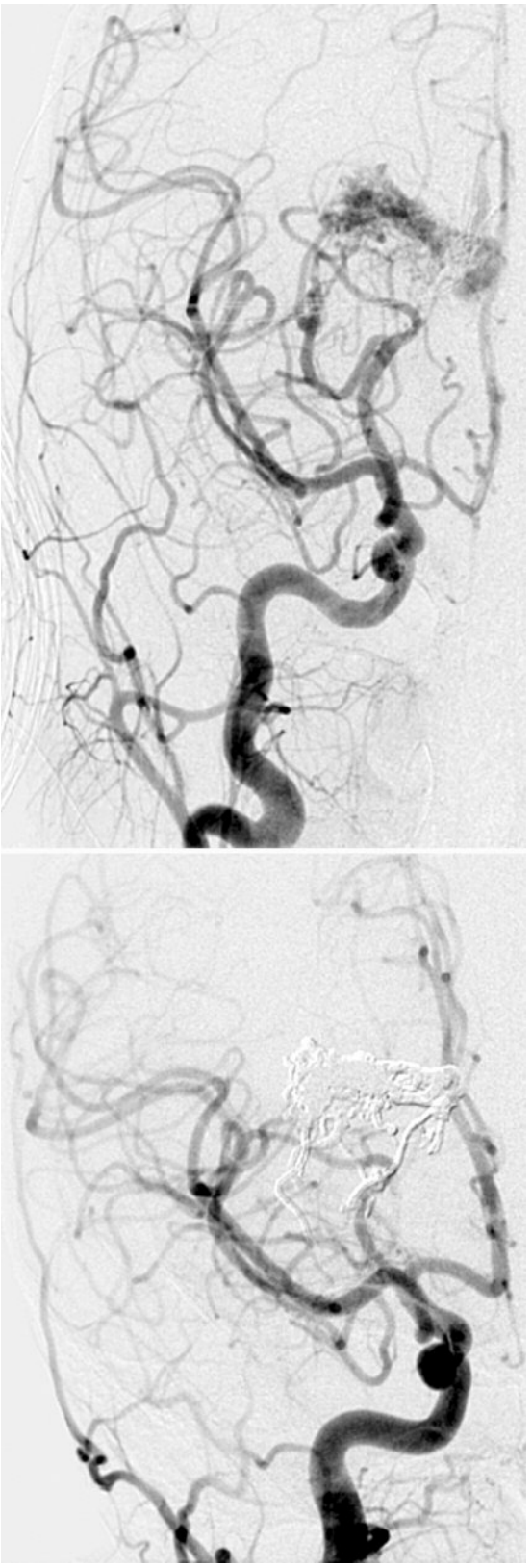

FIG. 2. Case 4. *Upper:* Right common carotid artery injection angiogram depicting a 3.5-cm parietooccipital AVM fed by the posterior medial choroidal artery. *Lower:* Right common carotid artery injection angiogram after Onyx embolization used to achieve 100% nidal obliteration.

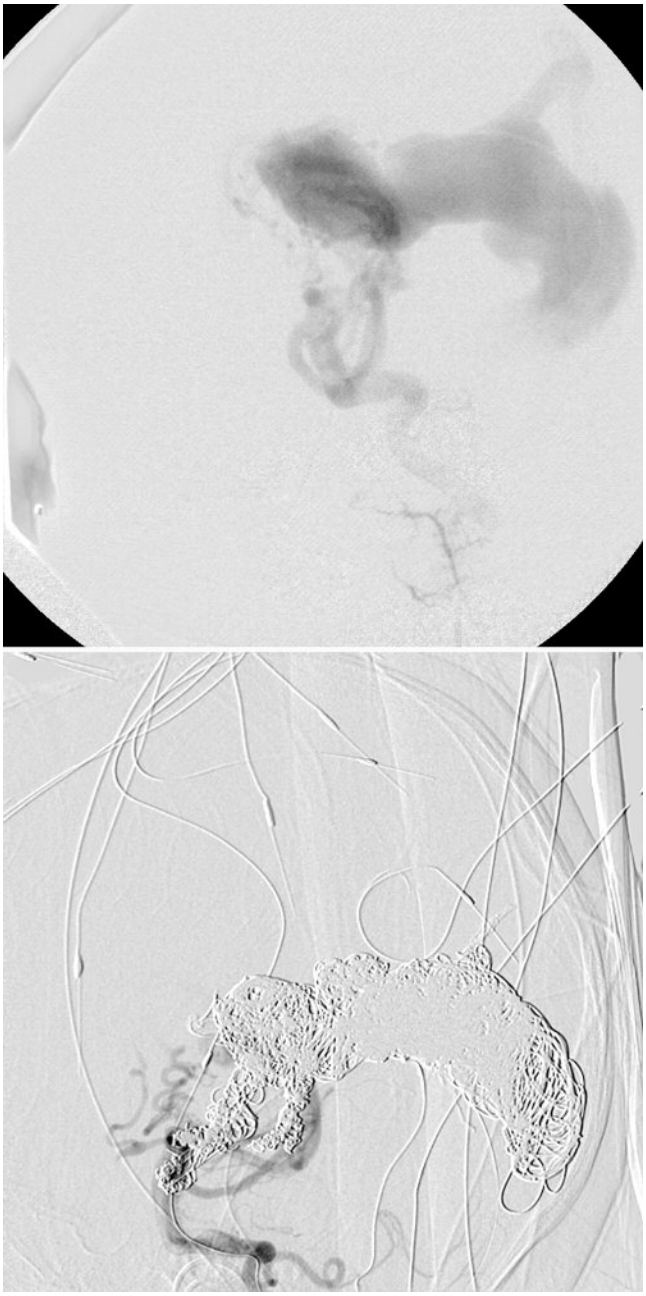

FIG. 3. Case 5. *Upper:* Left VA injection angiogram depicting a VOGM. *Lower:* Left VA injection angiogram after coil and Onyx embolization revealing a complete obliteration of the fistula.

tracting into the vessel lumen. The child suffered no neurological sequelae.

Another patient experienced transient left lower-extremity weakness after embolization of a right frontal A_3 branch. The weakness completely resolved over the ensuing month. Other known complications of liquid embolic agents, such as catheters glued into vessels or pulmonary embolisms, were not encountered. There was also no evidence of contrast-induced nephropathy. Serial serum creatinine levels were monitored daily; at no point did these levels rise > 10% above baseline throughout the treatment period.

There were 2 deaths in this patient series. The day after her fifth endovascular embolization, the patient in Case 5 became hemodynamically unstable with accompanying fixed and dilated pupils. The CT scan revealed a devastating ICH with diffuse subarachnoid hemorrhage and effaced basal cisterns. According to the parent's wishes, life support was withdrawn the following day. The patient in Case 6 also suffered a global ICH with IVH 12 hours after the procedure; treatment was withdrawn that night, and the patient died.

Discussion

Endovascular embolization of vascular malformations remains a reasonable adjunctive treatment modality for complex lesions in preparation for resection or irradiation. When radiosurgery is anticipated, even treatment of small AVMs may be warranted as evidence accumulates regarding the relationship between radiation dose and edema or volume and obliteration rates. Kiran and colleagues[5] reviewed the records of 103 children with AVMs treated using GKS. A significantly higher incidence of radiation edema was noted in patients with AVM volumes > 3 ml. In another review of the records of 40 children with AVMs, Smyth and associates[10] showed that lesions < 3 cm^3 were associated with a 6-fold increased obliteration rate. Embolization may also be considered as the sole treatment for small lesions with a limited number of distinct feeding vessels.

We have reviewed our initial experience with the application of Onyx-18 in a cohort of pediatric patients harboring intracranial vascular malformations. Although follow-up duration was limited, there were no immediate or short-term side effects from the use of Onyx in this group. We attempted to limit the dose of Onyx per treatment session due to the theoretical toxicity of DMSO. Per the manufacturer's recommendations, the maximum DMSO dose should be limited to 600 μg/kg, which is the lowest dose shown to produce systemic toxicity (Table 4). The average dose administered to adults during early trials for US Food and Drug Administration approval was 205 μg/kg (M. Horowitz, personal communication). One must also remember that the children emitted an unpleasant aroma consistent with systemic DMSO administration for ~ 24 hours. The nursing staff and parents should be forewarned of this normal finding.

All procedures were conducted via the femoral arteries and/or veins. Vascular access can often be problematic in neonates, particularly if multiple treatment sessions are necessary. As stated above, when we anticipated the use of a 5 or 6 Fr sheath in newborns, the pediatric surgeons were consulted to obtain femoral artery and venous access, usually via a femoral surgical incision that allowed direct repair of the vessel after decannulation. No sheath was left for > 2 treatment sessions or > 48 hours. The sheath was exchanged under sterile conditions prior to starting the next intervention. Although there were periods of limb mottling and thready distal pulses, there were no instances of a distal pulse lost for > 4 hours, limb ischemia, or lower neuromuscular compromise.

The complications in this patient series included 2 deaths. These cases involved the heroic treatment of infants with imminent cardiac failure secondary to high-output flow through a VOGM or hemispheric AVM. For those patients who survive to obtain treatment, mortality rates approach 50%, even in the most experienced centers.[6] Another child

TABLE 4

Manufacturer's recommendations of DMSO dose to administer in relation to a patient's weight and volume of Onyx

Volume of Onyx (ml)	Patient Weight (lb/kg)	DMSO Dose (μg/kg)
1.0	8/3	367
2.0	8/3	733
3.0	8/3	1100
1.0	25/11	97
5.0	25/11	484
10.0	25/11	968
1.0	50/23	48
5.0	50/23	242
10.0	50/23	484
1.0	75/34	32
5.0	75/34	161
10.0	75/34	323
1.0	100/45	24
5.0	100/45	121
10.0	100/45	242
1.0	125/57	19
5.0	125/57	97
10.0	125/57	194
1.0	150/68	16
5.0	150/68	81
10.0	150/68	161
1.0	175	14
5.0	175	69
10.0	175	138
1.0	200	12
5.0	200	61
10.0	200	121

experienced transient lower-extremity paresis in the expected anatomically correlating location after embolization of a distal ACA feeding vessel. Lidocaine injection did not change the SSEP or EEG recordings. Although the vessel appeared to solely supply the AVM and the microcatheter was abutting the nidus in this patient, the small amount of reflux we typically use to cap the catheter tip must have plugged vital microvasculature.

Conclusions

Pediatric vascular malformations often require multimodal treatment. Endovascular options continue to improve and will likely be incorporated into the treatment paradigm used by most physicians. Onyx should be considered a reasonable alternative embolization agent for use in this group. Safety and efficacy remain a primary concern, and thus continued follow-up will be necessary to rule out the possibility of Onyx toxicity or recanalization.

Disclosure

Michael Horowitz, M.D., is a consultant for ev3, Inc., the manufacturer of Onyx-18.

References

1. Bristol RE, Albuquerque FC, Spetzler RF, Rekate HL, McDougall CG, Zabramski JM: Surgical management of arteriovenous malformations in children. **J Neurosurg 105 (2 Suppl):** 88–93, 2006
2. Celli P, Ferrante L, Palma L, Cavedon G: Cerebral arteriovenous malformations in children. Clinical features and outcome of treatment in children and in adults. **Surg Neurol 22:**43–49, 1984
3. Germanwala AV, Vora NA, Thomas AJ, Jovin T, Gologorsky Y, Horowitz MB: Ethylenevinylalcohol copolymer (Onyx-18) used in endovascular treatment of vein of Galen malformation. **Childs Nerv Syst 24:**135–138, 2008
4. Gerosa MA, Cappellotto P, Licata C, Iraci G, Pardatscher K, Fiore DL: Cerebral arteriovenous malformations in children (56 cases). **Childs Brain 8:**356–371, 1981
5. Kiran NA, Kale SS, Vaishya S, Kasliwal MK, Gupta A, Sharma MS, et al: Gamma Knife surgery for intracranial arteriovenous malformations in children: a retrospective study in 103 patients. **J Neurosurg 107 (6 Suppl):**479–484, 2007
6. Lasjaunias PL, Chng SM, Sachet M, Alvarez H, Rodesch G, Garcia-Monaco R: The management of vein of Galen aneurysmal malformations. **Neurosurgery 59 (5 Suppl 3):**S184–194; discussion S3–13, 2006
7. Mori K, Murata T, Hashimoto N, Handa, H: Clinical analysis of arteriovenous malformations in children. **Childs Brain 6:**13–25, 1980
8. Sanchez-Mejia RO, Chennupati SK, Gupta N, Fullertron H, Young WL, Lawton MT: Superior outcomes in children compared with adults after microsurgical resection of brain arteriovenous malformations. **J Neurosurg 105 (2 Suppl):**82–87, 2006
9. Smith ER, Butler WE, Ogilvy CS: Surgical approaches to vascular anomalies of the child's brain. **Curr Opin Neurol 15:**165–171, 2002
10. Smyth MD, Sneed PK, Ciricillo SF, Edwards MS, Wara WM, Larson DA: Stereotactic radiosurgery for pediatric intracranial arteriovenous malformations: the University of California at San Francisco experience. **J Neurosurg 97:**48–55, 2002
11. Wilkins RH: Natural history of intracranial vascular malformations: a review. **Neurosurgery 16:**421–430, 1985

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