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ORIGINAL RESEARCH

Preoperative Embolization of Cerebral Arteriovenous Malformations with Onyx

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BACKGROUND AND PURPOSE: Preoperative embolization facilitates the surgical management of complex cerebral arteriovenous malformations (cAVMs). This analysis aims to investigate the risks for preoperative cAVM embolization with Onyx.

MATERIALS AND METHODS: We retrospectively analyzed clinical data of all patients who underwent embolization with Onyx as a preoperative treatment of cAVMs at our institution since 2005 (US Food and Drug Administration [FDA] approval). Patients with arteriovenous fistulas were excluded. A total of 107 patients were treated for cAVMs during the study period. Of those patients, 41 underwent cAVM embolizations with Onyx in 82 procedures.

RESULTS: After the embolization, the cAVM diameter was reduced from 3.71 ± 1.55 cm to 3.06 ± 1.89 cm ($P < .05$). Median volume reduction was 75%. Complete occlusion with embolization alone was achieved in 4 (10%) cAVMs. The recurrence rate for completely occluded cAVMs was 50% (2 patients). A total of 71% of the 41 patients treated with Onyx underwent surgery, and 15% underwent radiosurgery. There were 9% who have not yet received definitive treatment of their residual cAVMs. A new permanent neurologic deficit occurred in 5 patients (6.1% per procedure or 12.2% per patient).

CONCLUSIONS: A considerable risk for a permanent neurologic deficit remains for cAVM embolization with Onyx. The risk has to be carefully weighted against the benefit of volume reduction in the treatment of cAVMs.

Preoperative embolization of cerebral arteriovenous malformations (cAVMs) has been used successfully for many decades to facilitate surgical resection.[1-6] However, complications secondary to the embolization itself continue to limit its use. Onyx (ev3, Irvine, Calif) is a newer and promising embolic agent, which has become widely available in North America only after its approval by the Food and Drug Administration (FDA) in July 2005. Our study analyzes the risks and success associated with Onyx embolization of cAVMs at the University of Texas Southwestern Medical Center in Dallas.

Materials and Methods

Patient Selection

Between January 2005 and January 2008, a total of 107 patients were treated with various modalities for cAVMs at our institution. Patients with the diagnosis of a cerebral arteriovenous fistula are not included. Open surgical resection as definitive treatment was the most common treatment choice (65 patients [61%]). If preoperative imaging suggested a good possibility of early surgical control of feeding vessels, and/or the location and size of the AVM was favorable, surgical resection was performed without preoperative embolization in 15 patients (14%). In more complex AVMs with higher Spetzler-Martin grades (SMGs), preoperative embolization was used in 47 patients (44%). In 3 patients (3%), a small residual AVM after surgical resection was treated with the gamma knife. Small AVMs, particularly in deeper locations, were primarily treated with the gamma knife in 26 patients (24%). Some smaller AVMs with fistulous components were occasionally treated with embolization only (7 patients [7%]) or in combination with the gamma knife (9 patients [8%]).

After its approval by the FDA, Onyx quickly became the primary embolic material for the treatment of cAVMs because of its ease in handling and superior control, with the exception of fistulous components, where we often prefer *n*-butyl cyanoacrylate (*n*-BCA). As a consequence, 41 of the 107 patients underwent embolization with Onyx alone or in conjunction with other materials in a total of 82 separate stages. We identified patients retrospectively by reviewing hospital charts. Data on patient demographics, AVM characteristics, and endovascular procedures before surgery were analyzed. Approval of this study was granted by the Institutional Review Board following the standard protocol for retrospective reviews of patient charts and electronic records in accordance with the Health Insurance Portability and Accountability Act.

Patient and AVM Characteristics

The patients ($n = 41$) were relatively young with a median age of 41 years (age range, 12–62 years). The female sex was predominant (male-to-female ratio, 15:26). Nineteen patients (46%) presented with an intracerebral hemorrhage caused by the malformation. The remaining patients presented with seizures and/or headaches. The malformations were located supratentorially in 88% (36 patients). In 19 patients (46%), the lesion was left sided; the lesion was located in the midline in 2 patients (5%). Eloquent brain[5] was involved in 31 patients (77%). Mean maximal diameter of the cAVM nidus was 3.71 ± 1.55 cm. The measurements of the maximum AVM diameter were based on diagnostic imaging including angiograms, MR imaging, and CT scans. We measured the postembolization maximal cAVM diameter using the relative maximal diameter change as observed by comparison of preembolization and postembolization arteriograms and absolute measurements of the maximal preembolization diameter by CT or MR imaging. The average volume reduction of the cAVM was analyzed in categories according to Weber et al[7] in reference to the postembolization angiogram. Deep venous drainage was present in 22 patients. Median preoperative Spetzler-Martin

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Table 1: Demographics and arteriovenous malformation specifics in 36 patients who underwent preoperative embolization with Onyx

Characteristics	Before Embolization	After Embolization	*P* value
Age (y); median (range)	41 (12–62)		
Sex, no. pts (%)			
Male	15 (37)		
Female	26 (63)		
Presentation, no. pts (%)			
Hemorrhage	19 (46)		
Other (seizure/headache)	22 (54)		
AVM specifics			
Side, no. pts (%)			
Left	19 (46)		
Right	20 (49)		
Midline	2 (5)		
Location, no. pts (%)			
Supratentorial	36 (88)		
Infratentorial	5 (12)		
Eloquence*, no. pts (%)	31 (77)	18 (50)	1.00
Size† (cm), mean ± SD	3.70 ± 1.55	3.06 ± 1.89	< .05
Deep venous drainage, no. pts (%)	20 (54)	18 (50)	.16
No. (%) pts with reduced SMG		10 (24)	< .05

Note:—AVM indicates arteriovenous malformation; no. pts, number of patients; SMG, Spetzler-Martin grade.
*Eloquent regions included deep structures such as the hypothalamus, thalamus, brainstem, and cerebellar peduncles as well as cortical regions such as the sensorimotor, language, and primary visual areas.
†Maximal diameter of the perfused nidus.

grade (SMG) was III (range, I–V). Three patients presented with an SMG I cAVM, 14 patients with an SMG II cAVM, 15 patients with an SMG III cAVM, 7 patients with an SMG IV cAVM, and 3 patients harbored an SMG V cAVM. Demographics and AVM characteristics are summarized in Table 1.

Interventions

In 41 patients, a total of 82 separate embolization procedures were performed. Onyx was used in all 82 embolizations, either as the sole agent (62%) or in conjunction with other materials (38%) such as polyvinyl alcohol particles, detachable coils, and *n*-BCA. On the basis of preembolization arteriography information, the goal of the embolization was "cure" in only a few cases. Instead, the treatment intent was to reduce the flow in the cAVM by occlusion of feeding arteries while preserving the draining veins to reduce the risk and increase the success of a subsequent treatment, typically surgery. A median of 2 embolization procedures was performed per patient (range, 1–5). Most the patients (29 patients [71%]) then underwent surgical resection of the cAVM. Six patients (15%) were treated with stereotactic radiosurgery. Four patients (8%) did not yet receive additional treatment.

Statistics

We performed the statistical analysis using the statistics program SPSS 15.0 (SPSS, Chicago, Ill). Patient demographics, cAVM characteristics, endovascular procedures, results, and complications were described for all patients. Frequency and percentage values of categoric variables as well as median and range of continuous variables were determined. We compared data using the paired *t* test, Wilcoxon test, and χ^2 test. A probability value of less than 5% was considered significant.

Table 2: Complications of preoperative embolization of cerebral arteriovenous malformations with Onyx

Complication	No. of Procedures (%)	No. of Patients (%)
Death	0 (0)	0 (0)
Permanent neurological deficit (> 6 mo)	5 (6.1)	5 (12.2)
Transient neurological deficit (< 48 h)	2 (2.4)	2 (4.8)
Technical complication without deficit	16 (19.5)	15 (36.6)
Asymptomatic small infarction	3 (3.7)	3 (7.3)
Perforation	9 (11.0)	9 (22.0)
Catheter entrapment	4 (4.9)	4 (9.8)
No complication	59 (72.0)	19 (46.3)
Total	82 (100)	41 (100)

Results

Embolization with Onyx alone or in conjunction with other embolic materials reduced the size of the perfused cAVM by 75% (median; range, 8% to 100%). In 7 patients, the cAVM was reduced by less than 50%. Volume reduction was 50% to 59% in 4 patients, 60% to 69% in 2 patients, and 70% to 79% in 9 patients. The volume reduction reached 80% to 89% in 7 patients and 90% to 99% in 8 patients. The maximal cAVM diameter was reduced from 3.71 ± 1.55 cm before embolization to 3.06 ± 1.89 cm postembolization ($P < .05$; paired *t* test). Complete occlusion was achieved in 4 patients (10%). The cAVM partly recanalized in 2 of those patients (50%), who then underwent surgical resection. The presence of deep venous drainages was not significantly affected by the embolization. Permanent complications occurred in 5 patients (12.2% per patient) or in 5 of 82 procedures (6.1% per procedure). The first patient experienced a small but bithalamic infarct with a mild cognitive deficit and difficulties with calculations after the initial embolization of a pineal region cAVM. Two patients with cerebellar AVMs experienced mild ataxia and dysmetria after the initial embolization. CT scan revealed a new cerebellar hypoattenuation. Another patient experienced a new persistent hemiparesis after a fourth embolization of a large right frontal cAVM. The embolization was complicated by a perforation with a small intraparenchymal hemorrhage in the posterior frontal lobe.

A 59-year-old woman underwent partial Onyx embolization of a large, left-sided frontotemporoparietal cAVM with the intent to treat an intranidal feeding aneurysm, presumably the cause of the intraparenchymal hemorrhage. Although the feeding aneurysm was completely occluded, the procedure was complicated by a new aphasia and hemiparesis. Two patients experienced transient deficits that resolved within 48 hours after the procedure. Asymptomatic technical complications occurred in 16 patients (44%). An asymptomatic small vessel perforation (contrast extravasation or hemorrhage on the postprocedure CT) was observed in 9 patients. A new lacunar infarct without neurologic deficit was documented on postprocedure MR imaging or CT in 3 patients. The microcatheter was retained in situ in 4 procedures and was then removed during surgery without neurologic consequences. The effects of the preoperative cAVM embolization with Onyx are summarized in Table 1, and the complications are summarized in Table 2.

Table 3: Literature reporting on preoperative embolization of cerebral arteriovenous malformations with Onyx

			Surgery	Radiosurgery	"Cured"*	Mean	Per Procedure		Per Patient	
1st Author	Year	N†	No. Pts (%)	No. Pts (%)	No. Pts (%)	Size (cm)	Morb. (%)	Mort. (%)	Morb. (%)	Mort. (%)
Jahan	2001	23	12 (52)	11 (48)	0 (0)	3.6	3.0	0	4	0
Hamada	2002	57	54 (95)	3 (5)	0 (0)	–	3.4	0	5.3	0
van Rooij	2007	44	10 (23)	20 (45)	7 (16)	3.9	3.8	1.9	4.6	2.3
Weber	2007	47	47 (100)	0 (0)	0 (0)	3.4	12	0	28	0
Weber	2007	93	56 (60)	13 (14)	17 (18)	–	5	0	12	0
Mounayer	2007	94	7 (7)	20 (21)	26 (28)	–	3.8	1.4	8.5	3.2
Hauck	Current	41	29 (71)	6 (15)	2 (5)	3.7	6.1	0	12	0

Note:—N indicates total number of patients; Morb., morbidity; Mort., mortality.
*Complete occlusion without recurrence.
†Only patients treated with Onyx are included.

Discussion

Our study demonstrates that a considerable risk remains with the application of Onyx for the embolization of cAVMs. Advantageous is the "ease in handling," which allows a controlled and significant size and flow reduction of cAVMs to the degree of complete occlusion. After significant size reduction, surgery or radiosurgery may be used to treat the malformation (Table 3). It is important to acknowledge that many of the complications associated with Onyx embolizations are not primarily related to Onyx as the embolic agent itself, but rather "procedure" related. This includes vessel perforations with microguidewires or microcatheters. Furthermore, sometimes it is difficult to decide if an embolic complication was indeed the result of Onyx injection or possibly from injection of a second embolic agent. This particularly applies for procedures done with the patient under general anesthesia, in which occasionally an immediate neurologic change might not be recognized, despite electrophysiologic monitoring.

Morbidity and Mortality Rates after Preoperative Embolization with Onyx

Various studies have investigated the morbidity and mortality rates associated with preoperative cAVM embolization before the introduction of Onyx.[1,4,8-12] At that time, the morbidity and mortality rates with preoperative embolization ranged from 3.8% and 1.0% to 28% and 3.7%, respectively. Similar to other investigators, with use of Onyx, our results of a permanent morbidity rate of 12.2% and no deaths after preoperative Onyx embolization are within that range (Table 3). Ann H. Costello and Judy Chen presented clinical data regarding Onyx embolization collected from 17 centers (including Dallas) at the Neurologic Devices Advisory Panel Meeting on August 5, 2003 (http://www.fda.gov/OHRMS/DOCKETS/AC/03/slides/3975s1–02-fda.ppt). In this unpublished study, 51 patients were treated with Onyx embolizations of cAVMs. The observed stroke rate was 4.3%. The mortality rate documented in this analysis was 4.3% as well. The only experimental study from a single North American center was published by Jahan et al[13] in 2001. They found a permanent morbidity rate of 4% in 23 patients treated. In their series, there were no deaths. Other similar results are documented by Mounayer et al[13] in 2007 in a series of 94 patients. They described an overall morbidity rate of 8.5% per patient and a mortality rate of 3.2%. Hamada et al[15] documented a morbidity rate of 5.3% in a series of 57 patients, with no deaths occurring. van Rooij et al[16] experienced a morbidity rate of 4.6% per patient and a mortality of 2.3%. Two additional studies with contradictory results have been published by Weber et al.[7,17] In the first study, Weber et al examined the morbidity rate in 93 patients treated with Onyx for cAVMs, which apparently was 12% per patient, with no deaths. In a second consecutive study with 47 patients, they documented an even higher morbidity rate of 28%. The results of the second study seem less representative because the observed high morbidity rate of 28% is not only in contrast to the authors' own experience but also the other published and unpublished data presented above. In summary, the morbidity and mortality rates of preoperative Onyx embolization of cAVMs may be similar to the morbidity and mortality rates of embolization before the introduction of Onyx (overall range, 10% per patient [5% per procedure]).

Volume Reduction

Volume reduction is difficult to measure precisely. Unlike selective angiography, CT, MR imaging, or CT angiography allows depiction of the entire nidus with injection of all feeding vessels simultaneously. Furthermore, with CT, CT angiography, or MR imaging, no calibration is required to determine precise dimensions. However, the resolution of the angio-architecture details is inferior compared with standard angiography. Finally, measurements of a diffuse nidus may vary considerably depending on the investigator. Possibly because of these limitations, some studies with Onyx did not present precise measurements regarding volume reduction.[14-16] We measured the volume reduction of the cAVM postembolization in categories according to Weber et al[7,17] They calculated the AVM volume on the basis of standard arteriography with the formula suggested by Pasqualin et al[18]: $V = \frac{1}{2} \times w \times h \times l$ [V ~ volume, w ~ width, h ~ height, l ~ length]. Volume reduction was then determined on the basis of postembolization angiography. Weber et al[7,17] achieved an 80% to 84% volume reduction with a considerably high morbidity rate. In their presentation, Ann H. Costello and Judy Chen quote a volume reduction of $\geq$ 50% in 97.6% (41/42) of the patients after embolization with Onyx compared with 84.3% (43/51) with *n*-BCA (unpublished data). Jahan et al[13] reported an average volume reduction of 63% with a low morbidity rate and no deaths. On the basis of these reports, a volume reduction of 50% to 65% may be a desirable target with acceptable associated morbidity and mortality rates. The addition of Onyx to the endovascular armamentarium seems to improve occlusion rates.

"Cure"

Complete occlusion of a cAVM without recurrence on follow-up angiography may represent a "cure."[14,19] A prerequisite for "cure" is the complete occlusion of the draining veins. However, the primary principle of "preoperative" embolization is the preservation of the draining veins because the risk for hemorrhage increases with partial embolization and obstructed venous outflow.[13-16] As a consequence, a "cure" may occur either as the result of the planned sacrifice of the venous outflow in small cAVMs or is accidental with increased risk for the patient. With 2 competing goals, sacrifice of the draining vein(s) for cure versus preservation of the venous outflow with size reduction in preparation for additional treatment, the reported "cure" rates between different centers varies considerably (from 0% to 28%).[7,13-17,19] At our institution, "cure" is typically not the goal of the preoperative embolization. Complete occlusion of the cAVM was achieved in 10%. Half of these patients were found to have recurrence of cAVM during follow-up and then underwent surgery. Therefore, our "cure" rate was only 5%. Mounayer et al[14] as well as Katsaridis et al[19] achieved the highest percentage of "cure," both in 28%. Mounayer et al[14] report a morbidity rate of 8.5% and a mortality rate of 3.2%, respectively. Katsaridis et al[19] document a similar morbidity rate with 8% and a mortality rate of 3%. It is noteworthy that a higher cure rate as a result of more aggressive embolization may be associated with a higher mortality rate. However, no final conclusions can be drawn at this point. Additional experience with Onyx and long-term follow-up of "cured" cAVMs is required to determine the value of complete cAVM occlusion after embolization as stand-alone treatment.

Definitive Treatment

Surgical resection of the cAVM with or without preoperative embolization is the most definitive treatment of cAVMs with total removal of the lesion.[1,4-6,8-12] Accordingly, surgery was performed as definitive treatment after preoperative Onyx embolization in more than 50% of the study patients in 5 of 7 centers.[7,13-17] However, with improving obliteration rates with Onyx and/or *n*-BCA, radiosurgery is more frequently used as an alternative "definitive" treatment for small residual cAVMs.[13,14,16] Jahan et al[13] treated 48% of their patients with radiosurgery after embolization. At the time of the report, they had limited follow-up and documented complete occlusion after 20 months in only 1 patient. van Rooij et al[16] treated 45% of their patients with radiosurgery after Onyx embolization. There were 5 of 20 patients who had confirmed cAVM occlusion on follow-up arteriograms; the other 15 patients were still pending follow-up. Mounayer et al[14] treated 20 patients with radiosurgery as well but did not quote any occlusion rates. Our patients treated with radiosurgery are awaiting follow-up as well. In summary, embolization with Onyx followed by radiosurgery is a promising concept. More clinical data will be necessary for a more definitive analysis. Surgical resection remains the reference standard for residual cAVM after embolization.

Conclusions

On the basis of our results, a considerable risk (6.1% per procedure or 12.2% per patient) for a permanent neurologic deficit remains for cAVM embolization with Onyx. The risk has to be carefully weighted against the benefit of volume reduction in the treatment of cAVMs.

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