Embolization of traumatic and non-traumatic peripheral vascular lesions with Onyx

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Abstract: Purpose: The aim of our study is to verify the feasibility and the efficacy of Onyx as embolization agent in the treatment of traumatic and non-traumatic peripheral vascular lesions. Materials and Methods: In the period between September 2006 and March 2012, we treated with Onyx 26 patients (14 males/12 females; age range, 18–85 years old; mean age, 65 years old), 11 of which with traumatic peripheral vascular lesions and 15 with non-traumatic vascular lesions (9 neoplastic hemorrhagic lesions, 3 arteriovenous malformations (AVMs) and 3 aneurysms). Follow-up controls were performed with clinical examination and by multidetector computed tomography (MDCT) imaging 1, 6, and 12 months after the procedure. Results: All peripheral vascular lesions were embolized with Onyx; 3 patients with aneurysms were treated with Onyx associated with endovascular coils. Four elective and 22 emergency embolization procedures were performed. In all patients, we obtained cessation of bleeding and the complete and permanent embolization of all vascular lesions. Conclusions: Onyx is an effective and safe embolization agent for peripheral vascular lesions.

Keywords: embolization, Onyx, peripheral vascular lesions, safety, aneurysms

Introduction

Onyx is an elastic polymer comprised of ethylene-vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO) with micronized tantalum powder. The Food and Drug Administration (FDA) approved Onyx in 2005 for the treatment of arteriovenous malformations (AVMs). It is classified as a liquid, non-adhesive, non-absorbable, permanent embolic agent that can be used off-label for small and large vessels [1–3].

The new liquid embolic agent Onyx (ethylene-vinyl alcohol copolymer) has been reported to be effective in the treatment of cerebral, spinal, and neck arteriovenous malformations and aneurysms. It can also be used in those cases where previous treatment has failed to occlude the aneurysm, like giant aneurysms and wide neck aneurysms [1–3]. While Onyx is currently only approved for the treatment of intracranial AVM, it is becoming more popular among abdominal interventional radiologists for the treatment of peripheral AVMs and abdominal aorta stent graft-related endoleaks. In fact, it is relatively simple to use as long the correct technical details and recommendations are followed. This review seeks to describe some off-label peripheral applications for which this promising embolic agent may be used.

There are only few reports concerning peripheral treatment with Onyx [4–20]. We present our experience in the treatment of traumatic and non-traumatic peripheral vascular lesion with Onyx.

Materials and Methods

Patients

In the period between September 2006 and March 2012, we have treated with Onyx embolization agent...
(manufactured by Ev3 company – Plymouth, MN, USA) 26 patients (14 males/12 females – age range of 18–85 years old with mean age of 65 years old). Fifteen patients had traumatic peripheral vascular lesions and 11 patients had non-traumatic vascular lesions.

All peripheral vascular lesions were embolized with Onyx. A combination of Onyx and vascular coils was used when the lesion was very large and/or with a high flow.

**Treatment**

All patients underwent contrast-enhanced abdominal CT before embolization and underwent follow-up CT 1–3 months after the procedure. The contrast medium Ultravist 370©, Bayer-Schering Pharma, dose: 100 mL, flow: 3 mL/s with an early arterial and a delayed acquisition after 5 min. Informed consent was obtained from all patients. The time of the whole procedure for each patient was calculated from the entrance of the patient in the angiographic room until manual compression of the femoral artery for hemostasis.

All patients underwent diagnostic angiography via the femoral artery route under local anesthesia just before the embolization procedures. Catheterization was performed via a transfemoral approach with use of standard coaxial techniques. A dimethyl sulfoxide (DMSO)-compatible microcatheter–microwire combination (Rebar microwire catheter and Silver Speed microguide wire; Micro Therapeutics) was used to perform selective catheterization of the feeding arteries.

Onyx is a non-adhesive liquid embolic agent and is comprised of EVOH (ethylene-vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide), and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. The Onyx liquid embolic system (LES) consists of a 1.5-mL vial of Onyx, a 1.5-mL vial of DMSO, and three 1 mL Onyx delivery syringes.

Onyx is available in two product formulations, Onyx 18 (6% EVOH) and Onyx 34 (8% EVOH).

Onyx 18 will travel more distally and penetrate deeper into the nidus due to its lower viscosity compared to Onyx 34. Final solidification occurs within 5 min for both product formulations.

If the mixture comes into contact with aqueous solution, precipitation of the copolymer is initiated by diffusion of DMSO. This process begins on the surface while the core is still liquid, resulting in a soft, non-adherent mass, which does not adhere to the endothelium and to the top of the catheter. Therefore, Onyx has a lava-like flow consistency within blood vessels and does not fragment during injection. Onyx 18 is recommended for embolization of any plexiform nidus and Onyx 34 for embolization of large arteriovenous shunts (4–8).

The technique of embolization with Onyx was performed always in a systematic manner: a guiding catheter of 4 or 5 F was placed in the main vessel. A DMSO-compatible microcatheter (UltraFlow 1.5F, ev3) with aid of a 0.008-inch guidewire (Mirage, ev3) was navigated until the site of the embolization (the nidus of the AVM, the lumen of the aneurysm, the feeder of the AVM, and the hemorrhagic site of a traumatic or of a neoplastic lesion).

Once the microcatheter tip was in the desired position, the injection of Onyx was carried out as follows:

1. The microcatheter was flushed with 5 mL of normal saline.
2. 0.25 mL of DMSO was injected into the microcatheter to fill the dead space.
3. Onyx was aspirated into a 1-mL syringe, and 0.25 mL of this amount was injected slowly for 40 s to fill the microcatheter and replace the DMSO in the dead space.
4. Slow injection of Onyx was then continued under fluoroscopy. Pacing of the injection should be very slow to avoid reflux.

Onyx embolization required flushing of the microcatheter with saline solution first and then with 0.4 mL DMSO to fill the microcatheter’s “dead space.” After that, the Onyx was aspirated into a 1-mL syringe, and 0.25 mL of this amount was injected slowly for 40 s to fill the microcatheter and replace the DMSO in the dead space. Finally, Onyx was injected at a volume and rate low enough to prevent reflux of the agent around the microcatheter under fluoroscopic guidance.

The injection was maintained and repeated until the distal end of the feeding arteries and the abnormal malformed vascular communications were completely occluded. Because the estimation of injection volume of Onyx is very difficult, especially in high-flow lesions, as a result of the complex structure of the abnormal vascular communications, the volume and rate of Onyx to be injected were determined only by fluoroscopic monitoring during injection. We did not perform an occlusion injection test of contrast material to determine the volume of Onyx before the injection.

The reliable criteria used to determine the volume and rate of injection were based on the penetration of the Onyx to the abnormal vascular communications and avoidance of reflux.

Because Onyx is not adhesive, multiple injections could be performed. In multiple injections, we used the same catheter to catheterize another feeding artery, provided that the microcatheter had been withdrawn first and then flushed with DMSO and physiologic saline solution again before each catheterization process.

Onyx is supplied in ready-to-use vials. Each vial contains ethylene-vinyl alcohol copolymer, DMSO, and tantalum powder for radiopacity. Ethylene-vinyl alco-
hol copolymer is formed from 48 mol/L ethylene and 52 mol/L vinyl alcohols. The polymer is dissolved in DMSO and prepared in different concentrations. Onyx 18.0% contains 18.0% copolymer and 92% DMSO, Onyx 20% contains 22% copolymer and 78% DMSO, and Onyx 32% contains 32% copolymer and 68% DM-
SO. The lower the concentration of the copolymer, the less viscous the agent and the more distal penetration can be achieved. Systemic anticoagulation was achieved during the procedures with intraarterial heparin in 5000-IU bolus injections. Prior to use, the product must be maintained between 19° and 24 °C and shaken on a mixer for at least 20 min. When the Onyx compatible microcatheter is correctly placed, it must be flushed with saline. After that, the dead space of the catheter is filled with solvent DMSO, and the luer hub is overfilled before connecting the Onyx syringe in the microcatheter hub. After that, Onyx is first slowly injected to displace the DMSO, and then the injection is continued at a slow steady rate (recommendation, 0.16 mL/min) and under adequate fluoroscopic view to avoid occlusion of non-
target vessels.

The injection can be continued with additional sy-
ringes, when necessary. After completion of the injec-
tion, the catheter can be removed by pulling gently dur-
ing slight aspiration.

Postembolization angiography confirmed successful occlusion of the artery and the patency of the branches of the others arteries.

Results
All vascular procedures had zero mortality and morbid-
ity. The total procedure time was from 20 min to 124
min (mean time, 70 min).

In Table I, we show the all features of these patients (gender, age, site, and type of lesion, type of treatment, and complications). Traumatic vascular lesions were 8/15 in the pelvis, 3/15 in the upper abdomen, 1/15

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Type of pathology</th>
<th>Onyx concentration and coil</th>
<th>Complications</th>
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<tr>
<td>1</td>
<td>22 males</td>
<td>Sixth and seventh segment hepatic artery traumatic lesion</td>
<td>Onyx 18</td>
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<td>2</td>
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<td>Iatrogenic fistula of the uterus</td>
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<td>Diverticulum sigmoid colon</td>
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<td>4</td>
<td>80 females</td>
<td>Cecal avm</td>
<td>Onyx 18</td>
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<td>5</td>
<td>52 females</td>
<td>Uterine neoplasm</td>
<td>Onyx 18</td>
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<td>Uterine neoplasm</td>
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<td>Right gluteal artery traumatic lesion</td>
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<td>25 males</td>
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in thorax, and 3/15 in the limbs. Non-traumatic lesions were 3/11 in the upper abdomen, 1/11 in the limb, and 7/11 in the pelvis.

We show in the figures the treatment of a 22-year-old patient with a traumatic hepatic lesion (Fig. 1a, b), the treatment of splenic artery aneurysm treated with coils and Onyx 32 (Fig. 2a, b), the embolization of middle and inferior hemorrhoidal arteries (Fig. 3a, b), and the treatment of cecal AVM (Fig. 4a–c) and of an iatrogenic fistula of right uterine artery (Fig. 5a, b).

A few aneurysms were treated. These included two splenic arterial aneurysms – patients 17 and 18 in Table I, and one right internal iliac artery aneurysm – patient 19.

This aneurysm was larger than 3 cm in maximum diameter. It was treated by first placing detachable coils (Axium EV3) followed by injection of Onyx to complete the embolization.

The total amount of Onyx injected was between 1.23 mL and 2.56 mL.

All procedures succeeded in complete embolization of vascular lesion as verified from the angiographic control and on clinical follow-up of patients with traumatic lesions.

No major complication resulted, apart from a moderate degree of pain in 1 patient, which was well-controlled by local anesthetic and analgesic drugs.
Three patients with aneurysm tolerated the “mixed” procedure of coils and Onyx 32.

At the control done after 6 months by the angiographic procedure, all patients showed a complete embolization of the vascular lesions; also patients treated for an AVM of the cecum (patient 4) and of the left lower limb (patient 11) showed a complete embolization. The latest underwent a complete resection of the caecum after 14 months. Patient with AVMs of lower limb showed complete embolization of the AVMS treated, but had some pain and flush of the limb. Patients treated for traumatic vascular lesions and hemorrhage showed a sudden improvement of clinical conditions and a complete embolization at the angiographic control after the embolization.

Few patients showed fever in the 24 h after the embolization.

Fig. 3. (a) 82-year-old female patient with rectal hemorrhage. Selective angiography of left iliac internal artery shows (arrow) contrast medium blush from middle and inferior hemorrhoidal artery; (b) Complete embolization of middle and inferior hemorrhoidal artery with no blush evident at the angiography.

Fig. 4. (a) 78-year-old female patient with an important melena caused by a cecal AVM. At the angiography we observe a large area of contrast medium blush with a arterial feeder (black arrow) and a large single draining vein (white arrow); (b) Progressive embolization of the AVM.
All concentrations of Onyx were used: 18 LD (6% EVOH + 94% DMSO) was used for small vessels with low flow in 21 patients, 20 LD (6.5% EVOH + 93.5% DMSO) was used for small medium vessels with medium/high flow in 3 patients, and 34 LD (8% EVOH + 92% DMSO) was used for medium/large vessel with high flow and for aneurysms in 3 patients.

**Discussion**

The application of EVOH in the endovascular treatment of intracranial AVMs was first described by Taki et al. [9] and Terada et al. [10] in the early 1990s. Since that time, Onyx has been used for treatment of cerebral aneurysms and cerebral AVMs. However, few studies have examined its use in other organs [8, 9]. It was used for treatment of large intracranial aneurysms [5]; few cases of extracranial vascular lesions were treated with Onyx including treatment of type II endoleaks during EVAR (to embolize vessels that were feeding the aneurysm), for renal and celiac-mesenteric arterial aneurysms after the placing of protective balloons [7, 8], pelvic arteriovenous fistulas [3–12], and portal vascular anomalies [10].

Onyx 32 is the product formulation with higher viscosity, and it was used for large aneurysms or for high-flow aneurysm; coils were placed first to reduce the aneurysmal flow followed by injection of Onyx 32 to complete the embolization.

In the case of slow-flow vascular lesions and with arteries with a caliber varying from 2 to 4 mm, we used Onyx 18 and 20 with EVOH concentrations of 6% and 6.5%, respectively. With its relatively lower viscosity, it has the capacity of gradual slowing down of the blood flow through the lesion and has the capability of blocking numerous small feeding arteries until the nidus becomes embolized.

We think that Onyx is the ideal embolic agent for treatment of AVMs. The capacity of being not adherent makes Onyx more safe and handy compared with cyanoacrylates, which are rapidly polymerizing agents, adhesive to the vessel walls and the surrounding tissue.

Their toxicity and the strong inflammatory reactions associated with them can be ascribed to the degradation products of the polymer, which include formaldehyde and alkyl cyanoacetate [12, 13]. In comparison, when the inflammatory reaction caused by Onyx was evaluated on histologic specimens on humans, the inflammatory reactions of the vessel wall were less pronounced and were located mainly intravasally, while no reaction of the
surrounding interstitium, such as migration of lymphocytes into perivascular areas, was seen [13].

Microcatheter removal caused no complication and resulted in a safer and more effective treatment than the use of other adhesive embolic agents. The relative short time of preparation of Onyx and of the entire procedure indicates that Onyx is suitable for emergency department use. Our experience of treatment of several patients with traumatic vascular lesions distributed throughout the body is very effective. It is also an ideal agent for large vascular lesions in neoplasms with huge hemorrhagic potential.

The radiopacity of the product was optimal to control the entire procedure without any complications. From the studies of Duffner et al. [13], Onyx caused a smaller area of extravascular inflammatory tissue compared with cyanoacrylates, resulting in a more tolerable experience for patients. Since DMSO could cause vasculitic phenomena [14, 15], a slow and very careful injection pace (2–4 mL/min) is essential. For this reason probably, we did not have any cause of vasospasm in our experience which is different from some other authors [16].

We have used Onyx for embolization of different vascular lesions (malformation, traumatic, neoplastic, iatrogenic). For us, it remains the first choice product for the treatment of AVMs in any part of the body. It can be used alone or in association with other embolic agents for treatment of pathologies that cause hemorrhagic lesion.

Onyx seemed the most suitable agent in our group of patients mainly because it could be injected through the smallest most flexible catheters, which could be placed most distally within the lesions position, ideally at the point of the fistula, effecting a complete control of bleeding. Coils and catheters compatible with particulate agents may not go as far distally. Deposition of the embolic material within the point of lesions was essential for cure of the lesion in one treatment session.

Another reason of its effectiveness is that Onyx is a biocompatible polymer containing ethylene-vinyl alcohol dissolved in dimethyl sulfoxide (DMSO). It is characterized by a different solidification process consisting of a copolymer precipitation. As results from previous reports [17–19] unlike isobutyl-2-cyanoacrylate (IBCA) and n-butyl-2-cyanoacrylate (NBCA) polymerization, which is triggered by contact with ionic solutions such as blood or saline, Onyx presents a liquid form when injected and a solid form when in contact with blood through precipitation after the dimethyl sulfoxide evaporates, thus, allowing for slower and longer injection rates, which can be better controlled. Because Onyx is not absorbable, it is capable of producing permanent vascular occlusion. What is most important, Onyx has a lava-like flow pattern within blood vessels without any fragmentation during injection.

In conclusion, Onyx is highly effective in embolization of traumatic and non-traumatic peripheral vascular lesions.

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Authors’ contribution: RR, MDS, AR, VS, RC, VV performed all the embolization treatments reported. FP collected, analyzed the data and wrote the manuscript with RR. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: There is no conflict of interest.

References


