Online October 29, 2024
Journal of Neuroendovascular Therapy 2025; 19: 2024-0073 DOI: 10.5797/jnet.ra.2024-0073

Review Article

Onyx Liquid Embolic Agent: Basic Knowledge for Its Use in Interventional Neuroradiology

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Onyx (Medtronic, Minneapolis, MN, USA) is a non-adhesive liquid embolic agent composed of an ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO). Onyx is explicitly designed for use in interventional neuroradiological procedures. Onyx's unique formulation allows controlled delivery and solidification within the target vessel, providing durable occlusion of abnormal vascular structures such as arteriovenous malformations and dural arteriovenous fistulas. This report reviews the basic understanding of the use of Onyx in interventional neuroradiology. The hydrophilic properties of the agent facilitate its smooth delivery through microcatheters, ensuring precise navigation and deposition within vascular malformations under fluoroscopic guidance. When Onyx was injected into the target vessel, the vessel was embolized as the solvent (DMSO) diffused into the blood and EVOH precipitated to form a durable cast. Onyx liquid embolic agents substantially advance the endovascular treatment of intracranial vascular lesions.

Keywords Onyx, liquid embolic agents, embolization, intervention, neuroradiology

Introduction

Liquid embolic agents are crucial tools in interventional neuroradiology, used primarily to occlude abnormal blood vessels in the brain and spinal cord.[1–3] These agents are injected into the vascular system to block blood flow to specific areas, thereby treating conditions such as arteriovenous malformations (AVMs), dural arteriovenous fistulas (DAVFs), and certain types of tumors.[4,5] Liquid embolic agents are classified based on their composition, mechanism of action, and physical properties. Adhesive liquid embolic agents (e.g., N-butyl cyanoacrylate [NBCA]) polymerize upon contact with blood, adhere to vascular walls, and form solid embolus. Non-adhesive agents (e.g., Onyx; Medtronic, Minneapolis, MN, USA) form a solid mass upon precipitation without adhering to the blood vessel wall. Each type of liquid embolic agent has specific applications, advantages, and limitations, making them suitable for use in different clinical scenarios of interventional neuroradiology. This report describes the non-adhesive Onyx liquid embolic system.

Development of Liquid Embolic Agents

NBCA is an adhesive liquid embolic agent that is widely used to treat various vascular disorders, including AVMs and DAVFs. It is a permanent embolic agent that induces a substantial vascular inflammatory reaction. A potential risk of NBCA is that it polymerizes immediately upon contact with an ionic fluid, and its reflux can entrap a microcatheter within the vessel. NBCA reflux along the catheter tip should be avoided or accepted for a short distance and a very short period. Insufficient embolization induces recanalization if the NBCA is deposited proximal to the target lesion.

To overcome these disadvantages, non-adhesive embolic agents have been developed. Taki et al. developed a liquid material consisting of an ethylene vinyl alcohol (EVOH) copolymer and metrizamide dissolved in dimethyl sulfoxide (DMSO). The material was clinically applied in 3 AVM

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Received: July 20, 2024; Accepted: September 20, 2024
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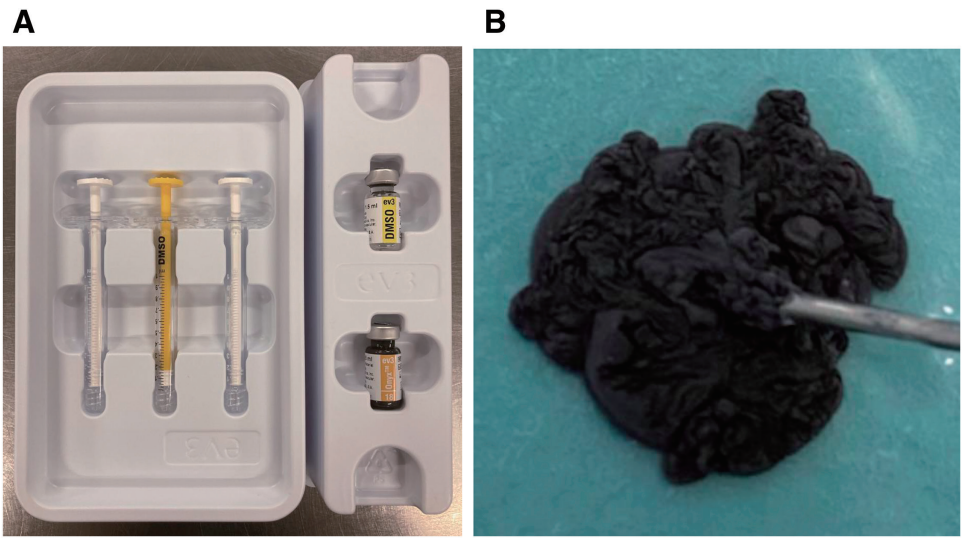

Fig. 1 The Onyx liquid embolic system consists of a 1.5 mL vial of Onyx, a 1.5 mL vial of DMSO, and three 1 mL Onyx delivery syringes (**A**). Onyx is available in 2 product formations: Onyx 18 and Onyx 34. The DMSO dissipates when injected into a target vessel, causing the copolymer to form a spongy occlusive cast. The tantalum is responsible for its dark color (**B**). DMSO, dimethyl sulfoxide; Onyx, Medtronic, Minneapolis, MN, USA

cases and satisfactory performance was obtained.[6] Other investigators undertook further experimental and preclinical research.[7–9] The radiopacifying agent was changed from metrizamide to micronized tantalum (Embolyx E; Micro Therapeutics Inc., San Clemente, CA, USA). Using an animal experimental model, Murayama et al. confirmed long-term anatomical occlusion by eliciting mild-to-moderate intra- and perivascular inflammatory responses to Embolyx E and DMSO.[10] The composition of Embolyx E was subsequently refined by changing the tantalum concentration, and name to Onyx. In 2005, the United States Food and Drug Administration (FDA) approved the use of Onyx for presurgical embolization of brain AVMs.

Onyx Characteristics

Onyx is a non-adhesive liquid embolic agent comprising an EVOH copolymer dissolved in DMSO and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy.[11] The Onyx liquid embolic system consisted of a 1.5 mL vial of Onyx, a 1.5 mL vial of DMSO, and three 1 mL Onyx delivery syringes (**Fig. 1**). Tantalum powder was prepackaged in an Onyx vial. A DMSO-compatible delivery microcatheter (e.g., Marathon Flow Direct Medtronic microcatheter; Medtronic), indicated for use in the neurovascular system, was used to access the embolization site. Onyx is available in 2 product forms: Onyx 18 and Onyx 34. The number indicates the viscosity in centipoise (cps) at 40°C. The viscosity of the EVOH/DMSO mixture was not linearly related to the EVOH.[9] Onyx 18 was composed of 6% EVOH/94% DMSO, and Onyx 34 was composed of 8% EVOH/92% DMSO. The physicians used 2 formulations for appropriate application based on their experience. Onyx 18 is a commonly used formulation that travels more distally and penetrates deeper into the nidus or fistula owing to its lower viscosity. High-viscosity Onyx 34 allows plug formation in high-flow feeders to be completed within a short distance. After plug formation, it is possible to switch to Onyx 18 and continue the embolization.[12]

DMSO dissipates into the blood and interstitial fluids, causing the EVOH copolymer and suspended tantalum to precipitate in situ into spongy and coherent substances. Onyx forms the skin and solidifies from the outside to the inside over time. DMSO rapidly diffuses into the blood and EVOH precipitates and hardens on the outer surface. Upon further injection, the interior fluid breaks the solidified fluid and the outer surface solidifies again (lava-like flow) (**Fig. 2**). To avoid DMSO toxicity, there should be a total exposure of no more than 4.5 mL per day (up to 3 vials) and the injection rate must not exceed 0.3 mL/min.

Onyx Preparation

Onyx vials were placed in a mixer and shaken for at least 20 min before use to obtain a homogeneous suspension of tantalum powder. Failure to continuously mix Onyx for the required time or an Onyx injection delay may result in

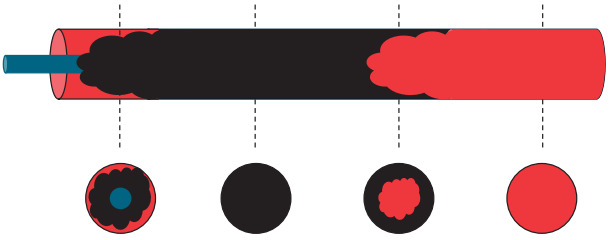

Fig. 2 Schematic illustration of the embolic behavior of Onyx (black), which features a rather lava-like behavior, forms a skin, and solidifies from the outside to the inside over time. This figure is adapted from Vollherbst et al.[4] Onyx, Medtronic, Minneapolis, MN, USA

inadequate suspension of tantalum, leading to insufficient fluoroscopic visualization during delivery.

Before Onyx injection, 10 mL saline was injected into the microcatheter to flush and push the contrast medium out, and 0.8 mL of DMSO was aspirated into a 1 mL syringe to inject a volume of DMSO that would fill the microcatheter. The dead space of the microcatheter was 0.23 mL for the Marathon Flow Direct microcatheter.

The well-stirred Onyx solution was aspirated into a 1-mL syringe using an 18- or 20-gauge needle, the syringe for DMSO was then removed from the microcatheter, and the catheter hub was held vertically, and washed with the remaining DMSO. The prepared Onyx syringe was immediately connected to the microcatheter. However, the air was not introduced into the hub, and the syringe was quickly inserted and connected upward to ensure that the DMSO and Onyx solutions were in contact. Contact with saline, blood, or a contrast medium at the hub of the microcatheter may cause the Onyx solution to precipitate quickly and occlude the microcatheter.

Onyx Injection Technique

With the Onyx syringe held vertically, Onyx was slowly injected at a steady rate to displace the DMSO in the microcatheter. The syringe was held appropriately after the Onyx passed through the microcatheter hub. The recommended injection rate is 0.16 mL/min, at most 0.3 mL/min. Several methods for effectively injecting Onyx have been proposed. Embolization is performed by selecting a method that achieves an appropriate therapeutic goal.

The plug-and-push technique embolizes a lesion by depositing Onyx over the tip of the microcatheter to block forward blood flow to the lesion and by controlling Onyx injection using a syringe.[13] Onyx was injected slowly from the tip of the microcatheter, and when it flowed back proximally, the pause technique was used to stop the injection and allow it to flow to the proximal side. Interruption of the Onyx solution injection for >2 min causes precipitation of the Onyx solution at the tip of the microcatheter, which may lead to microcatheter occlusion. During the plug-formation phase, it is important to determine the point at which the Onyx is allowed to flow back. A long pause (approximately 2 min) was repeated until the plug was fully formed and the injected Onyx moved anterogradely toward the nidus. A short pause (approximately 30 seconds) was allowed when the Onyx reached the proximal part of the drainer or flowed backward into another feeder to change the direction of the Onyx flow.[14] However, caution must be exercised to avoid the backflow of Onyx into the area proximal to the plug. The difficulty of microcatheter removal or entrapment is related to the distance at which the catheter tip is embedded in the Onyx and the tortuosity of the vessel.[14] It is advised to avoid backflow of Onyx by more than 1 cm from the tip of the microcatheter.[15] Excessive Onyx reflux beyond the multiple-vessel curves potentially increases the risk of microcatheter entrapment.[12] The excessive force applied during removal can cause vascular damage and intracranial bleeding.

The pressure-cooker technique is effective for forming a plug in the early stages of embolization, which is difficult.[16] The proximal side of the vessel where the microcatheter was implanted was occluded with NBCA or other means of blocking antegrade blood flow. This allowed Onyx injection through the microcatheter to be pushed initially. However, this method requires a detachable tip (e.g., Apollo Onyx delivery microcatheter; Medtronic). In Japan, where detachable microcatheters are unavailable, a variant method using a balloon catheter proximal to the embolized vessel blocks the flow.[17–19]

Although Onyx is non-adhesive, removal of Onyx could be difficult when the microcatheter is guided through a highly tortuous vessel. The distal access catheter (DAC) effectively supports the guide catheter and microcatheter during embolization and has been used frequently in recent years. When the microcatheter is entrapped, the DAC is advanced to the lesion, where it can be straightened to shorten the length of the microcatheter and provide a fulcrum to safely remove the microcatheter without exerting significant force or strain on the microcatheter or fixed vessel.[20] In case of failure, the hub of the microcatheter was cut off, and another microcatheter was placed as close as possible to the trapped area through a gooseneck snare. A difficult-to-extract microcatheter was held and pulled out.[21]

Onyx Indication

Onyx has the following indications in Japan[22]: (1) presurgical embolization of a brain AVM and (2) embolization of a DAVF that is difficult to treat adequately by transvenous embolization. In Japan, the use of Onyx for brain AVMs was approved in 2005 based on the results of a prospective, multicenter, randomized controlled trial initiated to support submission for FDA approval.[23] This study demonstrated the non-inferiority of Onyx compared to NBCA in the presurgical embolization of brain AVMs to achieve at least 50% volume reduction. It is important to select lesions to which the plug-and-push technique can be easily applied. A compact nidus with a large diameter and non-tortuous feeders is suitable for Onyx embolization. By contrast, low-flow feeders and diffuse nidi tend to reflux rather than allow Onyx to penetrate the nidus, resulting in proximal occlusion. The plug-and-push technique requires the anticipation of some backflow of the Onyx, which is difficult to use when there is a branching normal vessel proximal to the catheter tip.[14] A domestic clinical trial on transarterial Onyx embolization of DAVFs reported a curative occlusion rate of 85.2% 6 months after the procedure.[22] Based on the result, an expansion of the indication for DAVFs for which transvenous embolization was insufficient to achieve therapeutic objectives was approved in 2018. However, the efficacy and safety of DAVF embolization in the spinal cord and cavernous sinus have not yet been confirmed.

The following are the 2 recommended implementation environments for Onyx. The institution should have a high-performance angiography system and should be able to perform neurosurgery. Onyx infusion should be performed under the fluoroscopy of a biplane system using the blank roadmap function, which provides good visibility and helps perform the procedure safely. The physician involved in the procedure must be a Japanese Society of Neuroendovascular Therapy-certified endovascular specialist or a Japanese Society of Interventional Radiology-certified interventional radiology (IVR) specialist, who has completed the Onyx training program and an online training course.

Discussion

The advantage of Onyx is its non-adhesive properties. It solidifies slowly from the outside to the inside, whereas DMSO diffuses. The slow solidification process allows for more controlled and precise delivery. Prolonged and repeated Onyx injections are possible and allow better forward penetration of the target without increasing the risk of microcatheter entrapment.[23] Tantalum powder provides excellent radiopacity, enabling real-time visualization under fluoroscopy during the procedure. This property aids in precise Onyx injection and monitoring during the embolization procedure, avoiding unintentional collateral vessel damage that may occur instantaneously with NBCA injection.[13] Histopathological findings of the resected AVM nidus show a homogeneous distribution of EVOH in small nidal vessels, and the inflammatory response is mild compared to NBCA.[24] The Onyx cast is soft, formable, and elastic, making it easier for surgeons to handle.[25] The dense and cohesive nature of Onyx results in a lower risk of recanalization than other embolic agents.

A disadvantage of Onyx embolization is the risk of DMSO toxicity. DMSO can cause transient side effects such as pain, nausea, and hypertension. Rapid injection of DMSO can lead to endothelial damage, vasospasm, and angionecrosis,[8,10] which can be reduced by slow injection and an adequate volume.[10,26,27] Although the mechanism is not clear, seizures may be induced by edema and inflammation surrounding the nidus after Onyx administration. Peri-procedure anti-epileptic and steroidal medications and close neurological observation following Onyx administration are required.[28] Due to its metallic nature, residual Onyx can sometimes make follow-up imaging challenging because of artifact formation. Onyx appears highly radiodense on computed tomography (CT) and may be associated with significant streak artifacts.[29,30] These artifacts can present obstacles in detecting periprocedural hemorrhage or planning subsequent radiosurgery. Recent studies investigating the effects of artifact reduction using metal artifact reduction software may overcome this disadvantage.[31] The tantalum occasionally induces electrical arcing when monopolar electrocautery devices are used for surgical resection.[32] Therefore, the use of bipolar cautery is recommended. A slow polymerization process can lead to longer procedure times than other embolic agents, which increases the radiation dose. Onyx is relatively expensive compared with other embolic agents and can be considered in resource-limited settings.

Conclusion

Onyx offers significant advantages in treating brain AVMs and DAVFs, which are widely used in interventional neuroradiology, mainly because of their controlled delivery and non-adhesive properties. However, this presents

challenges, including procedural complexity and steep learning curves. This report summarizes the characteristics and applications of Onyx. Adequate knowledge of an agent is crucial for maximizing the benefits and minimizing the risks associated with its use.

Acknowledgments

The authors thank Editage (https://www.editage.jp) for the English language review.

Disclosure Statement

The authors declare that they have no conflict of interest.

References

1) Pal A, Blanzy J, Gomez KJR, et al. Liquid embolic agents for endovascular embolization: a review. *Gels* 2023; 9: 378.
2) Jiang Y, Zhang Y, Lu Z, et al. Liquid embolic agents for interventional embolization. *ChemPhysMater* 2022; 1: 39–50.
3) Brassel F, Meila D. Evolution of embolic agents in interventional neuroradiology. *Clin Neuroradiol* 2015; 25(Suppl 2): 333–339.
4) Vollherbst DF, Chapot R, Bendszus M, et al. Glue, Onyx, Squid or PHIL? Liquid embolic agents for the embolization of cerebral arteriovenous malformations and dural arteriovenous fistulas. *Clin Neuroradiol* 2022; 32: 25–38.
5) Triano MJ, Lara-Reyna J, Schupper AJ, et al. Embolic agents and microcatheters for endovascular treatment of cerebral arteriovenous malformations. *World Neurosurg* 2020; 141: 383–388.
6) Taki W, Yonekawa Y, Iwata H, et al. A new liquid material for embolization of arteriovenous malformations. *AJNR Am J Neuroradiol* 1990; 11: 163–168.
7) Terada T, Nakamura Y, Nakai K, et al. Embolization of arteriovenous malformations with peripheral aneurysms using ethylene vinyl alcohol copolymer. *J Neurosurg* 1991; 75: 655–660.
8) Chaloupka JC, Vinuela F, Vinters HV, et al. Technical feasibility and histopathologic studies of ethylene vinyl copolymer (EVAL) using a swine endovascular embolization model. *AJNR Am J Neuroradiol* 1994; 15: 1107–1115.
9) Yamashita K, Taki W, Iwata H, et al. Characteristics of ethylene vinyl alcohol copolymer (EVAL) mixtures. *AJNR Am J Neuroradiol* 1994; 15: 1103–1105.
10) Murayama Y, Vinuela F, Ulhoa A, et al. Nonadhesive liquid embolic agent for cerebral arteriovenous malformations: preliminary histopathological studies in swine rete mirabile. *Neurosurgery* 1998; 43: 1164–1172.
11) Ayad M, Eskioglu E, Mericle RA. Onyx®: a unique neuroembolic agent. *Expert Rev Med Devices* 2006; 3: 705–715.
12) The Japanese Society for Neuroendovascular Therapy: Continuing education program: the 38th annual meeting of the Japanese Society for Neuroendovascular Therapy. Osaka, Japan, 2022.
13) Saatci I, Geyik S, Yavuz K, et al. Endovascular treatment of brain arteriovenous malformations with prolonged intranidal Onyx injection technique: long-term results in 350 consecutive patients with completed endovascular treatment course. *J Neurosurg* 2011; 115: 78–88.
14) Taki K, Nakahara I, Ohta T. Perfect master: neuroendovascular therapy update of indispensable knowledge, 3rd edition. Medical View. Tokyo, Japan, 2021. (in Japanese)
15) Medtronic: Indications, safety, and warnings Onyx liquid embolic system. https://www.medtronic.com/us-en/healthcare-professionals/products/neurological/avm-embolization/onyx-liquid-embolic/indications-safety-warnings.html. (Accessed: March 1, 2024).
16) Chapot R, Stracke P, Velasco A, et al. The pressure cooker technique for the treatment of brain AVMs. *J Neuroradiol* 2014; 41: 87–91.
17) Berenstein A. Flow-controlled silicone fluid embolization. *AJR Am J Roentgenol* 1980; 134: 1213–1218.
18) Spiotta AM, James RF, Lowe SR, et al. Balloon-augmented Onyx embolization of cerebral arteriovenous malformations using a dual-lumen balloon: a multicenter experience. *J Neurointerv Surg* 2015; 7: 721–727.
19) Vollherbst DF, Chapot R, Wallocha M, et al. First clinical multicenter experience with the new Scepter Mini microballoon catheter. *J Neurointerv Surg* 2021; 13: 261–266.
20) Binning MJ, Yashar P, Orion D, et al. Use of the Outreach Distal Access Catheter for microcatheter stabilization during intracranial arteriovenous malformation embolization. *AJNR Am J Neuroradiol* 2012; 33: E117–E119.
21) Alamri A, Hyodo A, Suzuki K, et al. Retrieving microcatheters from Onyx casts in a series of brain arteriovenous malformations: a technical report. *Neuroradiology* 2012; 54: 1237–1240.
22) The Japanese Society for Neuroendovascular Therapy, The Japan Neurosurgical Society, The Japanese Society of Interventional Radiology: Guidelines for the proper use of liquid embolic substances in neurology 2022. https://jsnet.website/contents/%93K%90%B3%8Eg%97p%8Ew%90j/LQM%93K%90%B3%8Eg%97p%8Ew%90j2022-2.pdf. (in Japanese)
23) Loh Y, Duckwiler GR. Onyx Trial I: a prospective, multicenter, randomized trial of the Onyx liquid embolic system and N-butyl cyanoacrylate embolization of cerebral arteriovenous malformations. *J Neurosurg* 2010; 113: 733–741.

24) Natarajan SK, Born D, Ghodke B, et al. Histopathological changes in brain arteriovenous malformations after embolization using Onyx or N-butyl cyanoacrylate. *J Neurosurg* 2009; 111: 105–113.
25) Akin ED, Perkins E, Ross IB. Surgical handling characteristics of an ethylene vinyl alcohol copolymer compared with N-butyl cyanoacrylate used for embolization of vessels in an arteriovenous malformation resection model in swine. *J Neurosurg* 2003; 98: 366–370.
26) Chaloupka JC, Huddle DC, Alderman J, et al. A reexamination of the angiotoxicity of superselective injection of DMSO in the swine rete embolization model. *AJNR Am J Neuroradiol* 1999; 20: 401–410.
27) Pamuk AG, Saatci I, Cekirge HS, et al. A contribution to the controversy over dimethyl sulfoxide toxicity: anesthesia monitoring results in patients treated with Onyx embolization for intracranial aneurysms. *Neuroradiology* 2005; 47: 380–386.
28) de Los Reyes K, Patel A, Doshi A, et al. Seizures after Onyx embolization for the treatment of cerebral arteriovenous malformation. *Interv Neuroradiol* 2011; 17: 331–338.
29) Vollherbst DF, Otto R, Do T, et al. Imaging artifacts of Onyx and PHIL on conventional CT, cone-beam CT and MRI in an animal model. *Interv Neuroradiol* 2018; 24: 693–701.
30) Pop R, Mertz L, Ilyes A, et al. Beam hardening artifacts of liquid embolic agents: comparison between Squid and Onyx. *J Neurointerv Surg* 2019; 11: 706–709.
31) Schmitt N, Weyland CS, Wucherpfennig L, et al. The impact of software-based metal artifact reduction on the liquid embolic agent Onyx in cone-beam CT: a systematic in vitro and in vivo study. *J Neurointerv Surg* 2022; 14: 832–836.
32) Schirmer CM, Zerris V, Malek AM. Electrocautery-induced ignition of spark showers and self-sustained combustion of onyx ethylene-vinyl alcohol copolymer. *Neurosurgery* 2006; 59(Suppl 2): ONS413–ONS418.