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Liquid Embolic Agents in the Treatment of Intracranial Arteriovenous Malformations

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The morbidity and mortality associated with the surgical treatment of intracranial arteriovenous malformations (AVMs) has decreased over the past two decades, mainly because of advances in endovascular therapy and the increased use of stereotactic radiosurgery. Those AVMs traditionally associated with high surgical risk are now often treated with radiosurgery instead. Several studies have demonstrated the direct relation between AVM size and surgical difficulty and operative morbidity [1–8]. When considering endovascular therapy for AVMs, the aim is to obliterate the malformation or to reduce its size to enhance the patient's outcome through surgery or radiosurgery. The first embolization of an AVM was performed by Luessenhop and Spence [9] in 1960 by injecting silastic spheres through a surgical exposure of the cervical carotid artery. Although this method was technically simple to perform, it was nonselective and often resulted in inadvertent occlusion of normal vessels and neurologic injury [10,11]. In 1973, Djindjian et al [12] developed a technique of selective catheterization involving the external carotid artery, but it was Serbinenko [13] who, in 1974, succeeded in accessing the cerebral arteries using a detachable balloon mounted on a floating catheter. Unfortunately, this technique was not vessel specific, because the balloon was carried distally within the vessel with the most flow. Also, the balloon was too large to occlude anything distal to the arterial feeder and thus left the nidus of the malformation unpenetrated.

Polyvinyl alcohol (PVA) particles have also been used as embolic agents in the treatment of AVMs. Porstmann et al [14] first reported the use of PVA particles, but this agent proved to be problematic in the treatment of AVMs for several reasons [15,16]. First, the particles needed to be large enough to embolize the lesion effectively but small enough to be injected through the catheter without blocking the lumen. This problem was solved by later catheter innovations, but other problems with this agent have persisted and include the lack of radiopacity and inability to effect a permanent occlusion of the feeding artery or nidus.

Zanetti et al [17] first described the use of the monomer isobutyl-2-cyanoacrylate for endovascular embolization using canine renal arteries in 1972, but it was not until 1976 that Kerber [18] reported the use of a calibrated-leak balloon mounted on a microcatheter to navigate the intracranial circulation and deliver this novel adhesive agent to the small feeding vessels of an AVM. This technique required the repeated inflation and deflation of the balloon to flow-direct the microcatheter, which was technically difficult and linked with numerous complications [19–22]. In addition, although the initial acrylates were excellent embolic agents, they were associated with toxic reactions and reported to have carcinogenic properties [23,24]. The basic cyanoacrylate monomer was therefore modified, and the resulting embolic agent, N-butyl cyanoacrylate (NBCA; Trufill,

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Cordis Neurovascular, Miami Lakes, Florida), has become the standard liquid acrylic adhesive agent in endovascular neurosurgery. Recently, a nonadhesive liquid embolic agent known as Onyx (Onyx Liquid Embolic System, Micro Therapeutics, Irvine, California) has undergone evaluation for embolization at several centers [25–27]. Onyx and NBCA have in common the ability to be injected in liquid form through a microcatheter, although they differ significantly in their various properties and chemical composition. This article focuses on these two agents and the techniques used with each for the embolization of intracranial AVMs.

Provocative testing

The goal of therapeutic embolization is occlusion of the AVM without hindering flow to normal brain parenchyma; however, endovascular cerebral AVM procedures are reported to produce permanent neurologic deficits in approximately 10% of cases [28]. Once a microcatheter is in position, discerning whether embolization will result in a neurologic deficit can be difficult. Some neurointerventionists choose to place patients under general anesthesia and rely on the lack of normal cerebral vessel filling observed on superselective angiography to make this decision. The authors prefer to perform pharmacologic provocative testing while the patient is awake to predict the safety of embolization. The lack of normal cerebral vessels on superselective angiography does not guarantee a risk-free embolization [28]. Pharmacologic provocative testing has been shown to be extremely helpful in discerning whether embolization will result in a neurologic deficit [29–34]. The three main agents used for pre-embolic provocative testing are amobarbital, methohexital, and lidocaine. Traditionally, the short-acting barbiturates have been used to evaluate the potential for injury in the cerebral gray matter because of their action on the gamma-amino butyric acid A ($GABA_A$) receptor. Barbiturates may have little to no effect on cerebral white matter, however, because of a lack of $GABA_A$-ergic synapses. Lidocaine, through its blockage of voltage-gated sodium channels present on all nerve cell membranes, inhibits gray and white matter structures and has been used as an adjunct to barbiturate testing by some [29,35]. Fitzsimmons et al [35] have reported the use of amobarbital and lidocaine in preembolization assessment and argue that the addition of lidocaine may increase the sensitivity and predictive value of pre-embolization provocative testing. Although a negative provocative test result predicts the safety of permanent vessel occlusion, it does not eliminate the risk of neurologic injury. Any transient neurologic deficit produced by pharmacologic testing, however, should be expected to produce a permanent deficit with arterial embolization [29–35].

N-butyl cyanoacrylate

Particulate agents, such as PVA, were the mainstay of preoperative embolic therapy for AVMs before advances were made in microcatheter technology. The particles cause a temporary occlusion, which results in vessel thrombosis. This thrombus is subsequently broken down so that there is a relatively high recanalization rate when using PVA [36]. Histopathologic studies of NBCA demonstrate that cyanoacrylate provokes a more intense inflammatory reaction than that caused by PVA and involves the wall of the vessel and the adjacent interstitial areas [37–41]. This inflammatory reaction ultimately leads to vessel necrosis, fibrous ingrowth, and a fairly permanent occlusion [39,42]. The US Food and Drug Administration approved the use of NBCA for the endovascular treatment of AVMs in 2000. The results of the NBCA Trial, which demonstrated that NBCA was equivalent to PVA as a preoperative embolic agent for the treatment of cerebral AVMs, have been published [14].

Liquid monomeric NBCA is converted to a solid long-chain polymer by anionic initiators (nucleophiles), which are found in excess in blood and on endothelium. Once the polymerization reaction begins, it proceeds at a rapid rate to completion and generates heat in the process. The reaction proceeds so rapidly that the NBCA solidifies in a catheter without the addition of a medium that permits adjustments to be made in the polymerization time. Cromwell and Kerber [19] published their experience with iophendylate oil as an additive, and subsequent investigations have defined the optimal ratio of cyanoacrylate to oil to range from 1:5 to 2:5 [43,44]. Mixing the glue and oil at these ratios extends the polymerization time to allow for adequate penetration of the nidus. Iophendylate oil has been replaced by other oil-based mediums (eg, ethiodized oil, lipiodol) because of greater ease of use with these latter agents. The mixture of glue and oil enables a delay in polymerization; unfortunately, it changes the character of the adhesive so that it

comes out of the tip of the catheter in droplets, which can then pass uncontrolled through the AVM and to the lung. Powdered tantalum is also used to increase radiopacity during injection. The kit supplied by Cordis Neurovascular comes with NBCA, ethiodized oil, and tantalum powder. These are then combined at the operator's discretion, depending on the hemodynamics of the lesion. The authors often add glacial acetic acid to the mixture to prolong the polymerization time further, allowing for better control of the injection and fuller casting of the nidus.

Proponents of embolization with cyanoacrylate glue argue that it causes permanent occlusion and can even cure small AVMs if adequate nidal penetration is accomplished [22,42,45–48]. Lesions that can potentially be cured with NBCA embolization are small AVMs with a single feeding pedicle (Fig. 1). The multiplicity of arterial feeders usually seen in larger complex AVMs makes angiographic obliteration of the nidus difficult to obtain. The patent areas of the nidus retain flow and have the potential to recruit secondary feeders. These secondary feeders are often too small to catheterize; therefore, achieving a cure requires surgery or radiosurgery [49,50]. Advocates of NBCA embolization claim that the well-cast portion of the nidus is permanently occluded and that this effectively transforms an inoperable AVM into an operable one by reducing the size of the lesion as well as the number of its arterial feeders [42,45,51–57]. The permanence of the occlusion appeals to proponents of stereotactic radiosurgery because it reduces the risk of hemorrhage during the interval between radiation and vessel sclerosis. (If quadrants of the nidus are embolized, higher doses at the time of radiosurgery can be given, but if the perimeter of the nidus is unchanged, the radiation dosimetry would be the same as if the AVM had not been embolized). NBCA embolization also appeals to the neurosurgeon resecting the AVM because it softens the vessels and makes them retractable, thereby decreasing the amount of blood loss and serving to establish a boundary zone between the AVM vessels and those of normal brain parenchyma. Giant AVMs that are too large to be embolized completely or resected without incurring significant neurologic deficit can be treated in a palliative fashion with NBCA embolization. These lesions often cause symptoms because of the steal phenomenon generated by the blood volume shunted through the AVM. Partial embolization decreases the shunt volume and potentially reduces seizure activity and focal hypoxia.

The following is a general description of the technique used at the authors' institution for NBCA embolization. The tip of the microcatheter

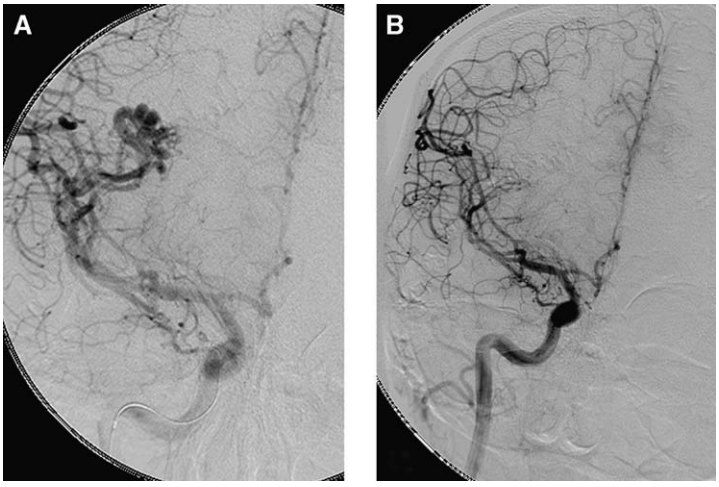

Fig. 1. (*A*) Anteroposterior intracranial angiogram of the right internal carotid artery in a 26-year-old woman obtained 2 months after she presented with an intracerebral hemorrhage. This small arteriovenous malformation is supplied by only one feeder. (*B*) Right common carotid artery angiogram obtained after embolization with N-butyl cyanoacrylate (Trufill; Cordis Neurovascular, Miami Lakes, Florida) demonstrating complete obliteration of the malformation. (*From* Howington JU, Kerber CW, Guterman LR, Hopkins LN. Liquid embolic agents in the treatment of intracranial arteriovenous malformations. In: Horowitz MB, Levy EI, editors. Neuroendovascular surgery series. Basel: Karger 2004;17:138.)

is advanced as close to the nidus as possible, and superselective angiography is performed. If normal vessels are not appreciated, provocative testing is performed. While this is being done, a second physician mixes the NBCA, ethiodized oil, and tantalum powder (and possibly glacial acetic acid) on a separate table, which must be uncontaminated by any ionizing material. The authors prefer to use a standard concentration of 30% (NBCA [0.9 mL] and oil [2.1 mL]) mixed with the standard vial of tantalum supplied by the manufacturer. The cyanoacrylate is modified with glacial acetic acid on the basis of the hemodynamic properties observed during the superselective angiogram. The glacial acetic acid is added to the mixture using a 3-mL syringe with a 30-gauge needle. It is critical that the preparation takes place in an ion-free environment to prevent premature polymerization. Each physician changes gown and gloves before handling the adhesive. Although the standard concentration of NBCA is 30%, this concentration can be adjusted to the hemodynamics of the AVM so as to provide adequate penetration of the nidus without occlusion of the venous drainage system. Before the embolization is performed, the microcatheter is manually flushed continuously with nonionic 5% dextrose in water (D5W). The operator who is to inject the NBCA should also be the one flushing the catheter so as to avoid an injection that is too weak or too strong. In a rapid exchange, the D5W syringe is removed (allowing no air entry) and replaced with the syringe containing the adhesive. With steady force, the NBCA is pushed through the catheter until the first drops appear at the tip of the catheter. The rate of injection is then adjusted to establish a good nidal cast by keeping the drops from coming out too fast or too slow. Reflux around the microcatheter must be avoided. When the embolization is complete, negative pressure is applied to the syringe containing the adhesive, and the microcatheter is quickly withdrawn. This final maneuver usually requires the cooperation of two physicians. Whether more pedicles are to be embolized is a decision made by the endovascular surgeon based on the amount of nidus occluded. As a general rule, the authors think that no more than 50% of the nidus should be embolized in the first attempt. The authors give credence to the theory of normal perfusion pressure breakthrough and think that a greater percentage of occlusion without complete nidal obliteration increases the risk of postprocedure hemorrhage [58]. Also, incomplete nidal obliteration in conjunction with significant occlusion of the venous drainage system increases the risk of postprocedural hemorrhage. Smaller AVMs with only one feeder can often be cured during a single embolization procedure, whereas larger more complex lesions usually require multiple sessions spaced over several months.

A long-known risk of using cyanoacrylates to embolize AVMs is that of rapid polymerization and reflux, which results in gluing the catheter in place [14,59]. Early polymerization can also result in the undesired effect of feeding vessel occlusion without nidal penetration. If the polymerization time is too long, the cyanoacrylate can pass into the venous circulation, resulting in pulmonary emboli. With a thorough understanding of the flow dynamics of the AVM, along with the ability to titrate the polymerization time with additive media, these risks can be largely minimized.

Onyx

Taki and colleagues [60] were the first to describe the use of ethylene-vinyl alcohol copolymer (EVOH) in combination with dimethyl sulfoxide (DMSO) for the embolization of cerebral AVMs. They combined the solid copolymer (5 g) with metrizamide powder (35 g, for opacification) dissolved in DMSO (60 g). DMSO is an organic solvent, and when the polymer-powder-solvent mixture comes in contact with an aqueous medium, such as blood, the DMSO diffuses away and the EVOH precipitates and solidifies. The resultant embolic material is cohesive without being adhesive, which means that it does not adhere to the wall of the vessel or the catheter but is thick enough to become lodged in the vessel. Subsequent studies led to a premixed solution of EVOH, tantalum, and DMSO known as Onyx, which comes in three different concentrations of EVOH (6.0%, 6.5%, and 8.0%) [26,61,62]. The varied concentrations of EVOH are used to vary the precipitation rate. The lower the concentration of EVOH, the less viscous the solution will be and the longer it will take to precipitate in the AVM.

Nonadhesive nature of Onyx enhances controllability during delivery

DMSO was chosen as the solvent for two main reasons: it readily diffuses in water, and its physiologic properties in human beings have

been well studied [60,63]. This compound is extremely angiotoxic, however, and its adverse effects range from vasospasm to angionecrosis and arterial rupture. The damage to the vessel wall can be so great that an occlusion occurs, which then alters the flow dynamics. As in cases of premature NBCA polymerization, an inadvertent reflux of Onyx can lead to inadequate nidal penetration or parent artery embolization. The angiotoxicity of DMSO is directly related to the volume infused and the length of time the compound is in contact with the vessel wall. In fact, Murayama et al [61] demonstrated that these factors were the two most important determinants of the angiotoxicity of DMSO. Some investigators have argued that the toxicity of DMSO actually benefits the embolization process, however, by speeding up the intravascular thrombosis, endothelial injury, and eventual inflammatory foreign body reaction that is seen with embolization [64]. The effectiveness of DMSO as a solvent is so great that it has been shown to damage some of the catheters used for its delivery [26,61,65]. For this reason, specially designed DMSO-compatible catheters must be employed when Onyx is used for AVM embolization. Currently, only three catheters are able to tolerate the infusion of DMSO without being destroyed, and they are the Radifocus GT III catheter (Terumo, Tokyo, Japan) and the Flow Rider Plus and Rebar catheters (Micro Therapeutics). Another potential drawback to the use of Onyx as an adjunctive modality for the treatment of cerebral AVMs is the discomfort that many awake patients report as it is injected. At times, this discomfort can be so severe that the induction of general anesthesia may be necessary. Therefore, institutions that routinely use provocative testing as part of their embolization protocol may have difficulty in using Onyx. Finally, the ready-made vials of the EVOH-DMSO-tantalum (Onyx) mixture settle out of suspension if not shaken. The operator must be aware of this fact and remember to agitate the vial constantly until the time of the injection. If the mixture is injected without the tantalum being adequately suspended in the EVOH-DMSO, the radiopacity might be lessened. In their report of 23 patients treated using Onyx, Jahan et al [26] advocate the use of the Vortex-Genie shaker (Micro Therapeutics) for keeping the tantalum evenly dispersed so as to maximize radiopacity.

The nonadhesive nature of Onyx as a liquid embolic agent gives it several advantages over NBCA. Inadvertent gluing of the catheter to the arterial pedicle is not a concern. Because Onyx is nonadhesive, it can be injected in a slower and more controlled fashion; during this time, serial angiograms can be used to evaluate the progress of the embolization. Some preliminary experience indicates that because Onyx hardens slowly, extended injection times are possible, which means that there might be higher AVM cure rates with Onyx compared with NBCA [25]. After one pedicle is embolized, the same catheter can be repositioned in another pedicle for another embolization, which is something that is not possible with NBCA embolization. Fig. 2 demonstrates an AVM with multiple feeding vessels that was treated with Onyx during one setting. The presence of tantalum darkens the Onyx and also aids at the time of surgical resection by delineating AVM vessels from normal cerebral vessels (the same is true for NBCA). At the time of operation, the Onyx-filled nidus is reported to be spongy and easily retractable, which also benefits surgical resection [26,60,64,66]. In an effort to analyze the form that embolic agents take with the involved vessel, their pliability for resection, and the degree of blood loss during resection, Akin et al [64] performed a surgical handling study comparing NBCA and Onyx using a swine AVM resection model. They found that vessels embolized with Onyx were soft and easily manipulated, whereas vessels embolized with NBCA tended to be considerably tougher to manipulate and not as easy to cut. Also, during the surgical resection, the rete mirabile embolized with Onyx bled less than those treated with NBCA.

The basic technique of embolization with Onyx is similar to that of NBCA except that no preparation of the embolic material in an ion-free environment is necessary. The catheter must be primed with normal saline and then with DMSO (0.27 mL) to fill the dead space and prevent premature solidification of the Onyx. The operator chooses the particular concentration of EVOH on the basis of the flow dynamics of the AVM. Using a 1-mL syringe, the DMSO is slowly (over the course of 40 seconds) injected and then replaced by the Onyx. Under fluoroscopy, the Onyx is injected slowly enough to achieve adequate nidal penetration without reflux. The catheter is withdrawn or primed again with DMSO if further embolization is warranted.

Histopathologically, vascular structures embolized with EVOH show mild inflammatory changes in the acute setting and chronic inflammatory changes after only several days [26,

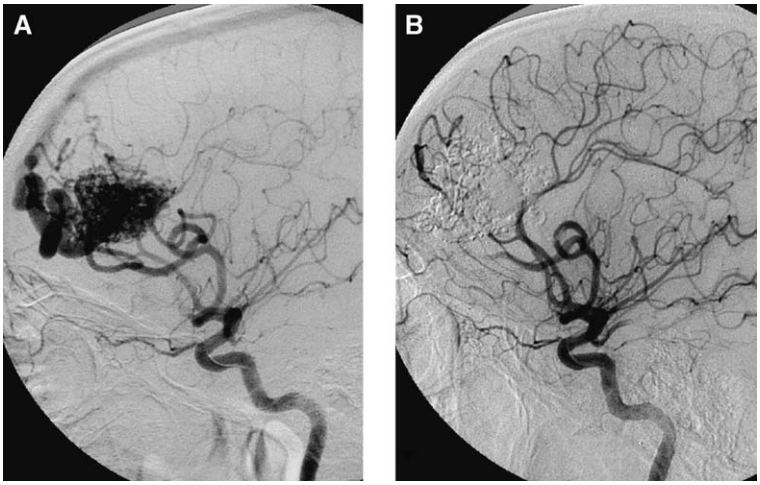

Fig. 2. (*A*) Lateral intracranial angiogram of the right internal carotid artery in a 37-year-old woman who presented with refractory epilepsy. The malformation is fed by branches from the anterior and middle cerebral arteries. (*B*) Lateral intracranial angiogram obtained after embolization with Onyx (Micro Therapeutics, Irvine, California) demonstrating no residual malformation. (*From* Howington JU, Kerber CW, Guterman LR, Hopkins LN. Liquid embolic agents in the treatment of intracranial arteriovenous malformations. In: Horowitz MB, Levy EI, editors. Neuroendovascular surgery series. Basel: Karger 2004;17:141.)

60–62,64–66]. These changes are usually found within the vessel lumen, with only focal areas of elastica disruption, and usually spare much of the vessel wall. This lack of necrosis allows the vessel to remain viable and makes future recanalization a possibility. Some authors have cautioned against the use of Onyx as an embolic agent for AVMs because of this recanalization risk [67,68]. Angionecrosis can occur, but this is thought to be caused by the improper injection of DMSO rather than by the presence of Onyx. Examination of resected AVMs treated with Onyx has revealed complete filling of some vessels, whereas others are only partially filled with the embolic material. The thrombus that fills the remainder of the vessel lumen can undergo recanalization over time. To date, there have been no long-term angiographic follow-up analyses of patients treated with Onyx. Late recanalization of AVMs treated with Onyx must be considered a possibility given the histopathologic findings published thus far and needs to be evaluated further.

Summary

The endovascular treatment of cerebral AVMs has advanced greatly in the four decades since Luessenhop and Spence [9] first described the use of silastic spheres to embolize an AVM. The innovations have been in the agents used to embolize as well as in the devices used to deliver the agent to the AVM. Endovascular therapies have helped to decrease operative morbidity by making it easier for the surgeon to resect the AVM and, in some cases, by eliminating the need for surgery altogether. The benefit of size reduction not only benefits the surgical treatment of AVMs but improves the efficacy of stereotactic radiosurgery. The authors expect that the future will bring continued advances; with such advances, the morbidity associated with AVM treatment should drop even lower.

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