Treatment Options for Cerebral AVMs and Dural AVFs

The second of a three-part series on diagnosing, treating, and researching management options for intracranial malformations.

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Intracranial vascular malformations, although uncommon, carry significant morbidity and mortality rates when symptomatic in patients. The standard of care in neurosurgical management and treatment of these pathologies is constantly being reviewed as underlying mechanisms are discovered. In our first article in the February 2015 issue of *Endovascular Today*, we discussed the pathology of cerebral arteriovenous malformations (AVMs) and dural arteriovenous fistulas (DAVFs). In this second part, we focus on various materials that are available for current treatment options for cerebrovascular lesions and the associated advantages and pitfalls.

TREATMENT OPTIONS FOR CEREBROVASCULAR LESIONS

The mainstay of treatment for cerebral AVMs and DAVFs is to reduce the risk of a catastrophic bleed. In order to evaluate the efficacy and feasibility of various types of therapy, postprocedure hemorrhage rates and long-term deficits need to be compared. Endovascular embolization (eg, vascular occlusion via the use of microcatheters, flexible stents, and detachable latex balloons) has been used in the treatment of intracranial AVMs as early as the 1970s. Although currently available endovascular techniques still hold many risks, preoperative embolization is thought to optimize surgical treatment of cerebral AVMs and DAVFs and possibly increase the efficacy of subsequent radiotherapy.[1,2]

Direct surgical treatment for AVMs is generally elective, unless conditions require emergent actions such as in the case of a large, life-threatening hemorrhage. Before treatment, it is critical to establish the AVM architecture through angiography. Intracranial lesions are typically resected using standard microneurosurgical techniques: first ligating arterial feeders, followed by excision of the lesion nidus, and finally the draining vein with postresection angiography. Published reports of surgical excision of cerebral AVMs suggest a high success rate (92% to 100%) for grade I patients. Surgery may be considered for higher-grade AVMs, but because of the high risk, it is typically used with an adjunct like embolization or radiosurgery.

SOLID EMBOLIC AGENTS

Embolization offers a minimally invasive treatment of vascular abnormalities by reducing AVM size, decreasing intraoperative blood loss, reducing the frequency and severity of normal perfusion pressure breakthrough, and in certain cases, facilitating surgical removal of hypervascularized tumors.[2,3] Furthermore, the rapid improvement of microcatheter technology has allowed more control over embolization procedures. Cerebral AVM embolization previously included image-guided injection of permanent solid embolics, such as polyvinyl alcohol (PVA) particles, thereby blocking the flow and subsequent thrombosis of the vessel.[4-6] PVA particles, although biocompatible, tend to clog microcatheters, yielding considerable hemorrhagic and ischemic complication rates and rarely lead to a permanent cure when used alone.[6,7]

In contrast to PVA particles, polyurethane microspheres loaded with the radiolucent material tantalum (for more facile visualization on angiography) do not obstruct catheters because its surface is modified by grafting methacrylic acid, which, when converted into its sodium salt, becomes

hydrophilic. Although in vitro studies have shown that microspheres are nonhemolytic, application of polyurethane microspheres has been limited because of the cytotoxic effect of its diluent, dimethyl sulfoxide.[8,9]

Polyhydroxybutyrate (PHB) microspheres have also been developed for therapeutic embolization, which have shown no evidence of any inflammatory reaction or tissue toxicity directly due to the microspheres. However, there was distorted morphology of the embolic agent within blood vessels and fresh thrombus formation.[10]

The use of large (400 µm), calibrated microspheres (Embozene microspheres, CeloNova BioSciences, Inc.) in the embolization of meningiomas has been shown to minimize hemorrhagic complications.[6] Furthermore, polypropylene sutures, surgical silk, and cyanoacrylate glues have been previously utilized for embolization procedures.[11] Even though sutures are relatively inexpensive and readily available, they are difficult to control after injection via a catheter and are not radiopaque. Silk causes an inflammatory response, leading to thrombosis of the vessel. Risks associated with cyanoacrylate glues include premature hardening while in the catheter as well as permanent lodging of the catheter into the embolus.

Temporary embolic agents have some advantages over permanent materials in cases when healing is desired before recanalization, such as in traumatic injuries. In the past, naturally induced thrombosis in vitro was used to occlude vessels for days to a few weeks. Due to its short-lived embolization, autologous blood clots have been replaced by gelatin sponges.[11] Gelfoam is an absorbable gelatin-compressed sponge that induces platelet aggregation and inflammation of the vessel wall.

In addition to longer thrombosis times than natural methods, gelatin sponges can also be administered in multiple ways, including forming a slurry, which is then loaded into a syringe filled with contrast. Bovine-derived collagen fiber preparations have been shown to effectively occlude at the arteriolar level for weeks to months. These fibers induce inflammatory reactions of the vessel wall in addition to mechanically obstructing the vessel lumen.[11] Temporary embolic agents, however, have increased risks of rebleeding, leading to premature recanalization of blood vessels.

Although a variety of solid embolic agents exist, improvements can be made to produce materials that are more easily administered, biocompatible, and cost-effective. Human collagen microbeads have been shown to be an effective embolic agent in experimental in vivo conditions. These biocompatible spherical particles have smooth surfaces that may prove to be more effective for human cerebral AVMs, producing total occlusion of blood vessels with effortless injection ability through flow-directed microcatheters (unlike PVA particles).[12]

LIQUID EMBOLIC AGENTS

Liquid embolic agents, such as cyanoacrylate-based materials and ethanol, have been used as fast-forming barriers against blood flow into a variety of lesions with vascular components, such as hypervascularized tumors and AVMs.[12,13] Factors such as polymerization time, injection rate, and blood flow influence the level of obstruction and whether embolization occurs proximal or distal to the site of injection.[14] In the past, the fast-polymerizing adhesive n-butyl cyanoacrylate (n-BCA)—chemically similar to cyanoacrylate-based superglues—was a routinely used liquid chemoembolic agent. Advantages of n-BCA include deep intranidal penetration, high thrombogenicity, permanent occlusion, and easy delivery via small atraumatic microcatheters.[2] Other nonadhesive embolic agents, such as coils and PVA particles, tend to result in recanalization over time, preventing treatment of large AVMs with multistaged embolization. Because n-BCA polymerization is a relatively quick and uncontrollable process, however, the introduction of the new liquid embolic agent, Onyx (Medtronic), a less-adhesive and slower-polymerizing material, has made significant improvements in eliminating small brain AVMs and reducing the size of larger AVMs for surgical or radiosurgical treatment.[15,16]

Onyx is an ethylene vinyl alcohol copolymer dissolved in dimethyl sulfoxide (DMSO) that is a biocompatible, precipitation-based system in which polymers precipitate out of solution upon contact with blood and has been shown to successfully treat aneurysms and tumors of the peripheral vascular system in conjunction with coils in selected cases.[1,9,17] Because the microcatheter tip is not glued within the blood vessel, it is possible to inject large volumes in a highly controlled manner without filling the draining veins.[11] When compared to patients who received only n-BCA treatment, patients treated with Onyx were less likely to experience permanent neurologic deficits related directly to the procedure.[17] In contrast to n-BCA, Onyx allows the occlusion of several different vessel feeders from a singe pedicle, thereby reducing operative time and risk of subsequent catheterizations.[7] Because Onyx is dissolved in DMSO, a potentially toxic solvent, injection must occur slowly and in stages, resulting in a relatively challenging delivery technique. If delivered too quickly, studies have shown that DMSO induces vessel necrosis, resulting in vasospasm.[18,19] However, the negative side effects related to hypotension, arrhythmia, or thrombosis of the embolized blood vessel were minimal when administered appropriately.[17] Furthermore, Onyx is available in various product formulations where the relative composition of ethylene vinyl alcohol, and thus viscosity, is altered. The different forms, such as Onyx 18, 34, and 500, have allowed more targeted therapy against different pathologies. For example, Onyx 34 has been used in the

treatment of high-flow DAVF and, only if needed, injection was continued with Onyx 18.[20] As a biomaterial that allows accurate control of the embolization process while avoiding unintentional occlusion of nearby vessels, Onyx is a promising embolic agent that has been used primarily for occluding cerebral AVMs, filling endoleaks, and more recently in a few clinical studies, for filling intracranial aneurysms.[21-26]

Although Onyx has become the common agent of choice in endovascular embolization, some studies have found issues with reflux surrounding the microcatheter and inadvertent venous penetration.[27] Moreover, complications related to the use of Onyx include nerve injury, soft tissue necrosis, and local skin ulceration.[28] Thus, while Onyx is an example of great advancement in the development of therapeutic embolization, discovery of these complications has led to diminished use.

In addition to cerebral AVM treatment, Onyx has also been used in the treatment of intracranial DAVF.[29,30] Approximately 10% to 15% of all intracranial AVMs are DAVFs, which result from abnormal arteriovenous connections within the dura. Symptoms of DAVFs range from headaches and tinnitus to intracranial hemorrhage, but also have the chance to be completely asymptomatic.[7] Management of DAVFs includes isolated endovascular, surgical, or radiosurgical repair or a combination of these procedures. Endovascular treatment is used against aggressive forms of DAVFs to eliminate the cortical venous drainage, thereby reducing the risk of intracranial hemorrhage. Treatment is considered complete when Onyx penetrates the draining vein of the DAVF. Before the advent of Onyx, endovascular management of DAVFs was limited to cyanoacrylate, ethyl alcohol, coils, and particles. Similar to AVM treatment, there was an increasing need for a nonadhesive liquid embolic agent in the endovascular treatment of intracranial DAVF. Transarterial administration of Onyx via microcatheterization has been shown to be a safe and highly effective embolic agent for DAVF treatment, reporting a low recurrence rate in the short-term postoperative follow-up and no significant morbidity or mortality.[7,30]

Although Onyx has multiple beneficial properties when compared to n-BCA, the latter confers many advantages in situations such as fistulous arteriovenous shunts, leptomeningeal collaterals, and catheter positions distant from the nidus.[11] Interestingly, hyperosmolar mannitol has been shown to act as an effective liquid tumor embolization agent particularly in treating meningioma by dehydration of endothelial and tumor cells and thus promoting intravascular thrombosis.[4] Studies have shown a low rate of permanent neurologic complications and a high degree of safety associated with the use of liquid embolic agents in the reduction of nidal volume in cerebral AVMs before surgical or radiosurgical procedures.[31]

CURRENT STANDARD OF CARE

When complete endovascular AVM occlusion cannot be accomplished, additional treatment options including surgery or radiation therapy are considered. Currently, Onyx is routinely chosen for embolization procedures due to its superior ability to fill a cerebral AVM nidus compared to other materials. In cases where Onyx cannot be administered safely, n-BCA may be utilized for cerebral AVM occlusion. Furthermore, in certain cases, such as when direct AVFs are present, the use of n-BCA is favored over Onyx due to its adhesive properties, thus limiting distal migration of the material in vivo. Of importance, intranidal catheter tip injection of Onyx carries a higher risk of vessel rupture when used in small vessels. If ruptures are not recognized during catheter manipulation, they can result in large hematomas that may only be noted on postprocedure CT scan. Staged embolization sessions are advised to reduce ischemic complications and microcatheter trapping.[17]

Other treatment modalities for the management of cerebral AVMs and DAVFs have proven valuable, such as stereotactic radiosurgery. This technique may prevent hemorrhage, reduce seizure rates, and relieve headaches by irradiating the AVM, causing progressive luminal obliteration. Through focused radiation, surrounding brain tissue damage can be minimized. Previous studies suggest that radiosurgery is a safe and effective AVM treatment with few reported complications.[32] However, radiosurgery is most effective for small AVMs with volumes < 10 cm^3 or maximum diameter < 3 cm.[32-34] Similar to the previous treatment modalities, angiography is still the standard to confirm complete obliteration of the lesion. Although dependent on the size of the cerebral lesion, radiosurgical procedures can be considered in the treatment of cerebrovascular malformations thought to be at high risk from an endovascular or direct surgical perspective.

Collagen and collagen-like materials have had a major impact on biomedical engineering, surgery, and treatment of vascular lesions. Concerns with species homology, immunogenicity, and rejection have been largely disqualified with several instances of safe use in surgical practice.[35-37] For example, collagen-coated platinum coils are a mainstay for embolization of saccular aneurysms (as previously described here).[38] Specific to vascular malformations, collagen/gelatin (heat/enzyme-denatured collagen) has been fabricated into microspheres with demonstrated utility in a variety of pathologies including renal, mandibular, uterine, and maxillofacial embolization.[39-44] Groups have also used collagen mixed with other embolic materials, such as PVA, for improved outcomes.[45]

CONCLUSION

In this second article of a three-part series, we hope to give the readership a view into current treatment options for cerebrovascular lesions while highlighting limitations of current clinical practices. Selection of endovascular embolization versus surgery or a combination must be reviewed on a case-by-case basis, relative risks and likelihood of acceptable occlusion. The final article in the series will summarize ongoing research and future directions for the development of novel therapeutics. ■

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