

An Overview of Embolics

How and when to use embolic agents for optimal clinical outcomes.

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Vascular embolotherapy, or embolization, is defined as the percutaneous endovascular use of one or more of a variety of agents or materials to accomplish vascular occlusion.

Embolization has made a remarkable surge during the last 2 decades, driven by improvement in imaging, breakthroughs in microcatheter technology, refinement of existing materials, and development of new embolic agents and devices. Numerous devices and materials have been used to achieve effective vascular occlusion. Broadly speaking, embolic materials can be classified based on their physical and biological properties. The majority of nonneurovascular embolization procedures are currently performed with coils, gelfoam, particles, and liquid sclerosants. There has also been increased interest in plugs, solidifying liquid mixtures, and tissue glues.

Of all the attributes and features of an embolic agent, the main factors influencing its selection in a specific application relate to the desired level of occlusion in the vascular tree and the desired permanency of occlusion. For example, when dealing with traumatic or degenerative hemorrhagic conditions, small particulate and liquid agents should be avoided because they can reach the capillary level, resulting in significant nontarget ischemia and infarction. On the other hand, such agents may be perfectly appropriate in treating some hypervascular tumors.

MECHANICAL AGENTS

Coils

Coils are available in a wide variety of sizes. They are made from either stainless steel or platinum and may have Dacron fibers placed at right angles to the long axis of the coil or other coatings, such as hydrogel, to increase the surface area and thereby increase the speed and permanence of thrombosis.

It should be noted that all coils are permanent devices and should be used when the desired occlusion is permanent. When larger nonterminal vessels are occluded

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with coils, collateral arteries form relatively rapidly, and the distal vascular bed is still perfused but at a lower pressure than before the embolization.

Catheter stability is essential to prevent coil migration or malposition. The use of a guiding catheter is therefore of primary importance. A study of the effect of sizing on stability suggests that a certain degree of oversizing is essential to minimize the risk of dislodgement. However, this should be weighed against the negative effect of an elongated and incompletely formed coil on hemostasis. An oversizing ratio of approximately 15% has been suggested in arteries, although more oversizing is required in veins. For the Azur peripheral hydrocoil (Terumo Interventional Systems, Somerset, NJ), no oversizing is required.

Newer detachable coil designs allow testing of stability before detaching the coil and may be preferred in high-risk situations. In high-flow arteriovenous malformation or arteriovenous fistula, embolization can be performed using detachable coils and the double microcatheter technique. After placing the first microcatheter at the desired level in the target vessel, the coil can be delivered but is still attached. This coil would be used as a filter to prevent migration while adding more coils through the second microcatheter. The distal coil would be detached at the end of the procedure.

Vascular Plugs

Vascular plugs are another type of mechanical occlusion agent. Because of their size and shape, the plugs have the

potential of occluding larger-sized vessels, and are used inside a larger sized sheath or guiding catheter. The Amplatzer Vascular Plug (AVP) (AGA Medical Corporation, Plymouth, MN) is made of nitinol layers attached to a detachable wire. There have been increasing reports of the usage of AVP and AVP II in different peripheral applications with great results. The most popular indication is hypogastric embolization prior to abdominal aortic aneurysm stent graft repair; however, they can be used in high-flow situations and proximal embolization in almost all indications. AGA Medical has also developed the AVP III and AVP 4, which are still under clinical evaluation. The AVP III has more nitinol layers and a modified design with faster occlusion; it is indicated in high-flow situations. The AVP 4, which is still under evaluation, can be used inside a 0.038-inch catheter.

PARTICULATE AGENTS

Particulate embolic agents are typically used for the embolization of tumor and tumor-related symptoms in addition to the treatment of certain hemorrhagic conditions. In general, these agents are administered from a selective position within the arterial vasculature of the target organ and are subsequently flow-directed toward the abnormal area being treated. Particulate agents tend to be classified as either absorbable or nonabsorbable. This may pertain to the agent itself and not necessarily to the occlusion induced by the agent.

Gelfoam

Gelfoam, a water-insoluble hemostatic agent prepared from purified skin gelatin, was the first embolic particle used in humans. The hemostatic properties are the result of induction of hemostasis by hastening development and providing structural support to the thrombus. This intense porous structure has no intrinsic hemostatic action, however, it has the potential to induce the clotting cascade. This might be possible because of the close contact of the platelets when entrapped in the porous gelatin sponge. The overall use of gelfoam is linked to its temporary effect; it is used mainly to either stop bleeding or to devascularize a lesion prior to surgical removal.

Polyvinyl Alcohol

Polyvinyl alcohol (PVA), another popular particulate agent, has historically been used in cements, packaging materials, water-resistant adhesives, cosmetics, and household sponges. The original PVA for use as an embolic agent is irregularly shaped. PVA has been successfully used to embolize vessels in patients with a variety of disorders. While the permanence of PVA as an embolic agent is well established, it is also clear that the occlusion caused by

PVA particles is not permanent. Proposed mechanisms for recanalization have included angiogenesis and capillary regrowth caused by vascular proliferation inside the organized thrombus, and resorption of the thrombus found among clumps of PVA in the lumen of an embolized vessel after the resolution of inflammation.

Spherical Embolics

Recently, the particulate embolics have been subject to the most interesting developments in the field of embolization. In the last decade, several spherical embolics have been developed. Embosphere Microspheres (BioSphere Medical, Rockland, MA) were the first to be developed and used in patients. This material has Food and Drug Administration approval for use in hypervascular tumors and uterine fibroid embolization. Based on the advantages of spherical materials in terms of ease of injection and less clogging inside the microcatheter, other spherical agents have been developed. Currently, there are five spherical embolics available in the market including Contour SE (Boston Scientific Corporation, Natick, MA), PVA microspheres; Bead Block (Terumo Interventional Systems), a PVA-based hydrogel; Quadraspheres (BioSphere Medical), a super-absorbing polymer; and Embozene (CeloNova BioSciences Inc., Newnan, GA), a hydrogel covered by a polyzene coating.

It is important to know that all spheres are not identical in terms of physical characteristics, level of occlusion, and clinical outcome. There are many parameters to consider before adopting a spherical embolic, because they can affect the clinical outcome. Some of those factors are compressibility, elastic recovery, and inflammatory reactions. Finally, all new particles should be tested in a clinical trial to prove safety and acceptable outcome.

Drug-Eluting Spheres

With the advent of spherical particles and the possibility of loading them with radioactive elements or active drugs, several new indications have been developed in this field. The theoretical advantages of drug-loaded implants are numerous: a higher local concentration and a lower total dose of drug compared with a systemic administration, and the possibility to use drugs that are otherwise potentially toxic using the systemic route.

Different types of drug-eluting spheres are available. They can behave like sponges that absorb large amounts of water or drugs in solution. The release system can be considered as a ready-to-load platform for water-soluble drugs, but a release could occur in the medium before and during injection. The electric charge of particles can be used to elute medications with an opposite charge.

Specific polymers are used to adsorb a given drug, which reaches high concentration inside the biomaterial. This product is able to release the drug on a long-term basis.

Novel drug-delivery systems have been recently evaluated for intra-arterial treatment of hepatic lesions.

Doxorubicin-eluting beads are designed for intra-arterial infusion and selective tumor targeting with or without a biodegradable matrix. Irinotecan-eluting beads for metastatic colon cancer are also under development.

The interaction between the drug and the polymeric microsphere is important when the drug is loaded in the microsphere. It has been shown that this interaction can decrease the average size of the microspheres by 50%.

In a recent study, PVA hydrogel microspheres (Bead Block, Terumo Interventional Systems) loaded with ibuprofen was studied in animals. The ibuprofen release was effective in tissues at least 1 week after embolization, which, interestingly, corresponds to the mean duration of prescription of analgesic used in clinical practice. It has been shown that the loading of doxorubicin has no impact on the handling and deliverability of the microspheres, and the locoregional drug delivery from microspheres caused targeted tissue damage with minimal systemic impact. Microspectrofluorimetry analysis of pig livers embolized with doxorubicin-loaded beads has shown very high levels of doxorubicin in liver tissue that persists over several months.

Resorbable Microspheres

The new trend and future of embolization is heading toward the use of resorbable microspheres. The ideal material should be loadable and visible in fluoroscopy and eventually in magnetic resonance with predictable resorption. The resorption speed is influenced by many factors such as nature, homogeneity, size, enzymatic potential, and local inflammatory response. In large sizes (150 μ m and over), the only available material to date is gelatin microspheres developed by Tabata in Japan. Recently, a new resorbable porous gelatin microsphere has been developed and used in Japan (Gelpart, Nippon Kayaku Co., Ltd., Tokyo, Japan). Because of its porosity, this material is also loadable. Preliminary studies have demonstrated that Gelpart conjugates strongly to cisplatin with sustained drug release. With the development of resorbable agents and the possibility of controlling the resorption in time, the embolic agents will become much more organ and indication dependent.

INJECTION TECHNIQUE

The injection technique of embolic particles is of paramount importance. Flow-directed injection of the particles respects the physiology of the circulation. Forceful injection

can result not only in vessel damage or reflux, but in some situations, it may provoke the opening of the normal vascular anastomosis with subsequent nontarget embolization.

LIQUID AND SCLEROSING AGENTS

Liquid and sclerosing agents permanently destroy the vascular endothelium through different mechanisms depending on the type of agent used: chemical (iodine or alcohol), osmotic effect (salicylates or hypertonic saline), and detergents (morrhuate sodium, Sotradecol, polidocanol, and diatrizoate sodium). If injected in the artery, they can pass the capillary level, allowing distal embolization. Their usage is therefore much more challenging. They are mostly used in organ ablation such as tumors, veins, or arteriovenous malformations.

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Alcohol

Absolute alcohol is a very effective embolization agent. It can be used intravascularly or through direct puncture of the lesion. It is important to consider the risk of necrosis of neighboring tissues and of the skin when using alcohol by a percutaneous or endovascular route. The risk of systemic toxicity increases in doses above 1 mL/kg or if a volume greater than 60 mL is used. Patients must be monitored closely, and some practitioners advocate the use of continuous pulmonary artery pressure monitoring during ethanol procedures.

Tissue Adhesives

Tissue adhesives, or glue, are fast and efficient nonresorbable, nonradiopaque embolic material based on polymerization of the acrylate monomer. Cyanoacrylate is composed of an ethylene molecule with a cyano group and an ester attached to one of the carbons. Glue starts to polymerize on contact with anionic substances such as plasma, blood cells, endothelium, or saline. When in contact with the vessel, glue provokes an inflammatory reaction resulting in fibrosis. Control of time and place of polymerization depends on many factors such as blood flow, caliber of vessel, dilution of the acrylate, velocity of injection, etc. The speed of polymerization is affected by the concentration of iodized oil. Tantalum or tungsten can be added to the solution before injection to increase the radio-opacity of the agent. Embolization with glue is always performed through

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a microcatheter. The microcatheter is typically changed after the injection. It needs to be positioned as close as possible to the embolization target. The microcatheter may become glued to the vessel. This is a potential complication that might occur in case of reflux, early polymerization, or delayed removal of the microcatheter. This issue occurs less frequently with a hydrophilic-coated microcatheter. Deep and diffuse penetration can cause ischemia or even infarction of neighboring tissue. The use of an over-diluted solution can result in delayed polymerization with the risk of distal artery or draining vein occlusion.

Onyx (ev3 Inc., Plymouth, MN), is a biocompatible liquid embolic agent. It is an ethylene vinyl alcohol copolymer dissolved in various concentrations of dimethyl sulfoxide (DMSO) and opacified with micronized tantalum powder. When this mixture contacts aqueous media, such as blood, the DMSO rapidly diffuses away, with resulting in situ precipitation and solidification of the polymer. It forms a soft elastic embolus without adhesion to the vascular wall or the catheter. The polymerization process is time-dependent and is mainly influenced by the amount of ethylene in the mixture (with less ethylene, the polymer becomes softer). Because the polymer will solidify on contact with aqueous media, the delivery catheter must be preflushed with DMSO. A DMSO-compatible catheter is required. Onyx is nonadhesive, allowing for easy removal of the delivery catheter and of the polymer itself. Unfortunately, it is quite expensive. This agent is mainly used for intracranial aneurysms. Onyx has been successfully used for the treatment of different conditions such as endoleak.

CONCLUSION

Embolization therapy has become a major arm of modern interventional therapy. Its applications have become fundamental cores in the multimodality treatment paradigms in trauma, oncology, and endovascular therapy of vascular malformations and aneurysms. This technique is rapidly evolving toward an excellent mode of drug delivery. The knowledge of different techniques, materials, and vascular anatomy and variants is essential to obtain good clinical outcomes and minimize complications. ■

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