Does Material Matter?

Particulate Embolics

The background, available options, and ideal applications of particulate embolics.

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The selection of an embolic agent should be based on the clinical indication for the procedure, the desire to produce temporary or permanent occlusion, the level of occlusion (proximal or distal), flow dynamics/collateral circulation, the risk of complications such as necrosis or nontarget embolization, and cost. Microparticles can be made of several types of materials, including polyvinyl alcohol (PVA foam embolization particles, Cook Medical, Bloomington, IN), acrylamido polyvinyl alcohol (Bead Block, Biocompatibles UK Ltd, Surrey, UK), hydrogel core with Polyzene-F coating (Embozene microspheres, CeloNova Biosciences, Inc., San Antonio, TX), trisacryl gelatin microspheres (Embosphere microspheres, Merit Medical Systems, Inc., South Jordan, UT), and a combination of vinyl acetate and methyl acrylate with sodium acrylate alcohol copolymer (HepaSphere microspheres, Merit Medical Systems, Inc.).

These particles can have an irregular surface (conventional PVA) or a smooth spherical shape. Conventional PVA and HepaSphere have the ability to expand in liquid solution. Most of the other common spherical microparticles are calibrated, compressible, and may be loaded with medications such as chemotherapeutic agents. All microparticles are classified as permanent, nonabsorbable, biocompatible, or flow-directed, with most of these embolic agents being nonradiopaque on fluoroscopy.

BACKGROUND

The first available generation of microparticles was conventional/irregular PVA, a petroleum-derived polymer similar to PVC, which promotes permanent vascular occlusion through mechanical obstruction, as well as a foreign body inflammatory reaction that promotes granulation tissue formation.[1] The original trade name of PVA was Ivalon and was initially used for furniture as stuffing in sofas. Ivalon sponge was also utilized in breast implants during the 1950s, and in the 1970s, Charles Kerber, MD, at the University of Pittsburgh, proposed its use as an embolic material.[2] Although biocompatible, fibrous tissue grows into the sponge structure, making it hard. Irregular PVA is relatively inexpensive and easy to use compared to other nonparticulated embolic agents and is considered the first generation of PVA microparticles. Due to its cost-effectiveness, this type of microparticle is most commonly used in our practice to successfully treat many pathologies, which we discuss later.

Figure 1. Ten- and 3-mL syringes connected by a three-way stopcock may be used to agitate the irregular PVA suspension in order to produce a homogeneous mixture. This maneuver should be avoided when spherical PVA is utilized due to the risk of damaging the microparticles.

The second generation of PVA demonstrated a more regular surface and included compressible and spherical PVA microparticles (Contour, Boston Scientific Corporation,

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Natick, MA). They are made through a method called "matched-density suspension" and are available in 45- to 1,800-µm sizes. The third generation of PVA microparticles evolved to a smoother contour—a compressible embolic agent that does not expand when suspended in saline or contrast, which produces a more consistent calibration. The third-generation microparticle Bead Block is a PVA hydrogel-based microsphere manufactured using N-fil technology. This material, acrylamido polyvinyl, was originally used in the manufacture of contact lenses. The spheres are colored blue for visualization within the syringe, are not radiopaque, and are available in sizes ranging from 100 to 1,200 µm. DC Bead (Biocompatibles UK Ltd) is another spherical PVA-based bead that can be loaded with chemotherapeutic agents (commonly used to treat primary and metastatic liver cancer) by an active process that involves ionic interactions between the microspheres and the chemotherapy agent (doxorubicin/epirubicin/irinotecan).

APPLICATIONS

Although considered a permanent embolic agent, recanalization of the blood vessels over time (weeks to months) is possible. This happens mainly in the midsized arteries, where the blood vessel flow tends to push the microparticles to the periphery of the vessel lumen, which experiences slower blood flow. Also, PVA particles can be excluded from the vessel lumen through encapsulation by the vascular intima and expelled into the surrounding tissues, even reaching the skin if the lesion is relatively superficial. Irregular PVA is available as dry particles, with sizes ranging from 50 to 1,200 µm, which allows adequate selection of the particle size to fit various applications (PVA foam embolization particles). Typical PVA microparticles are made by grinding the plastic material on a file to produce particles of diverse sizes. The particles are then passed through sieves of differing sizes, and the appropriate particle sizes selected.

PVA for catheter injection is prepared by forming a dilute suspension of contrast agents within a sterile cup. Many operators use a system with two syringes and a three-way stopcock for injection. The particles have a very irregular surface resembling small asteroids, which tend to form particle clumps inside the catheter and within the vessel lumen, where it may produce vascular occlusion more proximal than is desirable. PVA may be more difficult to inject through smaller microcatheters with internal diameters of 0.018 to 0.021 inches. It is therefore necessary to agitate the suspension, producing a more homogeneous mixture immediately before injection (Figure 1). Following this basic principle, the typical embolization with conventional/irregular PVA may be accomplished through a microcatheter without significant problems. Gentle agitation of the syringe containing spherical microparticles is preferred to create a homogenous solution as opposed to stirring it through the three-way stopcock, which could damage the surface.

Embolization using microparticles requires adequate arteriography to map out the vascular bed that is to be embolized. This has the potential to occlude arterial vessels at all levels, depending on the size of the particles used.[3] It is also important to check the compatibility of the microparticle size and the microcatheter diameter. PVA < 700 µm, 700 to 900 µm, and 900 to 1,200 µm can be used with 0.021-, 0.024-, and 0.038-inch catheters, respectively. When conventional PVA is used, it is important to mix the particles with a 50/50 iodine contrast:saline dilution. This permits acceptable blood vessel opacification while lowering the overall viscosity of the solution,

TABLE 1. TIPS AND TRICKS TO MINIMIZE COMPLICATIONS

- Selective and stable access with a microcatheter or diagnostic catheter should be achieved.
- Adequate diagnostic angiography is key for vasculature mapping and procedure planning. Watch for shunts and collateral circulation.
- Check the compatibility of the PVA microparticle size and the microcatheter internal diameter.
- Conventional PVA: mix with diluted contrast solution (50/50 iodinated contrast:saline).
- Conventional PVA solution must be homogenized just before injection through a three-way stopcock. This maneuver should be avoided with calibrated microparticles due to the risk of damage.
- Simulation: hand contrast injection should be performed immediately before microparticle embolization in order to test the force of injection to avoid reflux.
- Embolization must be performed under active fluoroscopy at all times to minimize the risk of reflux.
- Injection mode: continuous when there is no resistance to the blood flow, subtracting free flow. Consider changing to pulsatile injection as resistance builds up in the embolized vascular bed.
- Sluggish flow? Stop, observe, and avoid reflux!
- Blood vessel flow stasis is the typical endpoint. Wait a few minutes, and recheck before finishing the case.
- Most common particle sizes used: 300–500 µm and 500–700 µm.

TABLE 2. MICROPARTICLES: ADVANTAGES AND DISADVANTAGES

Advantages
- Relatively inexpensive, inert embolic agent, nonabsorbable
- Extensive experience; it has been utilized for decades
- Quick thrombosis in the absence of coagulopathy
- Effective embolic agent

Disadvantages
- Risk of nontarget embolization
- Conventional PVA: risk of clogging the microcatheter
- Nonradiopaque; requires admixture with contrast solution for visualization
- Higher risk of pain/undesired grade of ischemia if microparticles are < 100 µm

thereby decreasing the risk of microcatheter occlusion.

Microparticle injection produces mechanical vascular lumen occlusion and activation of the patient's platelet aggregation and clotting mechanisms. It is therefore strongly advisable to correct any coagulopathy or thrombocytopenia before or during the procedure to improve the efficacy of the embolization.

Currently, the most common indications for the use of microparticle embolic agents are for embolization of uterine arteries (uterine fibroid embolization for compressive symptoms and/or excessive bleeding), bronchial arteries (hemoptysis), external carotid artery branches (glomus jugulare tumor prior to resection), renal arteries (large renal cell cancer before to resection, angiomyolipoma), and in the preoperative embolization of primary bone tumors. Additionally, they can be used for the management of epistaxis, benign (large hemangioma) or malignant (hepatocellular carcinoma) liver neoplasms, thrombocytopenia associated with splenomegaly, solid organ bleeding posttrauma, arteriovenous malformations, and preoperative portal vein embolization to generate liver hypertrophy, among other less common indications.

TECHNICAL CONSIDERATIONS

There are numerous technical details related to the use of microparticles that should always be taken into consideration regardless of the experience of the interventionist: (1) target vessel flow (as the microparticles are delivered by flow direction, the presence of arteriovenous shunts typically requires larger microparticles than previously planned), (2) duration of vascular occlusion (expected recanalization of the midsized/proximal vessels of the vascular bed to be embolized), (3) risk of nontarget embolization (especially in high-resistance vascular beds [eg, liver tumor embolization after the patient has received antiangiogenic chemotherapy]), and (4) excessive tissue ischemia/necrosis due to the selection of small particles (PVA < 100 µm).[4] Table 1 outlines tips and tricks that may be employed to minimize the risk of complications related to microparticle embolization procedures. Table 2 outlines the numerous advantages and disadvantages associated with the use of these embolic agents.

ANIMAL AND HUMAN STUDIES

With the goal of understanding whether differences among the available irregular and spherical microparticles exist, various animal model studies and clinical trials have been conducted, especially in the uterine fibroid arena. In one animal model, Pelage and colleagues[5] compared the acute effects of PVA and calibrated microspheres (CMs) in uterine artery embolization. They found that PVA particles clumped more readily, produced more uterine necrosis, and occluded vessels of a wider range of sizes than CMs. Small particles had a higher score ($P = .02$) of uterine necrosis than large particles. The microparticle size and the diameter of the occluded vessels only had a statistically significant correlation in the CM group ($r = 0.762$; $P < .001$). The investigators concluded that PVA particles are associated with intense uterine necrosis in sheep and extensive arterial occlusion regardless of size.

CMs, which are associated with less uterine necrosis, permit a segmental arterial occlusion correlated with size. Senturk and colleagues[6] compared the most frequently used microparticles—conventional PVA (150–250 µm), spherical PVA (150–300 µm), trisacryl gelatin microspheres (100–300 µm), and expanding microspheres (50–100 µm)—in a rabbit model. Results showed an angiographic recanalization rate of 100% in the expanding microspheres group compared with 0% in the PVA and trisacryl gelatin microspheres groups ($P = .014$). Occlusion levels in the PVA group were more proximal than with any of the microspheres, whereas the expanding microspheres caused significantly less infarction than the other embolic agents ($P = .021$).

In human studies, Rasuli and colleagues[7] compared the efficacy of spherical PVA versus conventional/irregular PVA particles for uterine fibroid embolization. At 12-month follow-up, the use of spherical PVA particles resulted in less fibroid tumor shrinkage and less improvement in clinical symptoms. Siskin and colleagues[8] conducted a prospective randomized study comparing the degree of uterine fibroid infarction between trisacryl gelatin microspheres versus

PVA microspheres. Treatment failure was statistically higher in the PVA group versus the trisacryl gelatin microsphere group ($P = .025$). The investigators concluded that there was a significantly greater degree of tumor infarction in patients treated with trisacryl gelatin microspheres than in patients receiving PVA microspheres.

Spies and colleagues[9] compared the outcomes of uterine artery embolization for treatment of leiomyomas with the use of trisacryl gelatin microspheres versus spherical PVA particles. Follow-up with uterine magnetic resonance imaging showed that the group treated with trisacryl gelatin microspheres was significantly more likely to have complete fibroid infarction ($P = .02$) and were more likely to demonstrate at least 90% tumor infarction ($P = .03$) compared with patients treated with spherical PVA.

CONCLUSION

In our practice, conventional PVA microparticles are used in the majority of cases because they are relatively inexpensive, easy to use, and effective. Excellent clinical outcomes can be achieved (as confirmed during follow-up consults in the clinic) at low complication rates. Clinical endpoints and low cost should therefore prevail. ■

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