Do Particle Size and Type Matter?

Lessons learned from experience with uterine artery embolization.

BY ROBERT L. WORTHINGTON-KIRSCH, MD

During the last several years, we have seen an expansion in the devices available for particulate embolization. This expansion has been spurred on by the evolution of uterine artery embolization (UAE) for fibroid disease and regional cancer therapies, especially hepatic chemoembolization. It has become apparent that the various particle embolic agents are not identical and cannot be used interchangeably with the same embolization protocols. This article reviews the various agents available, the rationale for choosing a specific device, and considerations of the details of embolization protocols. The author speaks from his experience with UAE. The issues and decisions will be similar when considering embolization in other vascular beds.

The goal of UAE is occlusion of the blood supply to the fibroids, sparing the normal tissues. The clinical utility and safety of UAE as a primary therapy for fibroid disease was discovered more or less by accident (Ravina JH; personal communication,1998-1999),[1,2] although it has since been validated by large case series,[3-5] registry data,[6-8] and randomized prospective trials.[9,10] Because of this history and the lack of a good animal model[11] for fibroid disease, there are still significant questions about the pathophysiology of UAE. It does appear that the most important target vessels for UAE are the arterioles in the perifibroid plexus. This vascular bed was first described by Sampson.[12] These vessels, measuring approximately 650 µm in diameter, appear to be the site of deposition of embolic material after successful UAE.[13,14]

INITIAL EMBOLIC AGENTS

When UAE for fibroids started to become popular, there were two particulate embolic agents generally available—gelatin sponge and irregular ground PVA particles. Both were used for UAE, and in fact, the earliest protocols called for embolization of the uterine vascular bed with PVA particles followed by "capping off" the uterine artery with gelatin sponge pledgets or stainless steel embolization coils. The capping off was done both to ensure completeness of the embolization and to prevent any residual particles in the main uterine artery from refluxing due to Venturi effect and causing a nontarget embolization. It is fortuitous that the first series of UAE was performed with PVA particles in the 350- to 500-µm size range. It has been shown that these form aggregates that are the appropriate size for the target vessels of the perifibroid plexus.

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However, neither gelatin sponge nor irregular ground PVA is an ideal embolic agent. Gelatin sponge requires a significant effort to prepare, and it is difficult to obtain uniformly sized particles. Larger gelatin sponge particles provide a more proximal embolization than desirable. This may be effective, especially in the short term. However, there are significant drawbacks to a proximal embolization (or other proximal occlusions of the uterine artery, such as ligation or temporary tourniquetting). Proximal occlusion of the uterine artery does not reliably devascularize the fibroids. This is obvious given the known presence of collateral flow to the uterine body and fibroids from the ovarian arteries.[15-17] Additionally, gelatin sponge incites an aggressive inflam-

matory reaction.[18] This potentially can lead to permanent occlusion of the uterine artery, preventing a repeat embolization should it become necessary. In the author's experience of repeat arteriography in 10 patients who had received gelatin sponge pledgets in addition to PVA particles for UAE, 19 of 20 uterine arteries were completely occluded.

There are clinicians, particularly in Japan, who have had great success using gelatin sponge as an embolic agent for UAE. They use a meticulous and time-consuming technique of cutting the gelatin sponge into consistent 1-mm cubes[19] and have shown preservation of the main uterine artery segments in at least some patients after the procedure.

Irregular ground PVA also has drawbacks as an embolic agent. The most serious of these is that it is often difficult to work with because the irregular particles tend to clump and clog in catheters—both standard angiographic catheters as well as microcatheters. The irregular particle size means that the level of embolization is difficult to control, with a significant number of particles penetrating further into the vascular bed than desirable (acting as smaller particles) and others forming aggregates that cause a more proximal embolization than desirable.[20,21]

NEXT-GENERATION EMBOLICS

Conceptually, a spherical embolic agent would avoid the disadvantages of irregular shape and aggregation experienced with both gelatin sponge and irregular PVA preparations. We have had the opportunity to test this concept with a number of products during the last several years. The first of these on the market in the US was Embosphere (ES) (Biosphere Medical, Rockland, MA), which is a compressible spherical agent composed of trisacryl and gelatin. ES was approved for general embolic use in 2000 and specifically for fibroid embolization in 2002. Shortly after the appearance of ES on the market, Boston Scientific Corporation (Natick, MA) released a spherical embolic agent called Contour SE (CSE). Unlike ES and the other spherical embolic agents that have since been released, CSE appears to be composed of porous PVA foam.

In 2003, Biocompatibles International (Farnham, Surrey, UK) released BeadBlock (BB), which is a spherical agent composed of PVA hydrogel. The next device to become available in the US will probably be Embozene a particle with a hydrogel core and a proprietary biocompatible coating produced by CeloNova BioSciences (Newnan, GA). Embozene is already in use in the EU. The author has experience with all of these spherical embolic agents except Embozene.

These products can be divided into two groups. Contour SE appears to be a spherical foam ball, whereas the other three agents are hydrogel microspheres. The hydrogel microspheres have similar handling characteristics. They suspend in dilute contrast and are essentially effortless to inject through a catheter, even through a microcatheter with a narrower lumen than the nominal diameter of the microsphere. This is because they deform in a narrow lumen and rebound into their native spherical shape immediately after exiting the catheter tip. The hydrogel particles do not form aggregates in the way that irregularly shaped particles do.

> "Hydrogel microspheres offer distinct advantages as embolic agents . . . "

Contour SE has handling characteristics midway between irregular ground PVA and the hydrogel microspheres. The author's experience has been that it does clog and can be somewhat difficult to inject through a microcatheter, although not as badly as irregular ground PVA particles. When the particles are injected through a microcatheter smaller than their nominal diameter, they do not recover their original shape after release from the catheter tip.[22] The initial clinical reports suggested that CSE was as effective as other embolic agents for UAE.[23] However, later reports indicated that CSE caused significantly less fibroid infarction than either irregular ground PVA[24] or ES.[25] These findings led to the development of a defined protocol for using CSE,[26] which called for the use of 700- to 900-µm particles injected through a microcatheter with a .027-inch inner lumen. It should be noted that .027-inch is 662 µm, so that the effective embolic agent is apparently not sphere-shaped but football-shaped, which acts as a smaller embolic agent than its nominal size would suggest.[22] Despite the change in protocol, UAE with CSE has been shown to be inadequate compared to UAE with ES.[27]

UAE PROTOCOL

The generally accepted protocol for UAE with ES is to start the embolization with 500- to 700-µm particles and upsize to 700- to 900-µm particles after 6 to 8 mL (three to four syringes) of 500- to 700-µm particles have been injected into the uterine artery if the desired angiographic endpoint has not been reached. In some cases

(approximately one in 30 in the author's experience), further upsizing to 900- to 1,200-µm particles may be necessary. If there is reflux across the utero-ovarian collateral path on initial injection, embolization is started with 700- to 900-µm particles.

Because BB appeared so similar to ES, the same protocol was applied to BB when it first appeared on the market. However, it was discovered that UAE with 500- to 700-µm BB caused less complete fibroid devascularization than expected.[28] Further investigation has shown that BB is somewhat softer and more deformable than ES and thus penetrates further into the vascular bed than similarly sized ES.[29] Accordingly, the current recommendation is that when UAE is performed with BB, one should initially use 700- to 900-µm particles. Current ongoing studies suggest that this is as effective for devascularization of fibroids as embolization with ES.[28,30]

Hydrogel microspheres offer distinct advantages as embolic agents over other agents, such as gelatin sponge, irregular PVA particles, and CSE. They are easy to administer, practically never jamming or clogging in the catheter system. They afford consistent controllable embolization at defined levels in the vascular bed. These embolic agents are also emerging as drug delivery systems. The future of embolotherapy belongs to this type of embolic agent.

CONCLUSION

It must be remembered that the different embolic agents are not clones of one another. Despite similar appearances and handling characteristics, each one has specific physical and chemical properties that affect their in vivo behavior. Clinicians have to familiarize themselves with these differences to make the correct choice of embolic agent, and then to use the correct protocol for embolization. Size does matter. ■

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