A Novel Resorbable Embolization Microsphere for Transient Uterine Artery Occlusion: A Comparative Study with Trisacryl-Gelatin Microspheres in the Sheep Model

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ABSTRACT

Purpose: To evaluate angiographic recanalization, inflammatory reaction, and uterine damage after sheep uterine artery embolization (UAE) with a novel calibrated resorbable embolization microsphere (REM) and compare the results with control nonresorbable microspheres.

Materials and Methods: Six hormonally artificially cycled sheep underwent bilateral UAE until stasis with either REM or trisacryl-gelatin microspheres (TGMS). At 7 days, control angiograms were obtained to assess the residual vascularization at arterial and parenchymal phases. The animals were then sacrificed for analysis of the presence of microspheres, inflammatory foreign body reaction, and surface areas of uterine damage.

Results: Mean volume of microspheres injected per uterine artery (UA) or per animal did not differ between groups. At day 7, the flow was normal for six of six UAs that received embolization with REM versus only three of six UAs with TGMS ($P = .0455$, χ^2 test). Uterine parenchymography showed no defects in six UAs in the REM group versus five defects in six UAs in the TGMS group ($P = .0060$, χ^2 test). No REM or residual fragments of microspheres were observed on histologic analysis. TGMS were observed in tissues and accompanied by a mild inflammatory response. Necrosis rates were not significantly different between the two products, either in endometrium (REM 23.5% ± 28.8% [median 8.1%] vs TGMS 21.8% ± 23.7% [median 14.6%]) or in myometrium (REM 8.2% ± 22.7% [median 0.0%] vs TGMS 8.8% ± 20.8% [median 0.9%]). Endometrium alteration rate was lower with REM than with TGMS (39.7% ± 25.7% [median 34%] vs 60.6% ± 27.1% [median 71%]; $P = .0060$, Mann-Whitney test). Myometrium alteration rates were not significantly different between REM (45.7% ± 37.1% [median 63.0%]) and TGMS (37.8% ± 34.0% [median 19.1%]).

Conclusions: At 1 week after sheep UAE with REM, the recanalization was complete, the microspheres were completely degraded, and there was no remnant inflammatory response.

ABBREVIATIONS

IRFB = inflammatory reaction of foreign body type, PEG = polyethylene glycol, PLGA = polylactic-glycolic acid, REM = resorbable embolization microsphere, TGMS = trisacryl-gelatin microspheres, UA = uterine artery, UAE = uterine artery embolization

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For uterine fibroid embolization, nonbiodegradable particles are not ideal. After having played their occlusive role, they persist as remnant foreign bodies in the uterus and generate an inflammatory response, which sometimes may last months (1–3). Uterine arteries (UAs) that received embolization may recanalize, but this is inconstant and partial (2,4). It has been found in the sheep model that embolization particles could constitute a durable obstacle to flow in UAs, even after a partial recanalization, reducing fertility or lowering birth weight (4).

By contrast, biodegradable embolization materials are designed to generate an inflammatory reaction that is

limited to their period of resorption to ensure a full and constant recanalization of UA. The resorption time of degradable particles is long and associated with vascular damage and remodeling that delay and limit recanalization. Gelatin sponge particles undergo a prolonged degradation that lasts for weeks or months and is accompanied by a chronic inflammatory response, vessel remodeling, and a fibrotic reaction (5,6). Collagen-coated polylactic-glycolic acid (PLGA) microspheres degrade slowly over several months, they generate a local inflammatory response, and the UAs remain fully occluded by fibrous connective tissue at 6 months (7). The persistence of particles in the vessel wall and the remodeling of the UA could act as an obstacle to blood flow. The important dilation of the UA that occurs during pregnancy (8–10) could be compromised.

To remedy these drawbacks, we have designed a resorbable embolization microsphere (REM) that would satisfy two imperatives. First, it should occlude the vessel for a short time—between a few hours and a few days—to achieve ischemia of fibroids. Second, it should subsequently be quickly and completely eliminated, before the onset of a chronic inflammatory response and vessel wall remodeling. We postulated that the UA recanalization and the absence of chronic inflammation would facilitate the healing process of the uterus, which could sustain collateral damage during fibroid embolization. UA recanalization would be beneficial to changes in UA diameter during hormonal cycling and pregnancy.

We designed the REM from a polyethylene glycol (PEG) hydrogel cross-linked with hydrolyzable bridges (11). PEG hydrogel was chosen because it is used in many biomedical applications for its hydrophilicity, elasticity, and biocompatibility (11). The resorption speed of PEG hydrogel REM can be controlled by adjusting the polymer chemistry of the hydrolyzable cross-link. The components were chosen to generate, after hydrolysis, macromolecules that are water-soluble to avoid any accumulation in the organism leading to inflammatory reactions (12). Hydrolyzable linkages were incorporated into the hydrogel backbone to shorten the size of the polymer degradation products (< 50 kg/mol), facilitating renal elimination (13,14).

PEG hydrogel microspheres with high water content ($\sim 90\%$) have been synthesized with sizes ranging from 100–1,000 μm. Their biocompatibility was assessed in vitro by cytotoxicity tests of the microspheres and their degradation products on various cells in culture and in vivo by subcutaneous implantation in rabbits (15). Degradation of the microspheres by hydrolysis in phosphate-buffered saline is achieved in < 24 hours. An in vivo study demonstrated that this REM allowed targeted and efficient occlusion of renal arteries and angiographic recanalization at 1 week with no residual inflammation in tissue (16). The purpose of the present study was to evaluate recanalization, inflammation, and uterine damage with REM 7 days after uterine artery embolization (UAE) in the sheep model by comparison with a nonresorbable reference microsphere.

MATERIALS AND METHODS

Microspheres

REM (ResMic; Occlugel SAS, Jouy-en-Josas, France) were made by suspension polymerization of a PEG hydrogel cross-linked with PLGA-PEG-PLGA hydrolyzable bridges (15). The formulation was adjusted to obtain a resorption time of 24 hours in phosphate-buffered saline. Hydrated REM were soft and contained about 90% of water. After sieving at the size range of 500–700 μm, REM were freeze-dried and sterilized by β-irradiation (IONISOS, Chaumesnil, France). REM were compared with trisacryl-gelatin microspheres (TGMS) (Embosphere; Merit Medical Systems, Salt Lake City, Utah) at the nominal range 500–700 μm, which is the most common diameter used for uterine fibroid embolization in clinical practice.

Animals

All experiments were approved by the institutional animal care and use committee. Embolization (three procedures per type of embolic agent) was performed on six adult Préalpes Sheep (54 kg ± 3, 48 mo ± 22). For each animal, the type of embolic agent used was randomly assigned.

Embolization Procedure

Sheep were hormonally artificially cycled 16 days before the embolization procedure to obtain a maximal dilation of UAs (17). Sheep were not fed for 24 hours before the procedure. Anesthesia was induced by intramuscular injection of 15 mg thiopental sodium (Nesdonal; Merial, Lyon, France) per kilogram of body weight. Each animal was placed in supine position, intubated, anesthetized with a mixture of 1.5% isoflurane (Vetflurane; Virbac, Carros, France) and 98.5% oxygen (Linde, Paris, France), and ventilated using a Primus workstation (Dräger Medical, Antony, France). End-tidal carbon dioxide levels were measured continuously and maintained at 26–36 mm Hg with a monitor (Infinity Gamma XXL; Dräger Medical). Peripheral arterial oxygen saturation, maintained at $>95\%$, was monitored with a probe applied to the ear. Aliquots of 2 mL of embolization microspheres were suspended in a solution of contrast agent (Telebrix 35, 350 mg I/mL; Guerbet, Villepinte, France) and saline (Versol; Laboratoires Aguettant, Lyon, France) following the manufacturer's instructions for use (REM, 12 mL saline + 6 mL contrast agent; TGMS, 8 mL saline + 10 mL contrast agent). Animals were randomly assigned to receive REM or TGMS. A 5-F vascular sheath was placed in the femoral artery by using the standard Seldinger technique under sterile conditions. Selective