Clinical aspects of uterine artery embolization
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Smeets AJ, Nijenhuis RJ, van Rooij WJ, Lampmann LE, Boekkooi PF, Vervest HA, Lohle PN.

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EMBOLIZATION OF UTERINE FIBROIDS WITH POLYZENE F COATED HYDROGEL MICROSPHERES: INITIAL EXPERIENCE
Abstract

Purpose
To evaluate the efficacy and safety of precisely calibrated microspheres (Embozene) for uterine artery embolization (UAE) in women with symptomatic uterine fibroids.

Patients and Methods
Between August 2006 and August 2008, 86 consecutive premenopausal women (mean age 43.9 years, median 44, range 28-54) were treated with UAE. Embolization was performed via a bilateral femoral approach using two microcatheters. Calibrated microspheres of 500, 700 and 900 µm alone or in combination were used as embolic agent. MRI was used to assess the change in uterine and dominant fibroid volume as well as dominant fibroid and overall infarction rate. Clinical follow-up was evaluated by the Uterine Fibroids Severity and Quality of Life questionnaire (UFS-QOL) at baseline, at 3 months and in November 2008.

Results
At 3 months, mean volume reduction of the dominant fibroid and uterus was 45% and 42% from initial mean volume. Mean dominant fibroid and overall infarction rate at 3 months were 95% and 96%. No microcatheter blockage occurred and there were no technical complications. At follow-up, permanent amenorrhea developed in 7 women (8.1%). Four women (4.7%) had additional therapy after UAE; three had a hysterectomy and one was embolized for a second time. The UFS-QOL showed significant (p<0.0001) improvement in both symptom severity and quality of life after 3 months and continued to improve at last follow-up of mean 12.8 months.

Conclusion
The use of precisely calibrated microspheres for UAE is effective and safe. Microcatheter blockage did not occur. Clinical and imaging results are comparable to studies in which other microspheres are used.
Introduction

Uterine artery embolization (UAE) is increasingly used for treatment of uterine fibroids in symptomatic women unresponsive to medical therapy (1-5). Several embolic particles have been used successfully for UAE (6,7). Tight size calibration is considered important for effective embolization of arteries of the fibroids only and sparing the smaller arteries of the uterus. Particles that are larger than indicated on the vial may cause blockage of the catheter or too proximal embolization of uterine artery branches with insufficient infarction of the fibroid. On the other hand, particles that are smaller than indicated may penetrate deep in uterine arterioles with possible ischemic damage to the uterus. It is generally assumed that the optimal particle size for embolization of fibroids while sparing the uterus is 700-900 µm. Precise particle size calibration seems advantageous to avoid technical and clinical complications attributed to aberrant particle sizes (8-11).

In this study, we evaluated feasibility, efficacy and safety of a new biocompatible embolic agent consisting of microspheres calibrated with a narrow bandwidth.
Patients and Methods

Patients
This study was approved by the Institutional Review Board and written informed consent was obtained in all women. Between August 2006 and August 2008 86 consecutive premenopausal women (mean age 43.9 years, median 44, range 28-54) with symptomatic uterine fibroids were included. Seventy-four women presented with heavy menstrual bleeding, 46 with pelvic pain and 43 with bulk-related symptoms. All women were previously treated medically with insufficient clinical results. Before UAE, all patients had a gynecological consultation to confirm that presenting symptoms were caused by uterine fibroids and not by infection or malignancy. Exclusion criteria for UAE were pregnancy, pelvic inflammatory disease, gynecological malignancy, pure adenomyosis and thin-stemmed pedunculated fibroids.

Calibrated microspheres
The embolic material used in this study was Embozene Microspheres (CeloNova BioScience, Newnan, GA, USA). These microspheres consist of a hydrogel core of polymethylmethacrylate and a flexible shell of polyphosphazene: a synthesized inorganic biostable and biocompatible polymer (12,13). The microspheres suspended in contrast material are spherical, flexible and easy compressible. Embozene microspheres are precisely calibrated by sieving with a high uniformity of spheres (Fig. 1). The microspheres are color coded according to size and are available in sizes ranging from 40-1300 µm.

Figure 1. Photomicrograph of Embozene spheres 700 µm. Note uniform size.
**Imaging**

Pelvic MRI (native and gadolinium-enhanced T1 weighted sagittal and axial images) was performed at baseline and at 3 months follow-up. MRI’s were evaluated by 2 radiologists in consensus. Uterine and dominant fibroid volumes were calculated using the formula of a prolate ellipse (length x depth x width x 0.5233). Volume changes were calculated as proportions of initial volumes. Contrast-enhanced T1-weighted images were used to assess the percentage of infarction of the dominant fibroid and the overall uterine infarction by visual estimation of decrease in enhancement as compared to baseline. Infarction rates were classified as 100%, 0-99%, 80-90% and less than 80% (14).

**Embolization procedure**

Embolization was performed under local anesthesia with antibiotic prophylaxis. Via a bilateral femoral co-axial approach two microcatheters (EmboCath Plus, BioSphere Medical, inner lumen 710 µm) were positioned in the horizontal part of both uterine arteries distal to the cervicovaginal branches. Embolization was performed simultaneously on both sides using calibrated microspheres of 500, 700 and 900 µm alone or in combination. Technical success was defined as a complete stop in the ascending part of both uterine arteries (15). The size of calibrated microspheres used was recorded.

**Clinical follow-up**

The standardized and validated Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire (16) was filled out by all patients before UAE, at 3 months and at latest follow-up in November 2008. In addition, adverse events and additional therapies during follow-up were recorded (17).

**Data analysis**

Complications were expressed as a proportion with 95% CI. Mean volume reduction of dominant fibroid and uterus was calculated as a proportion of initial volume. Chi-square test was used for comparison of proportions. P-values <0.05 were considered significant. UFS-QOL questionnaires were evaluated with ANOVA. Statistical analysis was done with MedCalc statistical software (MedCalc, Mariakerke, Belgium).
Results

Embolization procedure
Embolization was technically successful in all 86 patients. In the 172 microcatheters that were used to deliver the microspheres, no blockage occurred (0%, 95% CI 0-1.8%). The microsphere sizes that were used are listed in Table 1. There were no adverse events during the hospital admission for embolization (0%, 95% CI 0-3.7%).

Imaging
Mean dominant fibroid volume before UAE was 185 cm$^3$ (median 123 cm$^3$, range 4-1373 cm$^3$) and at 3 months this was 102 cm$^3$ (median 60 cm$^3$, range 1-647 cm$^3$). Mean volume reduction of the fibroid was 83 cm$^3$ or 45% from initial mean volume. Mean uterus volume before UAE was 541 cm$^3$ (median 479 cm$^3$, range 63-1929 cm$^3$) and at 3 months this was 315 cm$^3$ (median 278 cm$^3$, range 18-1004 cm$^3$). Mean volume reduction of the uterus was 226 cm$^3$ or 42% from initial mean volume.
Mean infarction rate at 3 months of the dominant fibroid was 95% (median 95%, range 80-100%). Overall fibroid infarction rate at 3 months was 96% (median 95%, range 70-120%).

Clinical follow-up and additional procedures
Mean follow-up was 12.8 months (median 11, range 3-29 months). Minor complications occurred in 13 women (15%, 95% CI 8.9-24.3%) after UAE: transient amenorrhea developed in 4 women (all > 45 years), one reported vaginal dryness, 6 had transient vaginal discharge, and two had a urinary tract infection that was treated with antibiotics. Major adverse events occurred in 8 women (9.3%, 95% CI 4.6-17.5%): 7 developed permanent amenorrhea (2 were < 45 years) and one had transient ischemia of part of the right labia as a result of too proximal positioning of the microcatheter during particle injection. This last woman recovered completely without therapy.

The results of the UFS-QOL are shown in Table 2. Symptom severity score decreased significantly (p<0.0001) after 3 months and further decreased at last follow-up. Overall quality of life improved significantly (p<0.0001) after 3 months and continued to improve at last follow-up.
Four of 86 women (4.7%, 95% CI 1.5-11.7%) had additional therapy after UAE: one was embolized for a second time one year after UAE due to insufficient symptom relief and persisting enhancing fibroids on MRI. Three women had a hysterectomy: in 2 at 5 and 7 months after UAE because of persisting pain and in one woman hysterectomy was performed after incomplete fibroid expulsion 2 months after UAE.

<table>
<thead>
<tr>
<th>microsphere size</th>
<th>number of patients</th>
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<tbody>
<tr>
<td>500 µm only</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>500 µm and 700 µm</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>700 µm only</td>
<td>43 (50%)</td>
</tr>
<tr>
<td>700 µm and 900 µm</td>
<td>26 (30%)</td>
</tr>
<tr>
<td>900 µm only</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>500 µm and 700 µm and 900 µm</td>
<td>1 (1%)</td>
</tr>
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</table>

**Table 1.** Microsphere sizes used for uterine artery embolization in 86 patients

<table>
<thead>
<tr>
<th></th>
<th>baseline N=86</th>
<th>3 months after UAE N=85*</th>
<th>mean 12.8 months after UAE N=82**</th>
</tr>
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<tbody>
<tr>
<td>symptom severity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>concern</td>
<td>64</td>
<td>23</td>
<td>16</td>
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<tr>
<td>activities</td>
<td>50</td>
<td>86</td>
<td>92</td>
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<td>78</td>
<td>88</td>
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<td>control</td>
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<td>81</td>
<td>88</td>
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<tr>
<td>self-consciousness</td>
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<td>83</td>
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<td>sexual function</td>
<td>58</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td>overall</td>
<td>53</td>
<td>82</td>
<td>90</td>
</tr>
</tbody>
</table>

**Table 2.** Mean UFS-QOL score at baseline and during follow-up of 86 women treated with uterine artery embolization for uterine fibroids.

*One patient had a hysterectomy 2 months after UAE

** Four women had additional therapy after UAE
Discussion

This study demonstrates the feasibility, efficacy and safety of a precisely calibrated new embolic agent Embozene for UAE in a large cohort of patients with symptomatic uterine fibroids. Relief of clinical symptoms, volume reduction of uterus and fibroids, fibroid infarction rate, complications and proportion of women needing additional therapy during follow-up was comparable to other studies using different embolic agents (6,7). The Embozene spheres, color coded on particle size, were easy to use. Blockage of the microcatheter did not happen. This indicates that aggregation and clumping of the spheres inside the microcatheter does not occur with the sphere sizes used for UAE.

The new Embozene microspheres are calibrated with a narrow bandwidth. This precise calibration allows a more accurate prediction of the targeted vasculature that will be occluded by the microspheres. A relation between size of the microspheres and the diameter of the vessels that are occluded is established in several experimental and clinical studies of embolization of tumors and arteriovenous malformations (18,19).

Vessel calibre in myometrium and fibroids differ in several ways. The proximal larger arteries in the serosal part of the myometrium branch and taper to smaller arteries penetrating deep into the luminal part (8). The arteries of the perifibroid plexus are larger than the arteries feeding the myometrium (500-1000 µm versus <500 µm). The calibre of the arteries of the perifibroid plexus does not decrease distally (9). When particles are injected through the microcatheter into the uterine artery, almost all particles conglomerate in the larger arteries of the perifibroid plexus and not in the smaller arteries of the myometrium (10,11). This explains the selective ischemic effect of embolization on the fibroids only and sparing the normal myometrium. This selective fibroid devascularisation leads to a decrease of fibroid (and uterine) volume with alleviation of clinical symptoms.

On theoretical grounds the size of the microspheres used for UAE should ideally equal the diameter of the arteries of the perifibroid plexus to achieve a complete and selective devascularisation of the fibroids. Larger sizes microspheres might not penetrate deep enough into the target vessel to induce devascularisation of the fibroid and may cause microcatheter blockage. Smaller microsphere sizes might penetrate too deep with a risk
of necrosis of the normal myometrium. Therefore, the use of an embolic agent with a precise calibration to occlude the perifibroid plexus only seems to be advantageous in terms of better control of the extent of embolization and thus the clinical outcome. The particle size used for UAE should be > 500 µm, the diameter of arteries feeding the myometrium. Probably, the most appropriate size would be 700-900 µm. Whether or not tight calibration of microspheres results in better and more selective fibroid infarction with improved clinical outcome remains uncertain from our data.
References


