Clinical aspects of uterine artery embolization

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LIMITED UTERINE ARTERY
EMBOLIZATION FOR LEIOMYOMAS
WITH TRIS-ACRYL GELATIN
MICROSPHERES:
1-YEAR FOLLOW-UP
Abstract

Purpose
To assess the safety and efficacy of uterine artery embolization (UAE) using large calibrated tris-acryl gelatin microspheres.

Material and Methods
One hundred fifty-eight women with symptomatic uterine fibroids underwent UAE. Embosphere was used in 105 women and Embogold microspheres in 53 women. Major and minor complications were assessed. At 12 months, relief of symptoms and patient satisfaction were assessed and volume reductions of the uterus and dominant fibroid were calculated.

Results
Median age of the subjects was 43 years (mean, 42.3 y; range, 23-53 y). Preprocedural symptoms were heavy menstrual bleeding in 89%, pain in 64%, and bulk-related symptoms in 57%. At 12 months follow-up, the proportion of women with heavy menstrual bleeding, pain, and bulk-related symptoms had decreased to 9%, 8%, and 8%, respectively. Patient satisfaction was grouped as follows: very satisfied 57%, satisfied 36%, and not satisfied 7%. Mean uterine and dominant fibroid volumes before UAE were 532 cm$^3$ and 201 cm$^3$, respectively. At 12-month follow-up MR imaging, mean uterine volume decreased to 260 cm$^3$ and mean dominant fibroid volume to 78 cm$^3$. These differences were statistically significant (P<0.0001). There were no procedure-related deaths. No emergency hysterectomy was needed. Permanent amenorrhea occurred in 11% of women. Transient amenorrhea occurred in 13% of women, and fibroid expulsion occurred in 10% of women. Twelve women (7.6%) had additional therapy: nine underwent additional embolization and three had hysterectomy.

Conclusion
Targeted UAE using large calibrated microspheres is safe and effective in the relief of symptoms in the majority of patients. At 12 months, a marked fibroid and uterine volume reduction is obtained.
Introduction

Uterine fibroid, or leiomyoma, is the most common solid pelvic tumor in women during reproductive life (1). If symptomatic, hormonal therapy or surgery can be considered (2, 3). In addition to the risks associated with surgical procedures, there may also be emotional drawbacks in women (4, 5). Uterine artery embolization (UAE) is nowadays considered an effective alternative to medical and surgical therapy (6–10). Advantages of embolization over hysterectomy are preservation of the uterus, shorter hospital stay, and quick recovery (11).

In UAE, mainly nonspherical polyvinyl alcohol (PVA) particles have been used, usually aiming at complete occlusion of both uterine arteries (6–9). Targeted UAE with calibrated trisacryl gelatin microspheres (CTGM) is a relatively new technique in which occlusion of the perifibroid plexus is performed, leaving the uterine artery, cervicovaginal branches, and shunts patent. The material has demonstrated good biocompatibility and safety (12, 13). The use of CTGM has been approved by the Food and Drug Administration for UAE in cases of symptomatic uterine fibroids. In addition, it has been suggested that a less aggressive embolization of the uterine arteries may provide the same clinical success rate with lower complication rates compared to complete uterine artery occlusion using nonspherical PVA (14,15). Short-term results in a limited number of patients embolized with CTGM were favorable (16-19).

We assessed the safety and clinical and radiological efficacy of UAE using large CTGM in 158 consecutive symptomatic women with near-complete follow-up at 12 months.
Material and Methods

Patient Population and Selection Criteria
Between February 2001 and February 2004, 158 consecutive women with symptomatic uterine fibroids underwent targeted embolization using CTGM; 105 women were treated with Embosphere and 53 women with Embogold microspheres (Biosphere Medical, Roissy, France). The choice of embolic agent used was influenced by factors such as operator preference and availability in stock and was independent of patient or fibroid characteristics.

Of the 158 women, 142 were white, 11 Afro-Caribbean, and 5 Asian. Median age was 43 years (mean, 42.3; range, 23-53 y). Inclusion criteria were as follows: women with a uterine fibroid, reporting heavy menstrual bleeding, pain, and/or bulk-related symptoms in whom insufficient clinical results were obtained with previous medical therapy or myomectomy. Exclusion criteria were postmenopausal status, malignancy, pedunculated fibroids, and pregnancy. Women seeking future fertility were not excluded.

Our Institutional Review Board approved this study and informed consent was obtained in all subjects.

Procedure and Angiographic Endpoint of Embolization
Via a right femoral artery approach, the left internal iliac was catheterized with a hydrophilic 0.035-inch guide wire and a 4-F, Cobra C2 shaped glide-catheter. Selective digital subtraction angiography of the anterior division of the left internal iliac artery and uterine artery was performed. A microcatheter was used for small or tortuous arteries and in case of vasospasm.

The Waltman loop manoeuvre was applied to catheterize the right uterine artery. After positioning the (micro) catheter in the horizontal part of the uterine artery, embolization was performed using CTGM of 500 to 1200 µm. Each vial (2 cm³) of microspheres was mixed with 10 mL of contrast medium (Omnipaque) and 5 mL saline to obtain a stable suspension of the microspheres. The angiographic endpoint was defined as a complete occlusion of branches to the perifibroid plexus and sluggish flow in the ascending
segment of the uterine artery, leaving the main uterine artery, cervicovaginal branches, and utero-ovarian anastomoses patent (16). Any intra-catheter aggregation and blockage was recorded.

**Clinical and Imaging Follow-up Protocol**

Major complications, defined as events requiring immediate additional therapy (including emergency hysterectomy), permanent adverse sequelae (including permanent amenorrhea), or death were recorded. Transient amenorrhea, fibroid expulsion, skin rash, and infection requiring nominal therapy were considered as minor complications (20). Additional embolization or elective hysterectomy was considered a failure of initial treatment. At 12 months, evaluation of subjective symptoms and patient satisfaction were assessed by a questionnaire during an outpatient clinic consultation. The patients were asked to categorize their symptoms (bulk-related, pain, and bleeding) into improved or unchanged/worsened. They were asked to score overall satisfaction “very satisfied”, “satisfied” or “not satisfied.” Finally, the subjects were asked to estimate the number of days before returning to routine daily activities after UAE.

Prior to embolization, pelvic MR imaging was performed in all 158 women. The MR imaging protocol consisted of coronal, sagittal and axial TSE-weighted sequences and contrast enhanced sagittal T1 series. Volume calculation was done by using the formula of a prolate ellipse (length x depth x width x 0.5233). Volume reductions of the uterus and dominant fibroid were calculated by comparing volumes prior to embolization with the volumes at the 12-month MR imaging follow-up.

**Statistical Analysis**

Mean, median, range, and standard deviation (SD) of uterine volumes and dominant fibroid volumes were assessed before and after UAE. These differences were compared using the t-test, and P-values less than .05 were considered significant. The following results were compared for women embolized with Embogold versus women embolized with Embosphere microspheres: proportion of patient satisfaction, uterine volume embolized per cubed millimeter of injected microspheres, uterine volume reductions, number of days before returning to routine activities after UAE, the proportion of subjects with fibroid expulsion and skin rash.
Mean, median, range and SD of volume of injected microspheres were assessed and sizes were recorded. The same approach was taken for both types of microspheres. Uterine volume embolized per cubed millimeter of injected microspheres was assessed for both types.

Statistical analysis was performed with the t-test for continuous data and comparison of proportions with the χ² test (MedCalc statistical software, Mariakerke, Belgium). P values less than 0.05 were considered statistically significant.

Results

Immediate Results and Major Complications
Bilateral uterine artery embolization was performed in 152 of 158 women (96%). Failure of catheterization resulted in unilateral uterine artery embolization in 6 of 158 women (4%). Embolization through 4-F C2 catheters alone was performed in 25%, microcatheters alone in 57%, and a combination in 18%. Intracatheter aggregation and blockage did not occur in any of the embolization procedures.

Mean, median, range, and SD of volume of injected microspheres were 8.5 cm³, 6.5 cm³, 2 to 42 cm³, and 6.3 cm³, respectively. There were no procedure-related deaths in the 158 women treated with UAE (0%, 95% CI, 0–2.9%). No events requiring immediate additional therapy occurred and no emergency hysterectomy was required. Permanent amenorrhea occurred in 17 women (11%). All women who developed permanent amenorrhea were 45 years or older.

Minor Complications
After UAE, transient amenorrhea occurred in 20 women (13%) and fibroid expulsion occurred in 16 women (10%) between 4 weeks and 12 months after UAE. Vaginal fibroid evacuation from the uterine cavity by the gynecologist was needed in 5 of these 16 women, without hospitalization. Expelled fibroids were located submucously in 10 and intramurally in 6 women and size ranged between 4 and 13 cm.
Additional Procedures

Twelve women (7.6%) had additional therapy after UAE: nine women underwent secondary embolization and three women had a hysterectomy at 3, 8, and 12 months after embolization. Secondary embolization in the nine women was performed because of recurrent symptoms and acceptance of a second embolization. Hysterectomy was performed for recurrent symptoms in two women, these two refused secondary embolization. In one woman, hysterectomy was performed because of suspected uterine sarcoma but pathological examination showed a fibroid.

Clinical Follow-up and MR Follow-Up

At 12 months follow-up, 12 women (7.6%) had additional therapy after initial UAE: nine women underwent additional embolization and three women had a hysterectomy. So, 146 women were eligible for the 12-month clinical evaluation. Four women of these 146 were lost to follow-up (12-month clinical follow-up rate: 142 of 146, 97%). At 12 months clinical follow-up, resolution or improvement of symptoms in the 126 women initially presenting with heavy menstrual bleeding occurred in 113 women (91%). Resolution or improvement of symptoms in the 91 women initially presenting with pain occurred in 80 women (92%). Resolution or improvement in the 81 women initially presenting with bulk-related symptoms occurred in 70 women (92%). Patient satisfaction in the group of 142 women was as follows: very satisfied 81 (57%), satisfied 51 (36%), and not satisfied 10 (7%). Thirty-two of 158 women did not have a 12-month MR imaging follow-up for the following reasons: additional embolization (9), hysterectomy (3), pregnancy (2), and claustrophobia (1). So, 143 women were eligible for 12-month MR imaging follow-up. Of these 143 women, we were unable to follow-up 4 women, and 13 declined the 12-month MR imaging follow-up (12-month MR imaging follow-up rate: 126 of 143, 88%). Mean, median, and SD of uterine and dominant fibroid volumes as well as volume reduction in 126 women before and 12 months after limited uterine artery embolization are listed in Table 1. In the 126 patients with MR follow-up the median uterine volume before UAE was 465 cm³ and at 12-month follow-up this was 208 cm³. In the 126 patients with MR follow-up the median fibroid volume before UAE was 131 cm³ and at 12-month follow-up MR imaging this was 34 cm³. Using the t-test, these differences were statistically significant (P<.0001).
Prior to UAE

<table>
<thead>
<tr>
<th></th>
<th>Prior to UAE</th>
<th>12 Months after UAE</th>
<th>Volume Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean uterine volume, cm³</td>
<td>532</td>
<td>260</td>
<td>47</td>
</tr>
<tr>
<td>Median uterine volume, cm³</td>
<td>465</td>
<td>208</td>
<td>49</td>
</tr>
<tr>
<td>SD</td>
<td>375</td>
<td>190</td>
<td>34</td>
</tr>
<tr>
<td>Mean dominant fibroid volume, cm³</td>
<td>201</td>
<td>78</td>
<td>60</td>
</tr>
<tr>
<td>Median dominant fibroid volume, cm³</td>
<td>131</td>
<td>34</td>
<td>66</td>
</tr>
<tr>
<td>SD</td>
<td>249</td>
<td>100</td>
<td>40</td>
</tr>
</tbody>
</table>

**Table 1.** Uterine and Dominant Fibroid Volumes before and 12 Months after Limited Uterine Artery Embolization (n=126).

*Embosphere versus Embogold Results*

The comparison of relevant characteristics between the use of Embosphere and Embogold microspheres is listed in Table 2. Of 158 women, 105 were embolized with Embosphere and 53 with Embogold.

Uterine volumes before UAE in the two groups did not differ significantly. Of the 142 women with 12-month clinical follow-up, 47 had been embolized with Embogold and 95 with Embosphere microspheres.

The mean volumes of injected Embosphere and Embogold did not differ statistically (P=0.3). Uterine volume embolized per cubed millimetre of injected microspheres did not differ statistically (P=0.9) in the two groups. Of the 126 women with 12-month MR imaging follow-up, 82 had been embolized with Embosphere and 44 with Embogold.
Uterine volume reductions showed no significant difference (P=0.75). The frequency of fibroid expulsion did not differ statistically significantly between women treated with Embogold and those treated with Embosphere microspheres (P=0.94). Transient skin rash occurred more frequently in women treated with Embogold than in women treated with Embospheres (P=0.031). Sixty-four women reported the number of days before returning to routine daily activities after UAE. In 47 women treated with Embospheres, this number was mean 17.6 days, and in 17 women treated with Embogold microspheres, this number was mean 30.0 days. This difference was statistically significant (P=0.004). There was no difference in patient satisfaction in the two groups (4 of 47 unsatisfied for Embogold versus 6 of 95 unsatisfied for Embospheres; P=0.89).

<table>
<thead>
<tr>
<th></th>
<th>Embosphere</th>
<th>Embogold</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women</td>
<td>105</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Mean uterine volume before UAE, mL</td>
<td>396</td>
<td>516</td>
<td>0.11</td>
</tr>
<tr>
<td>Mean volume (SD) embolic agent used, cm$^3$</td>
<td>8.1 (5.2)</td>
<td>9.2 (8.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Uterine volume embolized per cm$^3$ embolic agent, mL</td>
<td>61.9</td>
<td>64.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean uterine volume reduction, %</td>
<td>46</td>
<td>48</td>
<td>0.75</td>
</tr>
<tr>
<td>Fibroid expulsion, %</td>
<td>9.5</td>
<td>11.3</td>
<td>0.94</td>
</tr>
<tr>
<td>Skin rash, %</td>
<td>1.0</td>
<td>9.4</td>
<td>0.031</td>
</tr>
<tr>
<td>Days before returning to routine activities</td>
<td>17.6</td>
<td>30.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Unsatisfied patients,%</td>
<td>6.3</td>
<td>8.5</td>
<td>0.89</td>
</tr>
</tbody>
</table>

**Table 2.** Relevant Characteristics of the Use of Embosphere versus Embogold Microspheres
Discussion

In this study with prospective data collection and a high rate of clinical and MR imaging follow-up, we confirmed that UAE using CTGM in symptomatic uterine fibroids has a low risk of procedural complications (6-11). Relief of clinical symptoms, patient satisfaction, adverse events, and uterine and fibroid volume reduction were in the same range as those in studies on the use of PVA (6-11).

The results are also comparable with those of studies reporting on the use of CTGM with shorter follow-up periods (16-19). To date, uterine and fibroid volume reductions after UAE using CTGM have not been published in a large series of patients with 12-month follow-up.

Our results also show the limitations of UAE in the treatment of symptomatic uterine fibroids: 7.6% of patients needed additional therapy and 7% of patients were unsatisfied with the results. Future developments should be aimed at lowering these percentages. The results of the present study show that the effectiveness of limited UAE using large microspheres is comparable to the effectiveness of UAE using nonspherical and smaller particles, as was demonstrated by Spies in a prospective comparative study (15).

The first embolic material used for UAE was nonspherical PVA particles. The usual angiographic endpoint with nonspherical PVA particles was occlusion of the uterine arteries to stasis or near stasis. Embolization was considered complete when a standing column of contrast material was present in the uterine artery or when reflux toward the uterine artery origin was observed. Physical properties of irregular nonspherical PVA particles were thought to be responsible for the tendency to aggregate and for a proximal vessel occlusion with an unpredictable level of occlusion. In addition, aggregation may also result in microcatheter occlusion.

Alternative embolic materials have been introduced, allowing further refinement of the UAE technique. Spherical embolization particles such as CTGM have been developed since 1994 with the aim to overcome the disadvantages of nonspherical PVA particles (13). CTGM was the first spherical embolic agent offering a more uniform and targeted
embolization of the perifibroid plexus. The compressibility of the microspheres made microcatheter clogging a rare event. The so-called limited UAE technique was introduced with a new embolization endpoint: embolization was completed when no residual hypervascularization related to the fibroids was visible, stasis was observed in the distal part of the uterine artery, or reduced flow was achieved in the proximal part of the uterine artery. The main uterine artery, cervicovaginal branches, and utero-ovarian anastomosis (if visible) were left patent, preserving vascularization to normal surrounding tissue, such as myometrium, cervix, vagina, tubes, and ovaries.

Limited UAE with microspheres is more subtle than a nonspherical PVA embolization procedure and requires careful judgment to determine the proper embolization endpoint. CTGM are intended to be injected gradually until complete occlusion of the perifibroid plexus only, maintaining forward flow within the uterine arteries and preserving blood supply to the myometrium. The objective of CTGM fibroid embolization is to achieve complete infarction of all uterine fibroids present while preserving vascularization to normal surrounding tissue. Failure of complete devascularization of the fibroids due to misjudgment of the angiographic endpoint may affect long-term clinical response and may lead to higher recurrence rates. Experience is required to become comfortable with this alternative endpoint. As demonstrated in this study using CTGM in combination with the limited UAE technique, good mid-term results can be obtained. The long-term outcome and possible recurrence of fibroid growth and symptoms are still under evaluation. Long-term studies of larger patient populations are needed to establish the recurrence rate.

To date, there is no consensus on the type and size of embolization materials most effective for UAE. The appropriate technique of embolization in terms of endpoint with each of the available products is the subject of ongoing debate. In our experience, CTGM larger than 500 µm were easy to use in targeted embolization of the perifibroid plexus without compromising the uterine artery. Intracatheter aggregation and blockage did not occur in any of the embolization procedures. This may be due to the more uniform size and different physical and chemical characteristics of CTGM compared to nonspherical PVA (12). Moreover, severe complications reported after embolization with PVA particles such as uterine necrosis, labia necrosis, and infection did not occur (21–26). Our use of CTGM larger than 500 µm may have prevented these
complications. However, permanent amenorrhea was seen in the same frequency range as with the use of PVA (15). In the comparison between Embogold and Embospheres, uterine volume embolized per micrometer injected microspheres, fibroid expulsion, patient satisfaction, and volume reduction did not differ. The occurrence of skin rash was significantly lower in patients treated with Embospheres, as was reported earlier (21). Women treated with Embospheres returned sooner to daily activities than women treated with Embogold. We do not have an explanation for this difference. These findings have led us to refrain from using Embogold in UAE.

In the meantime, the company no longer recommends the use of Embogold for UAE. In conclusion, targeted UAE using CTGM larger than 500 µm is safe and effective in the relief of symptoms in the majority of patients with symptomatic uterine fibroids. After 12 months, a marked fibroid and uterine volume reduction is obtained.
References


