

Initial Experience with Use of Tris-acryl Gelatin Microspheres for Uterine Artery Embolization for Leiomyomata

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PURPOSE: To assess the safety and effectiveness of tris-acryl gelatin microspheres (Embospheres) in the treatment of leiomyomata by uterine artery embolization.

MATERIALS AND METHODS: This was a Phase I study of 30 patients with symptomatic leiomyomata. Each patient underwent ultrasound imaging and completed questionnaires regarding symptoms and health status at baseline and 3 and 6 months after treatment. Bilateral embolization was performed with use of tris-acryl gelatin microspheres. Summary statistics were used to characterize the demographic and procedure data. Paired *t*-tests were used to assess change in the severity of menstrual bleeding and health-related quality of life.

RESULTS: Bilateral embolization was technically successful in all patients. Three months after treatment, menstrual bleeding was markedly improved as assessed by menorrhagia questionnaire ($P < .0001$) and menstrual calendar ($P < .0001$). Pelvic pain and discomfort was improved in 92% of cases. Physical component summary scores of the SF-12 also increased from baseline at 3 months ($P = .02$) and at 6 months ($P = .01$). Minor complications occurred in nine patients; there were no major complications.

CONCLUSION: Although limited, this initial experience suggests that tris-acryl gelatin microspheres are an effective and safe embolic agent for the treatment of uterine leiomyomata.

Index terms: Uterine arteries, embolization • Fibroid • Uterus, neoplasms

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Abbreviations: PBAC = pictorial blood loss assessment chart, PVA = polyvinyl alcohol, UAE = uterine artery embolization

IN recent years there have been a number of studies published reporting the safety and effectiveness of uterine artery embolization (UAE) for uterine leiomyomata. With the growth of this

new treatment, there has been renewed interest in the development and use of new embolic agents.

Embosphere Microspheres (Biosphere Medical, Rockland, MA) are tris-acryl microspheres embedded with gelatin. Initially developed and tested in France, they have recently been approved by the Food and Drug Administration for use in the treatment of hypervascular tumors. They are inert translucent spheres that have demonstrated biocompatibility (1). Initial *in vitro* data and clinical data suggest that they are an effective embolic agent (2–4), easy to deliver through microcatheters and unlikely to clump in vessels.

Given the characteristics of these microspheres, they are an attractive alternative to polyvinyl alcohol (PVA) particles for uterine leiomyomata.

With this in mind, this study was undertaken to obtain preliminary data as to the safety and efficacy of Embosphere Microspheres for embolization of uterine leiomyomata. The study had three objectives: to determine (i) whether UAE with tris-acryl gelatin microspheres reduces the volume of fibroids, (ii) whether UAE with tris-acryl gelatin microspheres reduces symptoms associated with uterine leiomyomata, and (iii) if UAE with tris-acryl gelatin microspheres is safe, without significant complications or adverse effects.

MATERIALS AND METHODS

The study was performed at three centers. At each site, the institutional review board approved the protocol and informed consent was obtained

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from each patient before entry into the study group. The Food and Drug Administration approved the protocol as a Phase I study of 30 patients.

Patient Population

Patients were recruited from the population presenting for evaluation for UAE for leiomyomata at the three participating centers. Thirty patients were enrolled and treated. The mean age of participants was 42.5 years (range, 30–50 y). Black patients comprised 43% of the study population, white patients 40%, Hispanic patients 13%, and others 3%. Follow-up data were available in all 30 patients at 3 months and 29 patients at 6 months.

Selection Criteria

Entry criteria for the study included age between 30 and 50 years and symptoms caused by uterine leiomyomata, such as heavy menstrual bleeding, pelvic pain, pelvic pressure, urinary pressure. Exclusion criteria included pregnancy, desired future fertility, history of gynecologic malignancy, endometrial hyperplasia, adenomyosis, or pelvic inflammatory disease, and known contrast or gelatin allergy. Additional exclusion criteria included postmenopausal status or follicle stimulating hormone levels >40 mIU/mL.

Anatomic criteria for exclusion were uteri smaller than 250 mL calculated volume, pedunculated submucosal leiomyoma, or dominant pedunculated serosal leiomyoma with a narrow attachment to the uterus. These determinations were made on the basis of baseline ultrasound (US) or, in some cases, magnetic resonance (MR) imaging examinations. The primary measures were obtained from the US studies and volumes were calculated with use of the formula for a prolate ellipse (length \times width \times depth \times 0.5233) (5).

Procedure

The embolization procedures were performed in a similar fashion in all patients. Selective bilateral uterine artery embolization was completed with either a unilateral or bilateral femoral approach. Either 500–700- μ m or 700–900- μ m tris-acryl gelatin microspheres

were used in all cases, based on operator preference. Catheter selection was also based on operator preference, but operators used a 4- or 5-F catheter in all cases to enter the uterine arteries. Microcatheter use was at the discretion of the operator. No vasodilators were used. No other embolic agent was used in addition to the microspheres. The preferred endpoint was complete occlusion of flow to the leiomyomata, with slow flow remaining in the main uterine artery. Each patient was admitted for overnight care, with pain management according to local practice.

Study Endpoints and Definitions

When each patient had met the inclusion criteria and had consented, she completed a baseline pictorial blood loss assessment chart (PBAC), as adapted by Janssen (6), for the menstrual period immediately before treatment. In addition, a menorrhagia questionnaire (7) and an SF-12 health-related quality of life questionnaire were also completed. The SF-12 is a 12-question brief general health-related quality of life survey, which is a subset of the SF-36, which is a very commonly used, well-validated general health-related quality of life questionnaire (8). Finally, a symptom severity questionnaire was completed, assessing the severity of menstrual bleeding and the impact of symptoms during and between menstrual periods on a scale from 0 (no impact) to 10 (severe impact).

After discharge, each patient was contacted between 1 and 3 weeks after UAE and at 3 and 6 months after UAE. The PBAC, menorrhagia questionnaire, SF-12, and symptom severity questionnaires were completed at 3 months and 6 months postembolization. Follow-up questionnaires also included questions on symptom change and satisfaction with outcome. In addition, at the 3 month and 6 month intervals, US or MR imaging was performed. Patients were also asked to rate their satisfaction with symptom change, from -3 (very dissatisfied) to $+3$ (very satisfied).

At each follow-up evaluation, all adverse events were recorded. Minor complications were defined as those needing nominal therapy, including additional hospital observation. Major

complications were adverse events that resulted in unanticipated increase in level of hospital care, required surgical or other major intervention, or resulted in permanent injury.

Statistical Analysis

Descriptive statistics, including means and SDs, were used to summarize the continuous variables in this study. Time points analyzed were baseline, 3 months, and 6 months. Percent change was calculated for the volume variables from baseline to 3 months and from 3 to 6 months. In addition to descriptive statistics being recorded for the change variables, paired *t*-tests and nonparametric sign tests were performed on the paired data continuous variables (PBAC score, menorrhagia score, and SF-12 scores). The latter were used because of the small sample size of this study. The results from the nonparametric analyses agree with those from the parametric *t*-tests for all variables. Statistical significance was assumed at a *P* value of .05.

RESULTS

Embolization was successfully completed in all patients. The majority of patients ($n = 23$) were treated with 700–900- μ m spheres and seven were treated with either only 500–700- μ m spheres or a combination of both sizes. An average of 8.0 mL per patient was used.

The mean uterine volume at baseline was 664 mL (SD = 443 mL). This decreased by 18% by 3 months and 28% by 6 months after treatment. The baseline mean dominant leiomyoma volume was 191 mL, which decreased 41% at 3 months and 49% at 6 months. Dominant leiomyoma measures in three patients had to be eliminated: the dominant leiomyoma was misidentified in two patients at 3 months and in another patient at 6 months. As a result, different leiomyomata were measured in these cases and the changes could not be evaluated.

Ten complications occurred in nine patients, all of which were minor. There was only one technical complication of a procedure, a minor vessel perforation not requiring therapy and having no sequelae. Another patient

Summary of Validated Outcome Measures before and after Therapy

Outcome Measure	Baseline	3 mo	Change from Baseline to 3 mo	P Value	6 mo	Change from 3 mo to 6 mo	P Value
PBAC score (<i>n</i> = 21)	481 (433)	204 (250)	277 (252)	.0001	159	44 (291)	.49
Menorrhagia questionnaire score (<i>n</i> = 28)	45 (16)	23 (14)	22 (15)	.0001	22 (13)	1 (11.5)	.51
SF-12 physical summary score (<i>n</i> = 29)	46.1 (9.8)	51 (8.3)	4.9 (8.4)	.004	52.2 (9.2)	1	.28
SF-12 mental summary score (<i>n</i> = 29)	47 (13.2)	49.5 (13)	2.5 (11.6)	.25	50.2 (12.4)	0.69 (1.6)	.75

developed a groin hematoma 7 days after therapy that lasted 22 days. There were five allergic reactions; three were directly attributable to specific medications given in the perioperative period. Of the other two patients with allergic reactions, one developed hives at the end of the procedure and it was unclear whether they were caused by contrast material, ketorolac, or possibly the Embospheres. It resolved with administration of diphenhydramine and methylprednisolone succinate. One patient developed a pruritic rash 8 days after therapy. The rash lasted 7 days and resolved with steroid cream. The cause of this reaction is unknown. One patient had an anxiety attack and vasovagal reaction on the day of the procedure. The complication requiring the longest hospital care was severe constipation causing pelvic pain. The patient required readmission for 4 days. This patient also had an allergic reaction to ketorolac (included in the five patients listed above). The final complication was fibroid expulsion in one patient.

At baseline, 87% of patients rated their menstrual bleeding as moderately heavy or extremely heavy. Only 43% of patients at 3 months and 31% of patients at 6 months rated their menstrual bleeding as moderately heavy or extremely heavy. Symptom impact also improved. Fifty-six percent had a substantial or severe symptom impact during menstrual periods at baseline, but this decreased to 4% at 3 months and 0% at 6 months. Similarly, 33% had substantial or severe symptom impact between periods at baseline, which reduced to 4% at 3 months and 0% at 6 months. Eighty-seven percent of patients reported at 3 months that they were satisfied to some extent, which increased to 93% at 6 months.

The results obtained from the validated measures (the PBAC, the SF-12, and the menorrhagia questionnaire) are summarized in the **Table**. The paired *t*-tests were performed on each variable on only those patients with complete data for that variable. Therefore, the number of data points varied with each variable. The PBAC results were the most difficult to obtain and a complete set was obtained in only 21 patients. This was most frequently because the patient did not have a menstrual period in the prescribed follow-up interval month or because the PBAC was completed for a different menstrual period.

Dramatic improvement in menstrual bleeding was detected with use of the PBAC, with scores that were reduced by more than half by 3 months after treatment. These changes persisted and were further improved at 6 months. Similar levels of improvement in the menorrhagia questionnaire were measured, confirming marked change in menstrual bleeding. Perhaps reflecting this improvement, significant change was also seen in the physical component summary of the SF-12. The mental component summary did not change in a significant way.

DISCUSSION

With the emergence of uterine embolization for leiomyomata, there has been renewed interest in the properties of embolic material. Initially, uterine embolization was performed with use of PVA particles exclusively (9,10). PVA has a number of desirable characteristics. Approved by the Food and Drug Administration for use in embolotherapy, it is a particulate material capable of penetrating the leiomyoma blood supply and occluding it. PVA is

relatively inexpensive and easy to deliver. However, there is data suggesting that PVA may have some undesirable characteristics as well. There is moderate variability in the size distribution of particles when measured dry (11). The particles swell after they mix with saline solution or contrast material. When wet, they tend to aggregate and may clump within vessels after injection (4). As a result, PVA's behavior during embolization for leiomyomata can be unpredictable, with demonstrated clumping in the main uterine artery.

Gelatin sponge has also been used for embolization of leiomyomata as well, although the reported experience is very limited (12). Used as a slurry or as cut pledgets, gelatin sponge usually results in complete occlusion of the uterine artery at the conclusion of the embolization. Although it generally behaves as a temporary agent in other vascular beds, its behavior in the uterine arteries is not known. In particular, it is not known whether the uterine arteries recanalize after embolization with gelatin sponge. Its use has been suggested for patients who may want to preserve their fertility because of its perception as a temporary agent, but further study is needed to determine the long-term recanalization rate of the uterine arteries.

Tris-acryl microspheres were developed to address some of the perceived shortcomings of other particulate embolic material (1). Previously used as a base material in chromatography columns and as a micro-carrier for cell culture, the spheres are compressible. This allows easy passage through a microcatheter with a luminal diameter smaller than that of the spheres. In a study exploring the in vitro and in vivo characteristics of the spheres, Derdeyn et al (4) noted that the 100-

300- μm size range had a mean of 210 μm ($\pm 43 \mu\text{m}$). Derdeyn et al (4) also compared the behavior of PVA and tris-acryl gelatin microspheres after injection into the rete mirabile of a pig. Examination revealed aggregations of PVA in the proximal rete. In contrast, the microspheres distributed throughout the rete without aggregation.

Pelage et al (13) first tested tris-acryl gelatin microspheres for UAE. Various sizes of microspheres and PVA were embolized into the uterine arteries of sheep. A significant difference was detected between PVA and microspheres in the degree of uterine injury, with greater ischemic injury in PVA-treated uteri. Microscopically, aggregation of PVA was noted, but none was seen with microspheres.

Our initial clinical experience with Embospheres (Biosphere Medical) is promising. The symptom change after UAE was substantial, resulting in a dramatic decrease in the impact of symptoms during and between menstrual periods.

This study used validated measures of quality of life and menorrhagia (the SF-12 and menorrhagia questionnaire) to assess the change that occurs after uterine embolization. To date, there have been few reports of outcome after uterine embolization using quality-of-life measures. Spies et al (14) used a fibroid-specific quality-of-life questionnaire to assess the effect of the treatment on health-related quality of life. The same group also presented initial results with use of the SF-12 at the 2000 Annual Meeting of the SCVIR (15). In patients treated with PVA, a change in the mental and physical component summary scores of the SF-12, similar to that found in the current study, was found, persisting through the 6-month follow-up interval (15). However, neither of these studies specifically used the menorrhagia measures presented in the present study, and the use of such measures may be of interest to others designing studies to measure menstrual bleeding outcome from therapies for leiomyomata.

We noted no unusual complications from therapy, but because complications are likely to be rare in UAE (16–19), additional experience is needed before any conclusions are drawn with regard to safety with the use of this product.

One issue that required some experience was determining the endpoint of embolization. Perhaps because the spheres do not readily clump or aggregate, they lead to devascularization of the leiomyomata without initially occluding the terminal portion of uterine artery or portions of the uterine arterial supply feeding normal tissues. The endpoint used in this study was a “pruned tree” appearance; ie, the primary leiomyoma feeding vessels occluded, perhaps with their proximal portions patent but without flow, and the main uterine artery open with slow flow or near stasis. This represents less extensive occlusion at the termination of the procedure than is typically achieved with use of PVA (16–19). Because this is the initial use of this product in the United States, we cannot state whether this endpoint is optimal and further study is needed in this regard.

One unanticipated problem we encountered was the misidentification of the dominant fibroid in multifibroid uteri on follow-up US examinations. This resulted in the elimination of the fibroid imaging data in three patients. The frequency with which this may have occurred in other studies of UAE is unknown. It is known that the interobserver variability in measuring leiomyomata is greater with US than MR imaging (20), but, to our knowledge, the frequency of misidentification has not been studied.

Because of the limited number of patients treated in this study, conclusions cannot yet be reached regarding the safety and efficacy of tris-acryl gelatin microspheres for uterine embolization. However, the results suggest that this embolic agent will prove to be an effective alternative to other materials currently in use for this therapy.

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