Embosphere®

Microspheres

INSTRUCTIONS FOR USE - VIAL

MERITMEDICAL®

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Microspheres

INSTRUCTIONS FOR USE

Embosphere® Microspheres in a Sterile Vial - For Embolization

CAUTION: Federal (U.S.A.) law restricts this device to use by or on the order of a licensed physician

INTENDED USE

Embosphere Microspheres are indicated for use in the embolization of:

- Hypervascular tumors, including symptomatic uterine fibroids
- Prostatic arteries for symptomatic Benign Prostatic Hyperplasia (BPH)
- Arteriovenous malformations
- Blood vessels to occlude blood flow to control bleeding/ hemorrhaging in the peripheral vasculature

CLINICAL APPLICATIONS FOR UTERINE FIBROIDS

Uterine fibroid embolization (UFE) is an alternative treatment for women requiring treatment for relief of symptoms attributed to uterine fibroids including heavy menstrual bleeding, pelvic pain or pressure, and/or urinary dysfunction.

CLINICAL APPLICATIONS FOR BENIGN PROSTATIC HYPERPLASIA (BPH)

Prostatic artery embolization (PAE) is an alternative treatment for men requiring treatment for relief of lower urinary tract symptoms (LUTS) attributed to BPH, such as urinary frequency, inability to urinate, incomplete emptying of bladder, difficulty starting urination, and straining to urinate or weak urine stream.

MAGNETIC RESONANCE IMAGING

Embosphere Microspheres are made of tris-acryl polymer impregnated with porcine gelatin and have no ferrous composition.

DEVICE DESCRIPTION

Embosphere Microspheres are part of a family of embolic materials based on Merit Medical's proprietary microsphere technology. These spheres are designed to offer controlled, targeted embolization.

Embosphere Microspheres are biocompatible, hydrophilic, nonresorbable, microspheres produced from an acrylic polymer and impregnated with porcine gelatin. Embosphere Microspheres are available in a range of calibrated sphere sizes.

DEVICE PACKAGING

- Embosphere Microspheres are contained in a sterile, 8.0 mL glass vial with a screw-top cap, packaged in a peel-away tray, available in 5 vials per package.
- Each vial contains either 1.0 mL or 2.0 mL of Embosphere Microspheres in pyrogen-free, sterile, physiological saline. Total volume of saline and Microspheres is 5 mL.

The following contraindications, warnings, precautions, and instructions for use are organized to present information applicable to all indications (i.e., hypervascular tumors, arteriovenous malformations, benign prostatic hyperplasia and uterine fibroids) first, followed by indication-specific information (i.e., UFE, PAE and neurological).

CONTRAINDICATIONS

All Indications

- Patients intolerant to occlusion procedures
- Vascular anatomy or blood flow that precludes catheter placement or embolic agent injection
- Presence or likely onset of vasospasm
- Presence or likely onset of hemorrhage
- Presence of severe atheromatous disease
- Presence of arteries supplying the lesion not large enough to accept Embosphere Microspheres
- Presence of collateral vessel pathways potentially endangering normal territories during embolization
- Vascular resistance peripheral to the feeding arteries precluding passage of Embosphere Microspheres into the lesion
- In large diameter arteriovenous shunts (i.e. where the blood does not pass through an arterial/capillary/venous transition but directly from an artery to a vein)

UFE Specific Contraindications

- Pregnant women
- Suspected pelvic inflammatory disease or any other active pelvic infection
- Any malignancy of the pelvic region
- Endometrial neoplasia or hyperplasia
- Presence of one or more submucosal fibroid(s) with more than 50% growth into the uterine cavity
- Presence of pedunculated serosal fibroid as the dominant fibroid(s)
- Fibroids with significant collateral feeding by vessels other than the uterine arteries

PAE Specific Contraindications

- Active urinary tract infection or prostatitis
- Prostate cancer
- Bladder cancer
- Chronic renal failure
- Bladder atonia, neurogenic bladder disorder, or other neurological disorder impacting bladder function
- Bladder stones
- Urinary obstruction due to causes other than BPH, including urethral stricture
- Excessive vessel tortuosity or severe atherosclerosis

Neurological Specific Contraindications

- Presence of patent extra-to-intracranial anastomoses or shunts
- Presence of end arteries leading directly to cranial nerves
- In any vasculature where Embosphere Microspheres could pass directly into the internal carotid artery, vertebral artery, intracranial vasculature or the above listed vessels

WARNINGS

All Indications

- Embosphere Microspheres contain gelatin of porcine origin, and therefore, could cause an immune reaction in patients who are hypersensitive to collagen or gelatin. Careful consideration should be given prior to using this product in patients who are suspected to be allergic to injections containing gelatin stabilizers.
- Studies have shown that Embosphere Microspheres do not form aggregates, and, as a result, penetrate deeper into the vasculature as compared to similarly sized PVA particles. Care must be taken to choose larger sized Embosphere Microspheres when embolizing arteriovenous malformations with large shunts to avoid passage of the spheres into the pulmonary or coronary circulation.
- Some of the Embosphere Microspheres may be slightly outside of the range, so the physician should be sure to carefully select the size of Embosphere Microspheres according to the size of the target vessels at the desired level of occlusion in the vasculature and after consideration of the arteriovenous angiographic appearance. Embosphere Microspheres size should be selected to prevent passage from artery to vein.
- Because of the significant complications of misembolization, extreme caution should be used for any procedures involving the extracranial circulation encompassing the head and neck, and the physician should carefully weigh the potential benefits of using embolization against the risks and potential complications of the

procedure. These complications can include blindness, hearing loss, loss of smell, paralysis and death.

- Serious radiation-induced skin injury may occur to the patient due to long periods of fluoroscopic exposure, large patient diameter, angled x-ray projections, and multiple image recording runs or radiographs. Refer to your facility's clinical protocol to ensure the proper radiation dose is applied for each specific type of procedure performed. Physicians should monitor patients that may be at risk.
- Onset of radiation-induced injury to the patient may be delayed. Patients should be counseled on potential radiation side effects and whom they should contact if they show symptoms.
- Pay careful attention for signs of mistargeted embolization. During injection carefully monitor patient vital signs to include SaO2 (e.g. hypoxia, CNS changes). Consider terminating the procedure, investigating for possible shunting, or increasing microsphere size if any signs of mistargeting occur or patient symptoms develop.
- Consider upsizing the microspheres if angiographic evidence of embolization does not quickly appear evident during injection of the microspheres.

UFE Specific Warnings

Warnings about UFE and Pregnancy

- The effects of UFE on the ability to become pregnant and carry a fetus to term, and on the development of the fetus, have not been determined. Therefore, this procedure should only be performed on women who do not intend future pregnancy.
- Women who become pregnant following UFE may be at increased risk for postpartum hemorrhage, preterm delivery, cesarean delivery, and malpresentation.
- Devascularization of the uterine myometrium resulting from UFE may theoretically put women who become pregnant following UFE at increased risk of uterine rupture.

Other UFE Warnings

- When using Embosphere Microspheres for uterine fibroid embolization, do not use microspheres smaller than 500 microns.
- An appropriate gynecologic work-up should be performed on all patients presenting for embolization of uterine fibroids (e.g., gynecologic history, fibroid imaging, endometrial sampling to rule out carcinoma in patients with abnormal menstrual bleeding).
- The diagnosis of uterine sarcoma could be delayed by taking a non-surgical approach (such as UFE) to treating fibroids. It is important to pay close attention to warning signs for sarcoma (e.g., rapid tumor growth, postmenopausal with new uterine enlargement, MRI findings) and to conduct a more thorough workup of such patients prior to recommending UFE. Recurrent or continued tumor growth following UFE should be considered a potential warning sign for sarcoma and surgery should be considered.

PAE Specific Warnings

- A thorough clinical evaluation should be performed on all patients presenting for embolization for BPH (e.g., urinalysis, digital rectal exam, symptom scores, prostate imaging, prostate-specific antigen test, and transrectal ultrasound) to rule out prostate cancer.
- Because of the tortuous vessels and duplicative feeding arteries in the pelvic area, extreme caution should be used when performing prostatic artery embolization (PAE). Complications of mistargeted embolization include ischemia of the rectum, bladder, scrotum, penis or other areas.
- When using Embosphere Microspheres for prostatic artery embolization, do not use microspheres smaller than 100 microns. It is recommended to use 300-500 microns.

Warnings About PAE and Fertility

- The effects of PAE on fertility have not been determined. Therefore, this procedure should not be performed on men wanting to father a child.

Bleeding/Hemorrhaging Specific Warnings

- Since Embosphere Microspheres have not been evaluated for neurovascular indications they should not be used to control bleeding or hemorrhaging in the neurovasculature.

Warnings About Use of Small Microspheres

- Careful consideration should be given whenever use is contemplated of embolic agents that are smaller in diameter than the resolution capability of your imaging equipment. The presence of arteriovenous anastomoses, branch vessels leading away from the target area or emergent vessels not evident prior to embolization can lead to mistargeted embolization and severe complications.
- Microspheres smaller than 100 microns will generally migrate distal to anastomotic feeders and therefore are more likely to terminate circulation to distal tissue. Greater potential of ischemic injury results from use of smaller sized microspheres and consideration must be given to the consequence of this injury prior to embolization. The potential consequences include swelling, necrosis, paralysis, abscess and/or stronger post embolization syndrome.
- Post embolization swelling may result in ischemia to tissue adjacent to target area. Care must be given to avoid ischemia intolerant, nontargeted tissue such as nervous tissue.

PRECAUTIONS

All Indications

- Patients with known allergy to contrast medium may require corticosteroids prior to embolization.
- Additional evaluations or precautions may be necessary in managing periprocedural care for patients with the following conditions:
    - Bleeding diathesis or hypercoagulative state
    - Immunocompromise
- Do not use if the vial, screw cap, or tray package appears damaged.
- For single patient use only - contents supplied sterile - never reuse, reprocess, or resterilize the contents of a vial that has been opened. Reusing, reprocessing or resterilizing may compromise the structural integrity of the device and or lead to device failure, which in turn may result in patient injury, illness or death. Reusing, reprocessing or resterilizing may also create a risk of contamination of the device and or cause patient infection or cross infection including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient. All procedures must be performed according to accepted aseptic technique.
- Select the size and quantity of Embosphere Microspheres appropriate for the pathology to be treated.
- Embolization with Embosphere Microspheres should only be performed by physicians who have received appropriate interventional embolization training in the region to be treated.

UFE Specific Precautions

- There is an increased chance of retro-migration of Embosphere microspheres into unintended blood vessels as uterine artery flow diminishes. Embolization should be stopped when the vasculature surrounding the fibroid can no longer be visualized but before complete stasis in the uterine artery.
- UFE should only be performed by Interventional Radiologists who have received appropriate training for treatment of uterine leiomyomata (fibroids).

PAE Specific Precautions

- The PAE procedure should only be performed by interventional radiologists who have received appropriate training.
- Collateral circulation may be present and can dilate and supply adjacent arteries as resistance within the prostatic bed increases. Therefore, there is potential for severe complications with nontargeted embolization.
- There is an increased chance of retro-migration of Embosphere Microspheres into unintended blood vessels as prostatic artery flow diminishes. Embolization should be stopped when the vasculature surrounding the prostate can no longer be visualized but before complete stasis in the prostatic artery.

POTENTIAL COMPLICATIONS

All Indications

Vascular embolization is a high-risk procedure. Complications may occur at any time during or after the procedure, and may include, but are not limited to, the following:

- Paralysis resulting from untargeted embolization or ischemic injury from adjacent tissue edema
- Undesirable reflux or passage of Embosphere Microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds, such as the internal carotid artery, pulmonary, or coronary circulations
- Pulmonary embolism due to arterial venous shunting
- Ischemia at an undesirable location, including ischemic stroke, ischemic infarction (including myocardial infarction), and tissue necrosis
- Capillary bed occlusion and tissue damage
- Vessel or lesion rupture and hemorrhage
- Vasospasm
- Recanalization
- Foreign body reactions necessitating medical intervention
- Infection necessitating medical intervention
- Complications related to catheterization (e.g., hematoma at the site of entry, clot formation at the tip of the catheter and subsequent dislodgment, and nerve and/or circulatory injuries, which may result in leg injury)
- Allergic reaction to medications (e.g., analgesics)
- Allergic reaction to contrast media or embolic material
- Pain and/or rash, possibly delayed from the time of embolization
- Death
- Blindness, hearing loss, loss of smell, and/or paralysis
- Additional information is found in the Warnings section

UFE Specific Potential Complications

- The most frequently anticipated post procedure complications are abdominal pain, discomfort, fever and/or nausea, collectively known as "Post-embolization Syndrome." Some patients may also experience constipation. This is generally managed with prescription or over-the-counter medications.
- Premature ovarian failure (i.e., menopause)
- Amenorrhea
- Infection of the pelvic region
- Uterine/ovarian necrosis
- Phlebitis
- Deep vein thrombosis with or without pulmonary embolism
- Vaginal discharge
- Tissue passage, fibroid sloughing, or fibroid expulsion post UFE
- Post-UFE intervention to remove necrotic fibroid tissue
- Vagal reaction
- Transient hypertensive episode
- Hysterectomy

PAE Specific Potential Complications

- Non-targeted embolization of the rectum, bladder, scrotum, penis, or other areas
- The most frequent post-procedure complication includes "Post-PAE Syndrome," which includes nausea, vomiting, fever, pelvic pain, burning sensation, dysuria, and frequent or urgent urination
- Skin burn (radiation exposure) from prolonged fluoroscopy time
- Blood in urine, semen, or stool
- Bladder spasm
- Urinary tract infection
- Urinary retention
- Constipation

Neurological Specific Potential Complications

- Ischemic stroke or ischemic infarction
- Neurological deficits, including cranial nerve palsies

STORAGE AND STERILITY

- Embosphere Microspheres must be stored in a cool, dry and dark place in their original vial and packaging.
- Use by the date indicated on the vial label.
- Do not freeze.
- Do not resterilize

INSTRUCTIONS FOR USE

Inspect packaging prior to use to ensure seal integrity for maintenance of sterility.

- Carefully evaluate the vascular network associated with the lesion using high resolution imaging prior to beginning the embolization procedure.
- Embosphere Microspheres are available in a range of sizes. Because of the potential for misembolization and the inherent variability in sphere sizes, the physician should be sure to carefully select the size of Embosphere Microspheres according to the size of the target vessels at the desired level of occlusion in the vasculature.
- When embolizing arteriovenous malformations (AVMs), choose an Embosphere Microsphere size that will occlude the nidus without passing through the AVM.
- When embolizing uterine fibroids, choose an Embosphere Microsphere size of 500 microns or greater.
- For prostatic artery embolization, it is recommended to use Embosphere Microspheres 300-500 microns.
- Choose a delivery catheter based on the size of the target vessel and the microsphere size being used. Embosphere Microspheres can tolerate temporary compression of up to 33% in order to facilitate passage through the delivery catheter.
- Introduce the delivery catheter into the target vessel according to standard techniques. Position the catheter tip as close as possible to the treatment site to avoid inadvertent occlusion of normal vessels.
- Embosphere Microspheres are not radiopaque. It is recommended that the embolization be monitored using fluoroscopic visualization by adding the appropriate amount of contrast medium to the physiologic suspension fluid.

To Deliver Embosphere Microspheres

- After gently agitating the vial containing Embosphere Microspheres, dilute Embosphere Microspheres with contrast medium either into a small sterile cup or directly into a large mixing syringe. It is recommended that 50% contrast and 50% physiological saline be used for best suspension. To ensure proper suspension, gently agitate the mixture of Embosphere Microspheres and contrast and wait 2-3 minutes after mixing, prior to injection. Draw the Embosphere Microspheres/contrast solution into a 1 mL or 3 mL injection syringe and attach the syringe to the delivery catheter. Inject the Embosphere Microspheres/contrast solution into the delivery catheter under fluoroscopic visualization using a slow pulsatile injection while observing the contrast flow rate. If there is no effect on the flow rate, repeat the delivery process with additional injections of the Embosphere Microspheres/contrast solution. Consider using larger sized Embosphere Microspheres if the initial injections do not alter the contrast flow rate. Exercise conservative judgment in determining the embolization endpoint.
- Femoral puncture can result in arterial spasm. This may predispose to femoral thrombosis (e.g. leg injury). Femoral patency should be re-assessed prior to final catheter removal.
- Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge Embosphere Microspheres still within the catheter lumen.
- Apply pressure to the puncture site until hemostasis is complete.
- Discard any open, unused Embosphere Microspheres.

Additional UFE Specific Instructions:

- At the discretion of the physician, pneumatic compression devices may be used for patients currently taking hormone therapy, uterine volume >1000cc, and patients that are overweight to lower the risk of deep vein thrombosis.
- Embolization should be stopped when the vasculature surrounding the fibroid can no longer be visualized but before complete stasis in

the uterine artery. There is an increased chance of retro-migration of Embosphere Microsphere into unintended blood vessels as uterine artery flow diminishes.

Additional PAE Specific Instructions

- A Foley catheter, with its balloon inflated with a mixture of contrast and saline, may be placed prior to PAE for use as a landmark during the embolization procedure.
- PAE can be performed by either radial or femoral access.

PATIENT COUNSELING INFORMATION

- Patients should have a clear understanding prior to embolization of who will provide their post procedure care and whom to contact in case of an emergency after embolization.
- Embolization patients should have an understanding of the potential benefits, risks, and adverse events associated with embolization. In particular, patients should understand that there is a chance their symptoms will not improve following embolization.

UFE CLINICAL STUDY SUMMARY

Study Design

A prospective multi-center trial was conducted to study UFE using Embosphere Microspheres for treatment of symptomatic uterine fibroids. A total of 132 women who desired to keep their uterus and avoid surgery were treated by UFE in the study; 30 in an initial feasibility study and 102 in the pivotal study. Those patients included in the pivotal study were followed for 3 years, with clinical measures of outcome obtained at 3, 6, 12, 24 and 36 months after treatment. Seven investigational sites participated in the study.

The study was designed to determine whether UFE using Embosphere Microspheres could reduce symptoms associated with symptomatic fibroids, such as abnormal bleeding, pain, discomfort, and urinary problems.

Primary Study Endpoints Included

- Reduction in menstrual bleeding from baseline to 6 months post-UFE as measured using a Pictorial Bleeding Assessment Chart (PBLAC)
- Improvement in bulk symptoms (pelvic pain, pelvic discomfort/bloating, and urinary dysfunction) as measured using a patient symptom questionnaire
- Improvement in quality of life as measured using the SF-12 Health Status Questionnaire

Secondary Endpoints Included

- Other measures of changes in menstrual bleeding
- Reduction of uterus and fibroid size
- Hospitalization time
- Time to return to normal activities
- Evaluations of patient satisfaction with the procedure

Adverse events and complications were also evaluated with respect to type, rate, and severity.

Eligibility criteria included age between 30 and 50 years, inclusive, infertile or no plans to become pregnant, one or more symptomatic uterine fibroids, uterine volume 250 cc or fibroid volume 4 cc, and baseline PBLAC ≥ 150. Women were excluded from the study if they were pregnant, had a history of pelvic inflammatory disease, submucosal fibroid(s) with more than 50% growth into the uterine cavity, pedunculated subserosal fibroid(s) as the dominant fibroid(s), significant collateral feeding by vessels other than uterine artery, adenomyosis as the dominant cause of symptoms, endometrial or pre-malignant hyperplasia, any malignancy of the pelvic region, any active infection of the pelvic region, known allergy to IV contrast or gelatin, bleeding diathesis, immunocompromised, post-menopausal or baseline FSH > 40 mIU/mL, or treatment with GnRH agonist within the previous 3 months.

Pre-treatment evaluations included routine gynecological exam and testing, standard laboratory testing, ultrasound or MRI, menstrual bleeding record (UFE group), and self-assessment questionnaires relating to overall health (SF-12), menstrual bleeding, and fibroid symptoms.

Study Results

Of the 102 patients enrolled in the pivotal study, 96 patients had complete baseline data and of these, 69 (72%) had known outcomes after 3 years after UFE treatment. Not all patients provided all outcome measures at the final follow-up interval, and the numbers providing follow-up are detailed in each of the tables provided.

Procedure, Discharge, and Recovery Information

All UFE procedures performed in both the feasibility and pivotal studies were technically successful with no intraoperative complications that prevented completion of the procedure. The majority (77%) of the UFE procedures were performed using a 5 Fr catheter with either a 4 Fr (19%) or 3 Fr (3%) in the remainder. Seventy-two patients were treated with 500-700 micron spheres, 66 patients with 700-900 micron spheres and 18 patients with 900-1200 micron spheres. Many of the patients were treated with more than one sphere size. The most common treatment approach was to start with a smaller sphere size and then to increase the size if necessary. The volume of spheres required varied inversely with the sphere size as an average of 7.2 cc of 500-700 micron spheres was used as compared to 6 cc of 700-900 micron spheres and 4.1 cc of 900-1200 micron spheres.

The majority of UFE patients underwent the procedure while under conscious sedation with a local anesthetic given at the puncture site. No UFE procedures were performed under general anesthesia. The average UFE procedure time from first arterial puncture to final catheter removal was 58 ± 28 minutes (range 10-140 minutes). Eighty-seven percent of the UFE patients were discharged from the hospital on the day following the embolization procedure and 12% on the same day as the procedure. UFE patients were back to work or returned to normal daily activities in an average of 10.7 days.

Primary Efficacy Endpoints

Menstrual Bleeding

To be eligible for UFE in the feasibility and pivotal studies, patients were required to have abnormally heavy menstrual bleeding, with a baseline score of ≥150 on the Pictorial Bleeding Assessment Chart (PBLAC) of Janssen et al. (1995). Additional measures were also used to assess changes in menstrual bleeding, including patient self-assessment of their bleeding level and a menorrhagia questionnaire. Changes in menstrual bleeding generally occurred quickly following UFE, with 92% of the patients showing improvement by 3 months. Out of the 102 patients from the pivotal study, only 48 patients completed the menorrhagia questionnaire at 36 months, and paired data were available from only 41 patients However, the results show a substantial and statistically significant improvement in scores (with lower scores being better) and the mean scores remained improved for the duration of the study (Table 1). These findings are well aligned with the patient self-assessment of menstrual bleeding (Table 2). At baseline, 54% of patients rated their bleeding as extremely heavy and 42% rated their bleeding as moderately heavy. During the 36-month follow-up, only 3% or less rated their bleeding as extremely heavy and less than 28% of patients complained of moderately heavy bleeding. At 36 months after treatment, 22% of patients noted that they were not having periods.

Table 1 – Results of the Menorrhagia Questionnaire

		All Data		Paired Data (n =41)*	
		Mean score standard deviation	Range	Mean score standard deviation	Range
Before Treatment (n =96)		47.9±13.1	14.29–83.33	45.2±13.5	14.3–83.3
After Treatment	3 mo (n =83)	24.5±13.1	7.1–64.3	22.9±10.7	7.1–54.8
	6 mo (n =83)	21.03±11.9	7.1–64.3	18± 8.6	7.1–52.4
	12 mo (n =78)	17.1±10.1	2.4–61.9	18.6±11.7	2.4–61.9
	24 mo (n =67)	19.7±11.8	0–54.8	17.8±9.4	0–54.8
	36 mo (n= 48)	19.2±11	0–57.1	20.1± 10.7	0–57.1

Note. —The difference between the scores at each time interval and that at baseline were statistically significant (P <.001). P value was calculated with tests, paired tests, and sign tests.

* Paired data are from those patients who had data available at each follow-up interval (N 41).

Table 2 – Patient Assessment of Menstrual Bleeding

		Description of Bleeding				
		Extremely heavy	Moderately heavy	Normal	Light	**No Periods**
Before Treatment (n =96)		54 (57)	40 (42)	1 (1)	0 (0)	0 (0)
After Treatment	3 mo (n =87)	3 (3)	38 (44)	27 (31)	13 (15)	6 (7)
	6 mo (n =88)	3 (3)	25 (28)	37 (42)	18 (20)	5 (6)
	12 mo (n =83)	1 (1)	17 (20)	38 (46)	21 (25)	6 (7)
	24 mo (n =71)	2 (3)	17 (24)	33 (46)	15 (21)	4 (6)
	36 mo (n=59)	1 (2)	14 (24)	27 (37)	9 (15)	13 (22)

Note. —Data are given as numbers of patients. Numbers in parentheses are percentages.

Bulk Symptoms

Bulk symptoms of pain, discomfort and urinary problems (Table 3) were substantially improved in most patients, although a smaller number of patients had substantially improved urinary symptoms at each of the data intervals.

Table 3 – Bulk Symptom Status: Proportion of Patients with Moderate to Substantial Improvement after Embolization

	Symptom		
	Pelvic pain	Pelvic discomfort	Urinary problems
3 mo (n =86)	63 (73)	61 (71)	46 (53)
6 mo (n =87)	68 (78)	71 (82)	58 (66)
12 mo (n =81)	77 (83)	67 (81)	56 (69)
24 mo (n =73)	60 (83)	61 (83)	44 (62)
36 mo (n =59)	49 (83)	49 (83)	42 (69)

Note. —Data are given as numbers of patients. Numbers in parentheses are percentages.

Quality of Life

The SF-12 Health Status questionnaire was used to assess changes in general physical and mental health status following treatment. The goal of this endpoint was to demonstrate at least a moderate improvement in the overall quality of life. Results of the SF-12 Health Status questionnaire are presented in Table 4. This 12-question questionnaire is scored and normalized to a mean score of 50 and a standard deviation of 10 for the general U.S. population. The mean physical and mental summary score for patients before embolization was 45. The physical summary score increased to 51.8 by 3 months and to 53.7 by 36 months, whereas the mean mental score was 52.1 at 3 months and 53.3 at 36 months. The patient's perception of health status correspondingly increased, from a mean of 69.5 to 86.3 by 36 months. At the conclusion of the study, 84% of patients were very or moderately satisfied with the symptom control of the procedure.

Table 4 – Results of SF-12 Questionnaire with Regard to Overall Health Status and Satisfaction with Outcome

		Parameter Evaluated								
		Physical status			Mental status			Overall health status		No. of patients who were moderately or very satisfied
		Mean score standard deviation	Range	*P* value	Mean score standard deviation	Range	*P* value	Mean score standard deviation	Range	
Before Treatment (n =96)		45±8.3	26–61.6		45±11.5	22.3–63.4		69.5±19.1	0–100	
After Treatment	3 mo (n =88)	51.8±6.7	22.3–58.5	<.001	52.1±7.7	23.8–61.6	<.001	82.6±14.2	28.7–100	78 (89%)
	6 mo (n =88)	52.4±6.2	23.3–62.6	<.001	52.9 ±7.9	20.5–60.8	<.001	85.1±11.3	43.8–100	78 (89%)
	12 mo (n =82)	53.6±5.9	23.1–64.1	<.001	52.6±7.8	23.2–61.7	<.001	86.4±14.2	0–100	84 (91%)
	24 mo (n =73)	52.5±6.3	24.8–59.8	<.001	53.8±7.7	21.8–64.3	<.001	83.9±15.3	0–100	64 (88%)
	36 mo (n=61)	53.7±5.1	30.7–62.8	<.001	53.3±7.4	25.2–63.1	<.001	86.3±11.2	48–100	52 (85%)

Secondary Efficacy Endpoints

Fibroid and Uterine Volume

Uterine imaging by MRI or ultrasound for UFE patients did not extend past the 6-month follow-up. Uterine and fibroid volumes were calculated using the formula for the volume of a prolate ellipse (LxWxDx0.52). Significant decreases in both uterine volume (measured as including the cervix) and uterine fibroid volume were recorded for the UFE group by the 3-month evaluation, with further improvements seen at 6 months ($p<0.001$ at both time periods as compared to baseline). Table 5 summarizes the percent changes in uterine and fibroid volumes at 6 months following treatment. This table includes uterine volume data from 91 of the 108 UFE Phase II patients (84%) and fibroid volume data from 83 of these patients (77%) who had complete and evaluable imaging reports at baseline, and at 3 months and 6 months following UFE treatment. Increases in uterine volumes were reported for 11 patients (12%) and increases in fibroid volumes for 8 patients (8%) by the 6-month evaluation.

Table 5 – Percent Change in Uterine and Fibroid Volumes from Baseline

	% Decrease at 6 Months
Uterine Volume (cc)	
N	91
Mean	33.2% (30.5%)
Range	-93.6% to 82.0%
Fibroid Volume (cc)	
N	83
Mean	50.9% (41.7%)
Range	-173.4% to 99.7%

A positive percent change indicates a decrease in volume, while a negative percent change indicates an increase in volume.

Patient Satisfaction

Ninety-two of 100 UFE patients (92%) who completed the patient satisfaction questionnaire at 6 months were slightly, moderately or very satisfied with the outcome of their procedure, with the majority being very satisfied. Satisfaction remained relatively high three years after UFE treatment, with 52 out of 61 patients (85%) surveyed reported they were moderately or very satisfied.

ADVERSE EVENTS

Adverse event data is reported for all 132 patients for up to 6 months after being treated by UFE (Table 6). There were no unanticipated adverse device effects or unanticipated adverse events reported in this study. Table 6 presents 51 adverse events judged to be probably or possibly associated with the procedure, which occurred in 34 of the 132 UFE patients (26%). Seven of the 51 events (14%) occurred during the UFE procedure, five (10%) between the procedure and hospital discharge, 17 (33%) from hospital discharge to 1 month post-procedure, 11 (22%) from 1 to 3 months post-procedure, 4 (8%) from 3 to 6 months post-procedure, and 7 (14%) greater than 6 months post-procedure. The most common adverse event was an allergic reaction or rash, which occurred in 8 of the 132 patients (6%), and which were generally judged by the treating physician to be related to the drugs or contrast agent used during the procedure. All reactions resolved spontaneously or with treatment. Four patients had hysterectomies following UFE, for an overall hysterectomy rate of 3%. One hysterectomy was performed at 2 months post-UFE due to sustained fever/possible infection. The other three were elective hysterectomies due to dissatisfaction with UFE outcome, which occurred at 2, 10, and 11 months post-UFE. One patient (<1%) had a repeat UFE after her uterine arteries were found to be patent.

Table 6 – Timing and Type of Probably or Possibly UFE-Related Adverse Events

Event Description	# of Patient Complaints	# of Events	Procedure	In Hospital	< 1 Month	1-3 Months	3-6 Months	> 6 Months
Hysterectomy following UFE	4	4				2		2
Allergic reaction/ Rash	8	8	2	3	3			
Fibroid/Tissue passage or removal	5	6			2	3		1
Pain related adverse events	4	4			3	1		
Catheter/ puncture site related injury	6	7	1	2	4			
Urinary Tract Infection/ Cystitis	3	4			1	1	1	1
Vaginal Infection/ Vaginatis	5	7			2	1	2	2
Vaginal Irritation/ Burning/ Discharge	2	2			1	1		
Other	9	9	4		1	2	1	1
Total	46	51	7	5	17	11	4	7

*A total of 34 out of 132 patients (26%) experienced one or more adverse event in this study. The number of patients in this column reflects the fact that some patients experienced more than one adverse event.

PAE CLINICAL SUMMARY

A Composite database from clinical trials and published literature containing information from a total of 286 patients who underwent prostatic artery embolization (PAE) using Embosphere Microspheres for treatment of symptomatic benign prostatic hyperplasia (BPH) was analyzed to evaluate clinical outcomes. All patients were suffering from lower urinary tract symptoms (LUTS) due to BPH with International Prostate Symptom Scores (IPSS) of moderate to severe. Prostate or bladder cancer, active urinary tract infections or prostatitis, bladder stones, and atonia or other neurogenic conditions impacting bladder function, and intolerance to contrast media or catheter-based interventions were exclusionary. Prior to embolization, patients underwent clinical evaluation, imaging of the prostate, and completed validated symptom and quality of life questionnaires. Follow-up evaluations included the IPSS and its quality of life (QOL) questionnaire and prostate imaging at a minimum. The primary effectiveness evaluations were change in IPSS and QOL scores post embolization, with reduction in prostate size as a secondary objective. Safety was assessed from reported adverse events.

RESULTS

Mean age of the evaluated cohort was in the seventh decade, lower urinary tract symptoms were severe as reflected in a mean IPSS score over 20, and quality of life was dissatisfied to unhappy. Fifty-four patients had indwelling bladder catheters at baseline.

Table 7 – Baseline Characteristics of the Patient Population

Characteristic	Mean ± SD	n
Age (years)	67.7 ± 9.7	286
IPSS	21.5 ± 6.8	251
Quality of life	4.8 ± 0.9	166
Prostate volume (gms)	85.1 ± 38.3	265
PSA (ng/mL)	5.4 ± 4.6	251
Qmax (mL/s)	6.9 ± 3.8	175

The majority of patients underwent bilateral embolization.

Table 8 – Unilateral versus Bilateral Embolization

Embolization	Patients (%)
Unilateral	29 (10.1)
Bilateral	254 (88.9)
No data	3 (1.0)

Mean symptom scores, which were severe at baseline, improved compared to pretreatment values at every follow-up interval. Values at the 9-16 month evaluation period were mildly symptomatic. A reduction of IPSS by at least 3 points was achieved at this latest evaluation in 97% of patients, and 90% dropped by at least 1 symptom category.

Table 9 – Mean IPSS at Baseline and Follow-up

Time Window	Mean ± SD	n
Baseline	21.5 ± 6.8	251
1 to 3 months f/u	6.3 ± 5.8	190
9 to 16 months f/u	6.2 ± 5.8	136

Table 10 – Proportion of Patients Achieving ≥ 3 point Improvement in IPSS

Time Window	Proportion (95% CI)
1 to 3 months f/u	0.931 (0.883-0.964)
9 to 16 months f/u	0.967 (0.917-0.991)

Table 11 – Proportion of Patients Achieving ≥ 1 IPSS Category Improvement

Time Point	Proportion (95% CI)
1 to 3 months f/u	0.842 (0.782-0.891)
9 to 16 months f/u	0.897 (0.833-0.943)

Not surprisingly, the reduction of lower urinary tract symptoms reflected in the IPSS changes affected mean quality of life. Mean QOL scores, which were categorized as mostly dissatisfied to unhappy pre-embolization, improved at every follow-up interval to pleased/mostly satisfied.

Table 12 – Mean Quality of Life at Baseline and Follow-up

Time Point	Mean ± SD	n
Baseline	4.8 ± 0.9	166
1 to 3 months f/u	1.4 ± 1.2	165
9 to 16 months f/u	1.4 ± 1.1	116

Mean prostate size at baseline was 85.1g, and demonstrated reduction throughout follow-up.

Table 13 – Mean Prostate Volume at Baseline and Follow-up

Time Point	Mean ± SD	n
Baseline	85.1 ± 38.3	265
1 to 3 months f/u	62.4 ± 27.1	193
9 to 16 months f/u	65.2 ± 28.6	118

In addition to the overall Composite population, analyses were done for subsets of patients age 80 or older, with prostates 90g or larger, and those with indwelling catheters at baseline for management of acute urinary retention. These categories are not mutually exclusive. Patients in these groups were of particular interest because they frequently are contraindicated for TURP: elderly patients have higher incidence rates of comorbid conditions, patients with prostate size larger than 90g are typically referred for open surgery, and patients in acute retention are not generally treated by transurethral procedures. For these reasons the successful outcomes from PAE in these cohorts is notable.

Other than being older, baseline evaluations of the ≥80-year subset were similar to those of the Composite group, including IPSS reflecting severe symptoms and mostly dissatisfied to unhappy quality of life.

Table 14 – Baseline Characteristics of Patients Age ≥ 80 Years

Characteristic	Mean ± SD	n
Age (years)	84.6 ± 3.8	39
IPSS	23.9 ± 9.9	32
Quality of life	4.6 ± 1.2	17
Prostate volume (gms)	78.1 ± 37.0	34
PSA (ng/mL)	3.9 ± 3.6	22

* 13 of 39 patients (33.3%) had indwelling bladder catheters at baseline

Although elderly patients might be limited in treatment options and/or might be more fragile due to comorbidities, this cohort achieved reduction in LUTS at all follow-up intervals. Over 80% had at least a 3-point reduction in IPSS and a substantial majority dropped by at least one symptom category.

Table 15 – Mean IPSS at Baseline and Follow-up of Patients Age ≥ 80 Years

Time Window	Mean ± SD	n
Baseline	23.9 ± 9.9	32
1 to 3 months f/u	13.4 ± 9.2	9
9 to 16 months f/u	7.0 ± 2.9	9

Table 16 – Proportion of Patients Age ≥ 80 Years Achieving ≥ 3 Point IPSS Improvement

Time Window	Proportion (95% CI)
1 to 3 months f/u	0.889 (0.518-0.997)
9 to 16 months f/u	0.889 (0.518-0.997)

Table 17 – Proportion of Patients Age ≥ 80 Years Achieving ≥ 1 IPSS Category Improvement

Time Point	Proportion (95% CI)
1 to 3 months f/u	0.778 (0.400-0.972)
9 to 16 months f/u	0.667 (0.300-0.925)

The mean quality of life for this group trended toward improvement from mostly dissatisfied to mostly satisfied.

Table 18 – Mean Quality of Life at Baseline and Follow-up of Patients Age ≥ 80 Years

Time Point	Mean ± SD	n
Baseline	4.6 ± 1.2	17
1 to 3 months f/u	1.4 ± 1.9	8
9 to 16 months f/u	1.1 ± 1.1	10

Bilateral embolization was possible in 80% of this group, and prostate size reduction was seen throughout follow-up.

Table 19 – Unilateral versus Bilateral Embolization in Patients Age ≥ 80 Years

Embolization	Patients (%)
Unilateral	8 (20.5)
Bilateral	31 (79.5)
No data	0 (0)

Table 20 – Mean Prostate Volume at Baseline and Follow-up of Patients Age ≥ 80 Years

Time Point	Mean ± SD	n
Baseline	78.1 ± 37.1	34
1 to 3 months f/u	55.1 ± 22.5	16
9 to 16 months f/u	64.6 ± 20.6	10

Among the subset of patients with prostate size larger than 90g, baseline characteristics were similar to those of the entire Composite group, other than gland volume.

Table 21 – Baseline Characteristics of Patients with Prostate Size ≥ 90g

Characteristic	Mean ± SD	n
Age (years)	68.4 ± 9.0	95
IPSS	19.8 ± 6.8	87
Quality of life	4.6 ± 0.8	53
Prostate volume (gms)	124.2 ± 35.5	95
PSA (ng/mL)	7.4 ± 5.5	88

* 12 of 95 patients (12.6%) had indwelling bladder catheters at baseline

Symptoms improved in this cohort post embolization at all time points, and a minimum 3-point reduction and drop of at least one symptom category in IPSS was achieved by 96% and 89% of patients respectively.

Table 22 – Mean IPSS at Baseline and Follow-up of Patients with Prostate Size ≥ 90g

Time Window	Mean ± SD	n
Baseline	19.8 ± 6.8	87
1 to 3 months f/u	5.0 ± 4.6	69
9 to 16 months f/u	4.6 ± 4.1	54

Table 23 – Proportion of Patients with Prostate Size ≥ 90g Achieving ≥ 3 Point IPSS Improvement

Time Window	Proportion (95% CI)
1 to 3 months f/u	0.955 (0.873-0.991)
9 to 16 months f/u	0.961 (0.865-0.995)

Table 24 – Proportion of Patients with Prostate Size ≥ 90g Achieving ≥ 1 IPSS Category Improvement

Time Point	Proportion (95% CI)
1 to 3 months f/u	0.870 (0.767-0.939)
9 to 16 months f/u	0.889 (0.774-0.958)

Mean quality of life scores also improved and prostate size demonstrated a reduction at each evaluation point, consistent with the reduced lower urinary tract symptoms.

Table 25 – Mean Quality of Life at Baseline and Follow-up of Patients with Prostate Size ≥ 90g

Time Point	Mean ± SD	n
Baseline	4.6 ± 0.8	53
1 to 3 months f/u	1.1 ± 0.9	49
9 to 16 months f/u	1.2 ± 0.9	40

Table 26 – Mean Prostate Size at Baseline and Follow-up of Patients with Prostate Size ≥ 90g

Time Point	Mean ± SD	n
Baseline	124.2 ± 35.5	95
1 to 3 months f/u	85.9 ± 27.2	70
9 to 16 months f/u	91.0 ± 27.8	44

The difference in size of the prostates relative to the entire Composite group did not impact technical success of embolization. Over 90% of patients underwent bilateral embolization.

Table 27 – Unilateral versus Bilateral Embolization of Patients with Prostate Size ≥ 90g

Embolization	Patients (%)
Unilateral	6 (6.3)
Bilateral	87 (91.6)
No data	2 (2.1)

Patients with indwelling catheters at baseline tended to be older than the Composite population as a whole, and the catheters led to unhappy to quality of life scores categorized as terrible.

Table 28 – Baseline Characteristics of Patients with Indwelling Catheters at Baseline

Characteristic	Mean ± SD	n
Age (years)	73.8 ± 8.4	54
Quality of life	5.8 ± 1.0	16
Prostate volume (gms)	79.0 ± 33.5	45
PSA (ng/mL)	6.3 ± 5.4	39

Baseline IPSS data were not analyzed for patients with indwelling catheters because their acute urinary retention made questions about urination habits moot. Consequently, no analyses of the proportions of patients whose symptoms improved from baseline could be conducted.

Post embolization, patients went from inability to answer IPSS questions to being only mildly symptomatic, and quality of life scores improved from categorization of unhappy to terrible at baseline to pleased after treatment.

Table 29 – Mean IPSS During Follow-up of Patients with Indwelling Catheters at Baseline

Time Window	Mean ± SD	n
1 to 3 months f/u	6.0 ± 4.8	22
9 to 16 months f/u	5.9 ± 4.3	22

Table 30 – Mean QOL at Baseline and Follow-up of Patients with Indwelling Catheters at Baseline

Time Point	Mean ± SD	n
Baseline	5.8 ± 1.0	16
1 to 3 months f/u	1.0 ± 0.8	25
9 to 16 months f/u	1.0 ± 1.0	23

Mean prostate size was reduced at all follow-up points, with over 80% of patients having received bilateral embolization.

Table 31 – Mean Prostate Size at Baseline and Follow-up of Patients with Indwelling Catheters at Baseline

Time Point	Mean ± SD	n
Baseline	79.0 ± 33.5	45
1 to 3 months f/u	64.3 ± 32.4	21
9 to 16 months f/u	54.3 ± 19.1	20

Table 32 – Unilateral versus Bilateral Embolization of Patients with Indwelling Catheters at Baseline

Embolization	Patients (%)
Unilateral	9 (16.7)
Bilateral	44 (81.5)
No data	1 (1.8)

Table 33 – Adverse Events

Event	PAE
Congenital, familial and genetic disorders	1 (0.3%)
Hydrocele	1 (0.3%)
Ear and labyrinth disorders	2 (0.7%)
Ear pain	2 (0.7%)
Endocrine disorders	1 (0.3%)
Hypogonadism	1 (0.3%)
Gastrointestinal disorders	33 (11.5%)
Abdominal pain lower	1 (0.3%)
Abdominal pain upper	1 (0.3%)
Abdominal rigidity	2 (0.7%)
Anorectal discomfort	1 (0.3%)
Constipation	4 (1.4%)
Dental necrosis	1 (0.3%)
Diarrhea	2 (0.7%)
Hematochezia	14 (4.9%)
Hemorrhoids	1 (0.3%)
Nausea	5 (1.7%)
Vomiting	1 (0.3%)
General disorders and administration site conditions	18 (6.3%)
Catheter site inflammation	1 (0.3%)
Chest pain	1 (0.3%)
Chills	1 (0.3%)
Facial pain	1 (0.3%)
Local swelling	3 (1.0%)
Pain	1 (0.3%)
Pyrexia	8 (2.8%)
Suprapubic pain	2 (0.7%)
Infections and infestations	13 (4.5%)
Cellulitis	1 (0.3%)
Localized infection	1 (0.3%)
Nasopharyngitis	2 (0.7%)
Sepsis	1 (0.3%)
Urinary tract infection	8 (2.8%)
Injury, poisoning and procedural complications	217 (75.9%)
Bladder injury	1 (0.3%)
Fall	1 (0.3%)
Post prostatic artery embolization syndrome	212 (74.1%)
Procedural pain	1 (0.3%)
Pubic bone injury	1 (0.3%)
Rectal injury	1 (0.3%)
Investigations	1 (0.3%)
Blood urine present	1 (0.3%)
Musculoskeletal and connective tissue disorders	11 (3.8%)
Arthralgia	1 (0.3%)
Chest wall mass	1 (0.3%)
Flank pain	1 (0.3%)
Groin pain	2 (0.7%)
Muscle spasms	1 (0.3%)
Musculoskeletal chest pain	1 (0.3%)
Musculoskeletal discomfort	1 (0.3%)
Musculoskeletal pain	1 (0.3%)
Pain in extremity	2 (0.7%)
Nervous system disorders	4 (1.4%)
Dizziness	2 (0.7%)
Headache	1 (0.3%)
Sciatica	1 (0.3%)
Renal and urinary disorders	65 (22.7%)
Bladder discomfort	3 (1.0%)
Bladder spasm	5 (1.7%)
Dysuria	22 (7.7%)
Hematuria	10 (3.5%)
Micturition urgency	6 (2.1%)
Pollakuria	2 (0.7%)
Renal failure acute	1 (0.3%)
Terminal dribbling	1 (0.3%)
Urethral pain	2 (0.7%)
Urethral trauma	1 (0.3%)
Urinary incontinence	2 (0.7%)
Urinary retention	9 (3.1%)
Urinary straining	1 (0.3%)
Reproductive system and breast disorders	36 (12.6%)
Decreased ejaculatory volume	14 (4.9%)
Epididymal cyst	1 (0.3%)
Hematospermia	12 (4.2%)
Pelvic pain	3 (1.0%)
Penile burning sensation	1 (0.3%)
Penile pain	1 (0.3%)
Perineal pain	1 (0.3%)
Prostatitis	1 (0.3%)
Testicular pain	1 (0.3%)
Varicocele	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	6 (2.1%)
Chronic obstructive pulmonary disease	2 (0.7%)
Dyspnoea	2 (0.7%)
Nasal congestion	1 (0.3%)
Pulmonary mass	1 (0.3%)
Skin and subcutaneous tissue disorders	2 (0.7%)
Skin discoloration	2 (0.7%)
Surgical and medical procedures	1 (0.3%)
Arthroscopic surgery	1 (0.3%)
Vascular disorders	2 (0.7%)
Hematoma	1 (0.3%)
Hypertension	1 (0.3%)

The most common adverse event was Post-PAE Syndrome.

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