

THE USE OF DURASPHERE® IN WOMEN:
A Minimally Invasive Treatment for Stress Urinary Incontinence
Data From Durasphere Clinical Trial, July 1996 – May 1999

DURASPHERE® INJECTION THERAPY:
Post-Market Long-Term Effectiveness
FDA Annual Report Submission, September 15, 2003

THE USE OF DURASPHERE® IN WOMEN: A Minimally Invasive Treatment for Stress Urinary Incontinence Data From Durasphere Clinical Trial, July 1996 – May 1999

INTRODUCTION

A new minimally invasive treatment option for women suffering from stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD) was evaluated in a multicenter trial. A total of 115 females were treated with the Durasphere® injectable bulking agent and followed for over one year in the period from July 1996 to May 1999. On September 13, 1999, the Food and Drug Administration (FDA) approved Durasphere for commercial distribution in the United States.

THE PRODUCT

Durasphere is an injectable bulking agent containing pyrolytic carbon-coated zirconium oxide beads suspended in a gel carrier agent. Pyrolytic carbon has long been used in implantable medical devices, including replacement heart valves for the past 30 years. The targeted bead size ranges from 251 to 300 microns, more than three times larger than the 80-micron threshold for particle sizes associated with migration in tissue.¹

The biocompatibility and safety of Durasphere was successfully demonstrated in extensive laboratory and animal studies (acute and long-term) prior to the initiation of the clinical study. Due to its high level of biocompatibility Durasphere does not require a skin test.

CLINICAL EVALUATION

The clinical trial of the Durasphere injectable bulking agent under an FDA approved investigational device exemption (IDE) began in July 1996. Women who met the following primary inclusion and exclusion criteria were considered as candidates for participation:

Inclusion Criteria

- SUI due to ISD for a period of at least 12 months, as evidenced from urodynamic or radiographic assessment
- 21 years of age or older
- Failure of prior non-invasive treatments, ie: pelvic floor exercises, timed voiding
- Post-void residual < 100 ml and abdominal leak point pressures ≤ 90 cm H₂O

Exclusion Criteria

- Primary incontinence types other than SUI due to ISD
- Uncontrolled bladder instability
- Positive urine culture
- Failure of prior urethral bulking treatment
- Medications affecting the evaluation of incontinence
- Pregnancy

¹Malizia *et al*, Migration and Granulomatous Reaction After Periurethral Injection of Polytef (Teflon) JAMA, June 22/29, 1984 – Vol 251, No. 24

The safety and effectiveness of Durasphere was evaluated by a number of tools. Efficacy measurements included:

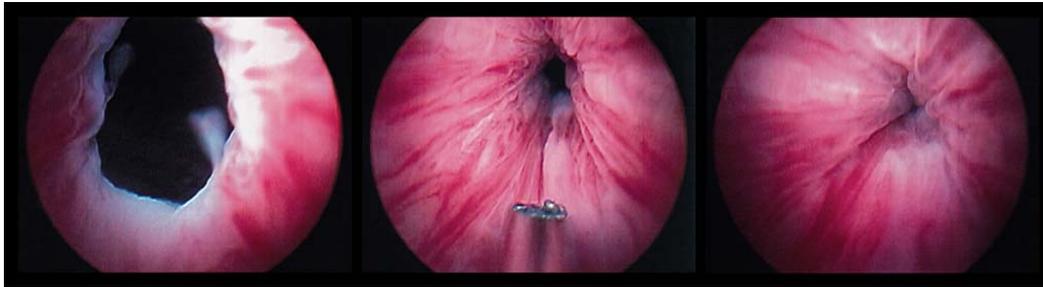
- Continenence grade evaluation using the Stamey classification of urinary incontinence²
- Pad weighing test³
- Incontinence episodes
- Quality of Life instrument⁴

Safety was evaluated by:

- Adverse events
- KUB x-rays

The transurethral injection procedure used for the injectable bulking agents is shown in the following illustrations [Figure 1].

Figure 1. Cystoscopic Photographs



RESULTS

Continenence Grade Evaluation

The change in continence grade from baseline to follow-up was used to evaluate this efficacy measurement. The continence grades used in this study were developed by Stamey² in 1979:

Degree of incontinence

Grade 0: Continent

Grade 1: Loss of urine with sudden increases in abdominal pressure, not in bed at night.

Grade 2: Incontinence worsens with lesser degrees of stress, such as walking, standing erect from sitting position, or sitting up in bed.

Grade 3: Total incontinence occurs and urine is lost without relation to physical activity or position.

Table 1 and Figure 2 display the improvement in continence grade by time periods for the study population. The mean continence grade was significantly improved (reduced) from baseline to follow-up at all time periods for patients receiving Durasphere.

² Stamey TA, Urinary incontinence in the female. In: Harrison JH, Gittes RF, Perimutter AD, Stamey TA, Walsh PC, eds. Campbell's Urology, 4th edn. WB Saunders Co, 1979; 2272-2293

³ British Journal of Obstetrics and Gynaecology, Supplement Number 6, March 1990; 4-5

⁴ Wagner TH *et al*, Quality of life of persons with urinary incontinence: Development of a new measure. Urology 47 (1), 1996

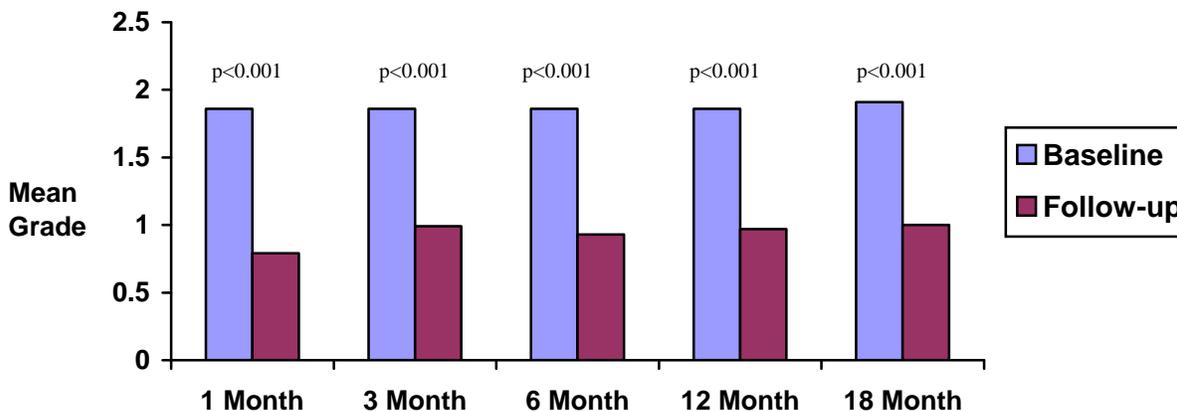
The mean continence grade for Durasphere patients was significantly improved (48% reduction) from 1.86 at baseline to 0.97 at 12 months ($p < 0.001$).

Table 1. Continence Grade by Time Periods

Follow-up Visit	Improvement in Continence Grade (Matched Pairs)				p-Value(1)
	n	Mean Baseline Grade (SD)	Mean Follow-up Grade (SD)	Mean Change	
1 Month	115	1.86 (0.46)	0.79 (0.79)	1.07	< 0.001
3 Month	115	1.86 (0.46)	0.99 (0.81)	0.87	< 0.001
6 Month	113	1.86 (0.46)	0.93 (0.82)	0.93	< 0.001
12 Month	115	1.86 (0.46)	0.97 (0.81)	0.89	< 0.001
18 Month	32	1.91 (0.39)	1.00 (0.80)	0.91	< 0.001

(1) Two-sided Student's *t*-test

Figure 2. Continence Grade by Time Period



Pad Weight

Pad weight was evaluated by measuring the urine loss of patients who underwent a prescribed set of activities that may induce stress incontinence. The urine loss was quantified through the use of pads, which were worn by patients and then weighed at the completion of the activities. The change in pad weight from baseline to follow-up was used to evaluate this efficacy measurement.

Table 2 and Figure 3 display the improvement (decrease) in pad weight by time periods for the study population. The mean pad weight was significantly improved (reduced) from baseline to follow-up at all time periods.

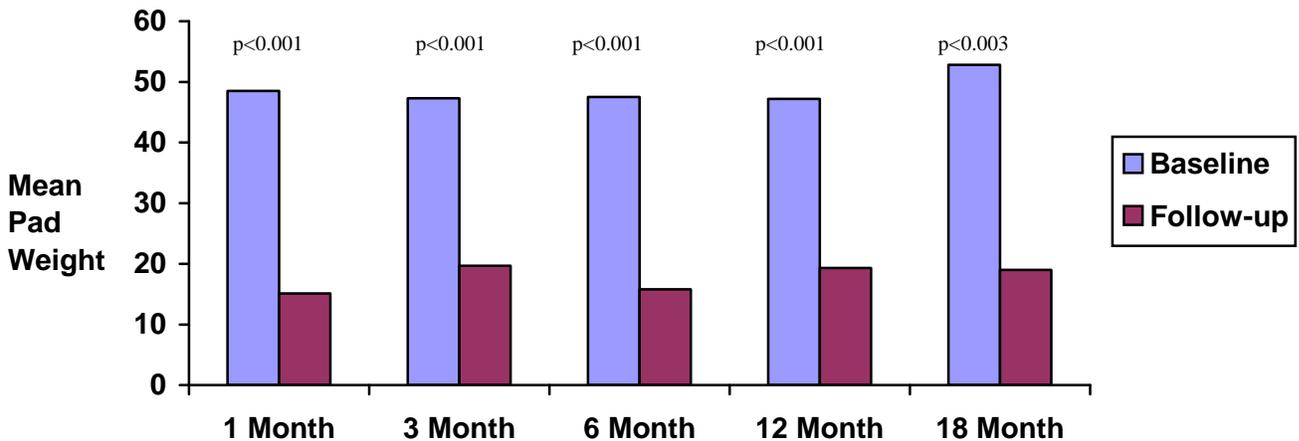
The mean pad weight was significantly improved (59% reduction) from 47.2 grams at baseline to 19.3 grams at 12 months ($p < 0.001$).

Table 2. Pad Weight by Time Periods

Follow-up Visit	Improvement in Pad Weight (Matched Pairs)				p-Value(1)
	N	Mean Baseline Pad Weight (gm) (SD)	Mean Follow-up Pad Weight (gm) (SD)	Mean Change (gm)	
1 Month	115	48.5 (50.4)	15.1 (39.8)	33.5	< 0.001
3 Month	113	47.3 (48.3)	19.7 (34.6)	27.6	< 0.001
6 Month	110	47.5 (48.7)	15.8 (33.5)	31.7	< 0.001
12 Month	113	47.2 (48.3)	19.3 (42.5)	27.9	< 0.001
18 Month	29	52.8 (48.1)	19.0 (49.0)	33.8	0.003

(1) Two-sided Student's *t*-test

Figure 3. Pad Weight by Time Periods



Incontinence Episodes

Patients were required to complete a voiding diary one week prior to each follow-up visit. Table 3 displays the improvement in incontinence episodes per week by time periods for the study population. The mean number of episodes per week was significantly improved (reduced) from baseline to follow-up at all time periods for these patients.

The mean number of episodes per week was significantly improved (51% reduction) from 20.8 at baseline to 10.2 at 12 months ($p < 0.001$).

Table 3. Incontinence Episodes/Week by Time Periods

Follow-up Visit	Improvement in Incontinence Episodes (Matched Pairs)				p-Value(1)
	n	Mean Baseline # of Episodes (SD)	Mean Follow-up # of Episodes (SD)	Mean Change	
1 Month	112	24.4 (26.4)	12.1 (25.0)	12.3	< 0.001
3 Month	99	25.2 (27.6)	14.8 (29.4)	10.4	< 0.001
6 Month	101	20.5 (18.4)	7.8 (7.8)	12.7	< 0.001
12 Month	96	20.8 (18.2)	10.2 (15.7)	10.6	< 0.001
18 Month	25	20.3 (19.1)	12.0 (15.3)	8.9	0.062

(1) Two-sided Student's *t*-test

Quality of Life

The Incontinence Quality of Life (IQOL) validated instrument, developed by Wagner *et al*⁴, was used in Phase 2 of the clinical study. This instrument contains 20 incontinence symptom specific items. Each item was rated on a scale of 1 to 5, and the total score for each subject was normalized to a scale of 20-100.

Table 4 displays the improvement in IQOL scores by times periods for the study population. The mean score was significantly improved (increased) from baseline to follow-up at all time periods for patients receiving Durasphere.

The mean score was significantly improved (33% increase) from 55.5 baseline to 73.7 at 12 months ($p < 0.001$).

Table 4. IQOL Scores by Time Periods

Follow-up Visit	Improvement in IQOL Scores (Matched Pairs)				p-Value(1)
	n	Mean Baseline Score (SD)	Mean Follow-up Score (SD)	Mean Change	
6 Month	91	54.5 (18.3)	72.1 (21.0)	17.6	< 0.001
12 Month	91	55.5 (18.1)	73.7 (20.9)	18.2	< 0.001

(1) Two-sided Student's *t*-test

Adverse Events

Safety was measured by the physician through physical examinations, and by questioning patients immediately post-injection, and at all subsequent follow-ups. All complications or symptoms lasting longer than 24 hours were reported as Adverse Events in the study, and were classified by study investigators as *Mild*, *Moderate*, or *Severe*.

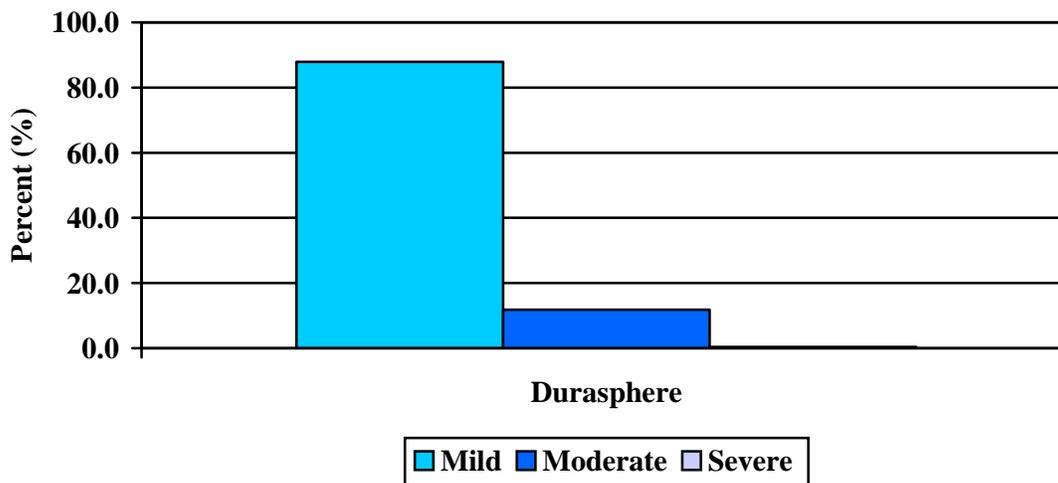
Mild events were defined as not life threatening and requiring minimal medical treatment.

Moderate events were defined as not life threatening but resulting in temporary disability, and/or requiring medical intervention or surgical intervention (either inpatient or outpatient).

Severe events were defined as one that was life threatening or resulted in a fatality.

Figure 4 shows the distribution of severity (*Mild*, *Moderate*, *Severe*) for Durasphere was 87.9%, 11.8%, and 0.4%. There were no deaths or unanticipated adverse device effects reported. The one (0.4%) severe adverse event was reported as unrelated to the device or procedure. None of the adverse events reported for Durasphere had significant clinical sequelae.

Figure 4. Distribution of Severity of Adverse Events



KUB X-rays

X-rays were taken of the kidney, urethra, and bladder (KUB) at the 1 and 2 year follow-up visits. All x-rays were evaluated by an independent expert urologist, per a pre-determined grading system.

There was no evidence of migration of the Durasphere beads reported during the study, which, unlike other injectable bulking materials, can be visualized radiographically after the injection procedure. The maintenance of the beads at the site of injection is illustrated on the following KUB x-rays taken of a study subject at one and two years post-injection [Figure 5].

Figure 5. One Year and Two Year KUB X-rays



One Year X-ray



Two Year X-ray

Summary

The following summarizes the results of Durasphere patients.

Efficacy Results

Continence Grade

- The mean continence grade was significantly improved (48% reduction) from 1.86 at baseline to 0.97 at 12 months.
- The mean continence grade was significantly improved (reduced) from baseline to all follow-up periods for all intervals.

Pad Weight

- The mean pad weight was significantly improved (59% reduction) from 47.2 grams at baseline to 19.3 grams at 12 months.
- The mean pad weight was significantly improved (reduced) from baseline to follow-up at all time periods at 1, 3, 6, 12, and 18 months.

Incontinence Episodes

- The mean number of episodes per week was significantly improved (51% reduction) from 20.8 at baseline to 10.2 at 12 months.
- The mean number of episodes per week was significantly improved (reduced) from baseline to follow-up at 1, 3, 6, 12 months for Durasphere patients.

Quality of Life

- The mean score was significantly improved (33% increase) from 55.5 at baseline to 73.7 at 12 months.
- The mean IQOL score was significantly improved (increased) from baseline to follow-up at all time periods.

Safety Results

- The *Mild* category accounted for 87.9% of adverse events, with 11.8% reported as *Moderate*, and 0.4% reported as *Severe* (all of the *Severe* events were reported as unrelated to the device or the procedure).
- No evidence of migration was observed from the patient KUB x-rays taken at 12 and 24 months post treatment.
- There were no deaths or unanticipated adverse events.

Conclusion

Durasphere injectable bulking agent is effective in reducing SUI due to ISD, as consistently measured by improvement in continence grades, pad weight tests, incontinence episodes, and quality of life instruments. Durasphere is safe to use in treating the symptoms of SUI due to ISD, as measured by adverse events and X-rays.

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In order to evaluate the long-term effectiveness of Durasphere without subjecting patients to rigorous on-going testing (i.e., pad weight test, urodynamics, visits to the investigational site etc.), 76 patients treated with Durasphere and improved at one-year follow-up, were asked to participate in a post-approval study.

Of the 76 potential participants, 70 responded by signing consent to participate in the post-approval study and subsequently completed a baseline self-assessment questionnaire. The mean time from initial injection within the IDE study to the post-approval “baseline” self-assessment collected within this Post-Approval Study was 2.2 years (range 1.4 – 3.5 years).

Of the 70 patients who consented to participate in this study, 65 patients responded to the follow-up self-assessment at an average of 5.2 years (range 4.7 – 6.0 years) post initial injection during the IDE study.

Continence Grade Evaluation

From the assessment completed by these participants, 42 of the 65 participants (64.6%) reported their continence grade at a mean of 5.2 years post initial injection to be the same or better than their continence grade at a mean of 2.2 years post initial injection. Patients opting for surgery to further improve incontinence were considered worse for this analysis.

Quality of Life Assessment

When asked the following question, “In the past year, have your incontinence symptoms improved, remained the same or worsened?” at a mean of 5.2 years post initial injection, 39 of the 55 participants (70.9%) reported that their symptoms had improved or remained the same in the past year. Nine patients were excluded from this analysis due to having further treatment for incontinence which could have affected the answer to this question.

Brief Summary Statement - Indication: Durasphere is indicated for use in the treatment of adult women with stress urinary incontinence (SUI) due to intrinsic sphincteric deficiency (ISD). Contraindications: Durasphere must not be used in patients with acute cystitis, urethritis, or other acute genitourinary infection. Warnings/ Precautions: Do not inject Durasphere into blood vessels. This may cause vascular occlusion, platelet aggregation, infarction or embolic phenomena. Adverse Events: Adverse events related to Durasphere that were reported by >5% of patients during the clinical study include: retention, dysuria, urinary urgency, urinary tract infection and hematuria. Caution: Federal law (U.S.A.) restricts this device to sale, distribution and use by or on the order of a physician trained in diagnostic and therapeutic cystoscopy.