

A NEW INJECTABLE BULKING AGENT FOR TREATMENT OF STRESS URINARY INCONTINENCE: RESULTS OF A MULTICENTER, RANDOMIZED, CONTROLLED, DOUBLE-BLIND STUDY OF DURASPHERE

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ABSTRACT

Objectives. To assess the safety and effectiveness of Durasphere compared with bovine collagen in the treatment of stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD).

Methods. This multicenter, randomized, controlled, double-blind trial was composed of 355 women diagnosed with SUI due to ISD and used a standardized pad test and the Stamey continence grade as the primary endpoints. The participants' ages ranged from 26 to 84 years. All patients had an abdominal leak point pressure of less than 90 cm H₂O (average 51).

Results. At 12 months after the first injection, the two materials were equivalent with respect to the improvement in continence grade and pad weight testing. Less Durasphere was injected to obtain comparable clinical results (Durasphere 4.83 mL versus bovine collagen 6.23 mL, $P < 0.001$). When examined 1 year after the date of the last treatment, 49 (80.3%) of the 61 women treated with Durasphere showed improvement of 1 continence grade or more compared with 47 (69.1%) of 68 women treated with bovine collagen (P value for difference = 0.162). Although the adverse events reported for both groups were similar, the Durasphere group had an increased short-term risk of urgency and urinary retention.

Conclusions. The use of Durasphere for the treatment of SUI due to ISD was equally effective as bovine collagen and used less material. The U.S. Food and Drug Administration granted market approval for Durasphere on September 13, 1999. The product design and initial clinical data suggest the potential for greater durability of the clinical benefit, with the possibility of a permanent solution for SUI due to ISD in some patients. *UROLOGY* 58: 12–15, 2001. © 2001, Elsevier Science Inc.

Injectable bulking agents have become popular in the treatment of stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD). Although the procedure is safe, well tolerated, and effective, concerns have been raised about the long-term durability of the available urethral bulking agents.

Appropriate urethral bulking agents should be nonimmunogenic, produce minimal inflammatory

responses, and yet be durable. The absorption and/or adverse tissue changes associated with previously investigated materials have put their long-term benefit in doubt.^{1–3}

Durasphere, a new injectable bulking agent, is designed to be biocompatible and is composed of nonmigratory and nonabsorbable pyrolytic carbon-coated zirconium oxide beads suspended in a carrier gel. Pyrolytic carbon is nonreactive, having

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been used in implantable medical devices, including replacement heart valves, for the past 30 years.⁴ The targeted bead size ranges from 251 to 300 μm , more than three times larger than the 80- μm threshold for particle sizes associated with migration in tissue.⁵ The absorbable carrier gel is 2.8% glucan—a simple polysaccharide used in several medical applications, including wound healing.

The purpose of this study was to assess the safety and effectiveness of Durasphere compared with bovine collagen (Contigen Bard Collagen Implant) in the treatment of SUI due to ISD.

MATERIAL AND METHODS

From July 1996 to December 1998, 355 women (178 Durasphere, 177 bovine collagen) were recruited to a randomized, controlled, clinical study at 10 geographically diverse clinical centers. Keeping the clinical investigator unaware of the material injected was impossible; however, the research staff were kept unaware of which material was injected on all evaluations. The patient population consisted of women diagnosed with SUI due to ISD as evidenced from history and urodynamic studies. As current Medicare guidelines for the use of urethral bulking agents require, the weakened sphincteric mechanism was demonstrable in all patients in this study by an abdominal leak point pressure of less than 90 cm H_2O (average 51 for Durasphere patients and 50 for bovine collagen patients). The average patient age was 57.7 years in the Durasphere group and 57.0 in the bovine collagen group. The baseline 1-hour pad weight was 46.4 g (Durasphere group) versus 41.5 g (bovine collagen group, $P = 0.384$). The average duration of incontinence in those receiving Durasphere was 10.3 years; it was 10.1 years for those receiving bovine collagen. The prior surgical and medical history factors were comparable in the two study groups.

Furthermore, although patients may have been previously treated with either conservative treatment or anti-incontinence surgical procedures that failed, no patient had received any prior injections of any urethral bulking agents. Intradermal test injections of bovine collagen and beta-glucan were given to all patients. Any positive skin test resulted in patient exclusion.

The study design permitted any patient to be retreated as many as five times with a minimum 7-day interval between treatments, as required on the current bovine collagen product labeling.

The clinical parameters were measured with an interview and urodynamic assessment at 1, 3, 6, and 12 months after the initial treatment.

The safety and efficacy of Durasphere relative to bovine collagen was examined with three primary study endpoints:

1. Improvement in the continence grade (Stamey)
2. Improvement in the weight of involuntary urine loss occurring during a provocative 1-hour pad test
3. Strict safety assessments, with reporting of any complications or adverse events discernible by detailed questioning of the patient or by direct observation during the study period

A continence grading system was used to measure the patient's incontinence before treatment (baseline) and at each follow-up period, ranging from grade 0 (dry) to grade 3 (continuous urinary leakage)⁶ and used here as required by the Food and Drug Administration investigational device exemption.⁷ Most patients (72%) had exertional activity-related leakage (grade 2).

Urine loss was quantified through a standardized provoca-

tive 1-hour pad test,⁸ with volume lost at each follow-up visit compared with the volume lost in the baseline study.

Complications and adverse events were monitored using an incontinence quality-of-life questionnaire and patient interview.

All urethral bulking agent injections were performed transurethraly at the level of the bladder neck under direct vision. As urethral bulking agents injected inadvertently into a blood vessel can become embolic, we do not believe that urethral bulking agents should be injected periurethraly.⁹ Patients randomized to Durasphere underwent injection with prepackaged syringes containing 1.0 mL Durasphere and an 18-gauge needle-delivery device. Patients randomized to bovine collagen underwent injections according to the manufacturer's guidelines. The type of anesthesia and antibiotics used before and after injection was at the discretion of the investigator.

RESULTS

Continence data are shown for 235 women completing 12 months of follow-up (mean 14, range 9 to 30). Adverse events are reported for all 355 women, with a mean follow-up of 11 months (range 1 to 26).

The results are presented for each of the primary study endpoints. A total of 76 (66.1%) of the 115 women receiving Durasphere had improvement of 1 or more continence grades at 12 months of follow-up from baseline compared with 79 (65.8%) of the 120 receiving bovine collagen (P value for difference = 1.000). When examined 1 year after the date of the last treatment, 49 (80.3%) of 61 women in the Durasphere group had an improvement in continence grade of 1 or more compared with 47 (69.1%) of 68 women in the bovine collagen group (P value for difference = 0.162) (Fig. 1). The mean number of injections was 1.69 for the Durasphere group and 1.55 for the bovine collagen group ($P = 0.253$), noting that repeated injections were patient and not investigator driven.

Urine loss as measured by the mean change in the pad weight test from baseline to 12 months of follow-up was 27.9 g (SD 43.6) for women receiving Durasphere and 26.4 g (SD 63.7) for those receiving bovine collagen (P value for difference = 0.835) (Fig. 2).

At the initial treatment, the mean volume of Durasphere injected was 4.83 mL (range 0.50 to 9.10) versus a mean collagen injection volume of 6.23 mL (range 2.0 to 12.50) ($P < 0.001$). The total volumes injected, when inclusive of those receiving repeated injections, also demonstrated lower total volumes for Durasphere compared with bovine collagen. The mean total volume for Durasphere was 7.55 mL (range 0.5 to 22) versus a mean of 9.58 mL (range 2.0 to 30) for collagen ($P < 0.001$).

The adverse event profile was similar for both groups, except for a higher incidence of urgency and acute retention in the women in the Durasphere group (24.7% and 16.9%, respectively) than in those in the bovine collagen group (11.9% and

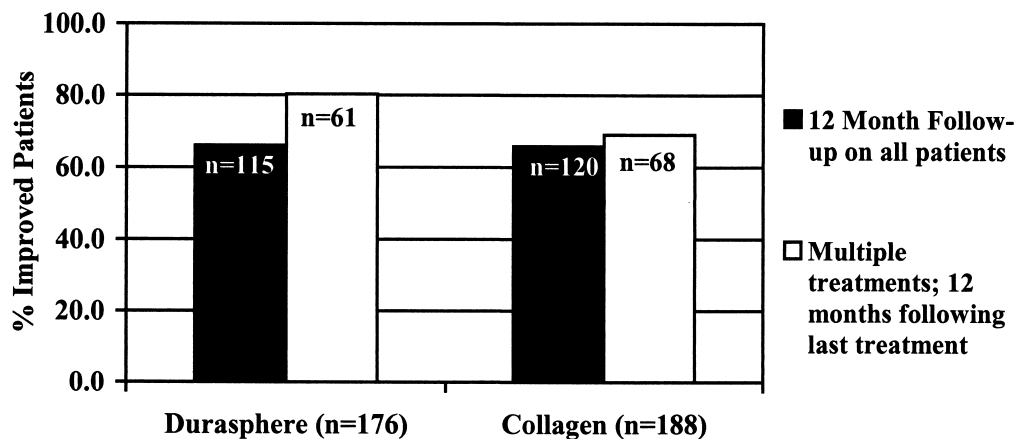


FIGURE 1. Improvement of greater than 1 continence grade at 12 months of follow-up ($P = 1.000$ for a single injection, $P = 0.162$ for multiple injections).

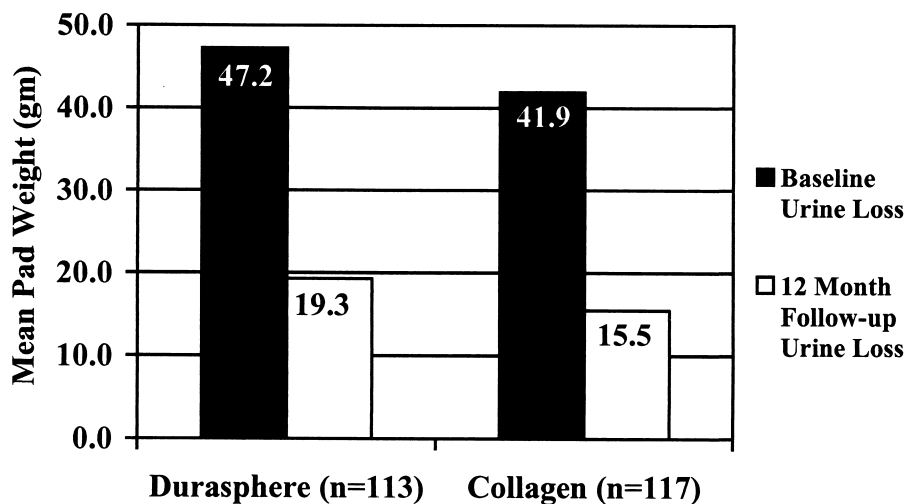


FIGURE 2. Results of pad weight test to determine urine loss at baseline and after 12 months of follow-up ($P = 0.835$).

3.4%, respectively) ($P = 0.001$). Acute retention was treated with intermittent self-catheterization and resolved in all patients by 7 days. Although more patients in the Durasphere group experienced urgency, in a higher percentage (90%) the urgency had resolved by the end of the study than had resolved in the bovine collagen group (65%) ($P = 0.021$).

No evidence of an immunologic response to Durasphere was observed during the clinical trial. No evidence of local migration of the Durasphere beads was reported during the study. Pelvic x-rays taken of study patients after injection and repeated at 1 and 2 years after injection demonstrated the stability of the bulking agent at the injection site, with no evidence of spread beyond the local confines of the pelvis.

COMMENT

Urethral bulking agents offer a less-invasive augmentation of the urethra than sling procedures and artificial sphincters. By adding bulk to the bladder neck and the proximal segment of the urethra, the increased coaptation of the urethral mucosa protects against increases in intravesical pressure by improving the resistance to the outflow of urine.

Although bovine collagen injection therapy has proved to be a safe and effective form of treatment for ISD, the material has completely degraded within 9 to 19 months,¹⁰ requiring repeated injections to sustain its successful result.¹¹ Durasphere, however, was designed to be permanent. This study demonstrated the equivalent safety and efficacy of Durasphere compared with bovine colla-

gen. It is anticipated that in ongoing post-approval studies, Durasphere will prove to be more durable.

The initial difficulties in injecting the material have largely been overcome by responding to increases in resistance to flow with a counterintuitive slight withdrawal of the needle. Extrusion of the carrier gel by continuing to inject under pressure will cause severe packing of the beads within the needle and limit the successful delivery of the Durasphere beads. Likewise, the larger needle size required for the injection of Durasphere may have resulted in the increased but transient irritative and obstructive symptoms seen in the Durasphere group.

CONCLUSIONS

Durasphere is a safe and effective alternative to the use of bovine collagen in the management of SUI due to ISD. The product design and initial clinical data suggest the potential for greater durability of the clinical benefit; post-Food and Drug Administration approval studies are ongoing in this patient group to define this possible benefit. Furthermore, Durasphere can be used without prior skin tests to determine allergic response, as is currently required for bovine collagen.

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