Efficacy and Safety of Polyacrylamide Hydrogel for the Treatment of Female Stress Incontinence: A Randomized, Prospective, Multicenter North American Study

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Purpose: Bulkamid® is a new polyacrylamide hydrogel bulking agent for stress urinary incontinence that is injected in the urethral submucosa using a specifically designed device. We evaluated the safety and efficacy of Bulkamid vs Contigen® collagen gel for stress urinary incontinence or stress predominant mixed urinary incontinence.

Materials and Methods: This was a single-blind, randomized, prospective, 33-center, 2-arm parallel study of hydrogel vs collagen gel with followup to 1 year. At baseline patients underwent physical examination and bladder testing, and completed quality of life questionnaires and bladder diaries. After randomization patients could receive up to 3 injections at 1-month intervals. Patients were assessed 3, 6, 9 and 12 months after bulking. They completed bladder diaries and quality of life questionnaires, and pad weight was tested. At the last visit Valsalva leak point pressure was measured. Subjective and objective incontinence outcomes and adverse events were compared.

Results: Of the 345 women 229 were randomized to hydrogel and 116 were randomized to collagen gel. At 12 months a 50% or greater decrease in leakage and incontinence episodes was seen in 53.2% and 55.4% of patients who received hydrogel and collagen gel, respectively. At 12 months 47.2% of patients with hydrogel and 50% with collagen gel reported zero stress incontinence episodes, and 77.1% and 70%, respectively, considered themselves cured or improved. Major adverse events were rare in each group.

Conclusions: Bulkamid is not inferior to Contigen. It has a favorable, persistent effect on stress urinary incontinence with a low risk of serious adverse events. Bulkamid is a new, simple, office based bulking system that shows promise as a treatment in women with stress urinary incontinence, particularly since Contigen is no longer commercially available.

Key Words: urethra; incontinence, stress urinary; hydrogel; collagen; female

Abbreviations and Acronyms

ICIQ-UI = International Consultation on Incontinence Modular Questionnaire-Urinary Incontinence-Short Form

I-QOL = Urinary Incontinence Quality of Life Scale

ITT = intent to treat

SUI = stress UI

UI = urinary incontinence

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Study received institutional review board approval at all sites.

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Stress UI is a debilitating and socially disruptive condition that affects women of all ages. The prevalence of UI is 24% to 45% and half of patients experience SUI. The number of women with UI is also increasing, given the continued increase in key risk factors such as obesity and diabetes in aging populations, and the tendency for increasing age in mothers giving birth.[1,2]

Transurethral injection of bulking agents is a well-known, well tolerated procedure in women who experience

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mild to moderate SUI.[3] The procedure is minimally invasive, can be performed using local anesthesia in an office or ambulatory setting and is associated with a low complication rate.[3] The ideal bulking agent would be biocompatible without producing fibrosis or calcification and it should preferably have a permanent bulking effect and optimal injection technique.

Bulkamid is a nondegradable, cross-linked polyacrylamide hydrogel (2.5% dry matter and 97.5% water) that does not contain microparticles but instead is integrated into host tissue by vessel ingrowth.[4] The gel is injected in the urethral submucosa under cystoscopic guidance using a specifically designed device for exact placement.

The hydrogel demonstrated efficacy with minimal complications in a pilot study with 1 and 8 years of followup[5,6] and in a European multicenter study with 1 and 2 years of followup.[7,8] Good results were also obtained in a survey of 82 women treated on an outpatient basis[9] and in 44 of 514 who received Bulkamid for SUI with the remainder treated with other bulking agents for comparison.[10]

This prospective, randomized multicenter trial describes the efficacy and safety of Bulkamid compared to the control, Contigen collagen gel, for the treatment of SUI or stress predominant mixed UI.

MATERIALS AND METHODS

The FDA (Food and Drug Administration) approved an IDE (Investigational Device Exemption) for this randomized, controlled trial. Groups at 28 centers in the United States and 5 in Canada participated in this study. Institutional review board approval for the study was obtained at all sites and the study was done according to updated CONSORT guidelines.[11] The first treatment was performed on June 4, 2008 and enrollment closed on June 6, 2011. The supplementary Appendix (http://jurology.com/) lists inclusion and exclusion criteria for entering the study.

Baseline Visit

At the baseline visit a skin test for bovine collagen allergy was performed in all women and read after 4 weeks. Those with positive results were excluded from study and those with negative results proceeded to randomization. We also assessed demographics, body mass index, history and physical examination with quantification of pelvic organ prolapse, cystometry with measurement of detrusor overactivity, Valsalva leak point pressure, voiding volume per 24 hours, 24-hour pad test, cotton swab test, post-void residual urine measurement and urine dipstick test (and, if positive, culture and sensitivity evaluations). Study participants completed bladder diaries, incontinence and sexual health questionnaires, including ICIQ-UI, I-QOL, PISQ (Pelvic Organ Prolapse-Urinary Incontinence Sexual Function), and questions on incontinence.

Randomization

Women who met study eligibility criteria were randomized to hydrogel or collagen gel treatment in a 2:1 ratio, stratified by site using a permuted block randomization scheme. Patients were masked to treatment for study duration.

Treatment

Participants could receive up to 3 injections spaced 1 month apart as part of the study protocol. Hydrogel was injected under endoscopic control using the Bulkamid Urethral Bulking System (fig. 1). The procedure was done with the patient under local anesthesia and injection was performed under endoscopic guidance by an 11 cm disposable Bulkamid cystoscope connected to a reusable 0-degree optic. The rotating sheath over the cystoscope allowed the 23 gauge $\times$ 12 cm needle to rotate 360 degrees (fig. 1). The Bulkamid needle was inserted in the scope working channel and 1 to 2 ml hydrogel were injected at 3 sites with no more than 0.6 ml at each site.

Collagen gel injections were administered in standard fashion in accordance with instructions for use. If the woman was not dry after the first bulking, she was offered a second and ultimately a third bulking if not dry after the second treatment. Injections were repeated at a mean $\pm$ SD of 35 $\pm$ 7 days.

Followup

Study participants were reevaluated at 1, 3, 6, 9 (telephone interview only) and 12 months after the last bulking procedure. Urinalysis, blood analysis, urine or serum pregnancy test, 24-hour pad test, 3-day bladder diaries and a sexual function questionnaire (only at 6 and 12 months followup) were obtained. Adverse events were monitored by a data safety monitoring board. Subject perception of effectiveness (cured/dry, much improved, improved, no change or worse) was measured starting 3 months after last bulking procedure. This and any adverse events were also recorded at the 9-month

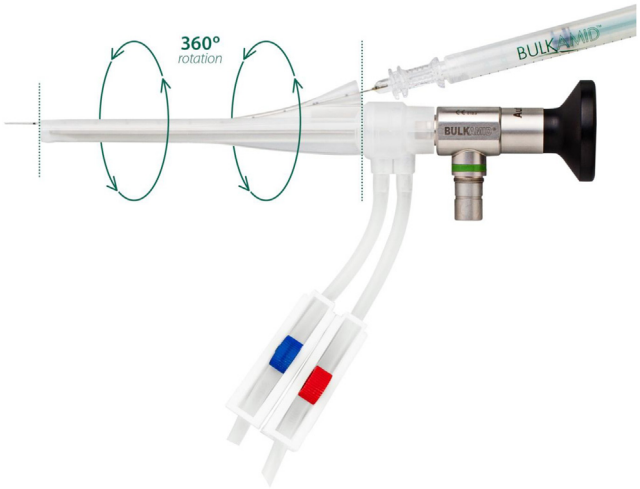

Figure 1. Bulkamid Urethral Bulking System. Injection is performed under endoscopic guidance with single use 11 cm cystoscope.