

Periurethral bulking agents for female stress urinary incontinence in Canada

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Abstract

Urethral bulking aims to improve urethral mucosal coaptation, and thus outlet resistance, in an effort to limit stress-induced leakage. While efforts have been made to employ bulking agents to treat stress urinary incontinence (SUI) for more than 100 years, we remain wanting for the perfect injectable. Regardless of the agent studied, efficacy is modest at best, repeat injections are the norm, and long-term followup is conspicuously lacking. This treatment, however, fills an important need in our armamentarium against SUI, serving those patients who are not candidates for more invasive interventions and those with multiple prior failed surgeries. This review offers a contemporary discussion on the role of periurethral bulking therapy in Canada, along with practical aspects of its application.

Introduction

Stress urinary incontinence (SUI) is a common patient presentation to the urologist's office. A variety of management options are available for appropriately selected patients; these range from pelvic floor physiotherapy to surgical methods.¹ Injectable urethral bulking agents fall along this spectrum and offer a less invasive treatment option for selected women with SUI. The use of bulking agents has been reported as early as 1900, when Gersuny described the injection of periurethral paraffin wax for SUI.² In the century since this report, the use of urethral bulking agents has evolved to include new materials, injection techniques, and a growing body of clinical data. The role for urethral bulking agents in current management of SUI remains a matter of debate.

The mechanism of action of urethral bulking is through augmentation or restoration of normal mucosal coaptation (Fig. 1). The bulking agent is injected into the submucosal space to elevate the urethral mucosa, thereby increasing coaptation and urethral resistance.³ The ideal bulking agent would be easily injectable, cost-effective, biocompatible, non-migratory, and cause little to no tissue inflammation.⁴

While many agents have been developed and used for urethral bulking, none has been ideal. Many agents have been introduced to the market and since removed due to clinical concerns or marketing reasons.⁵

Polyacrylamid hydrogel (PAHG, Bulkamid™) is the only injectable bulking agent currently approved and marketed in Canada with an indication for female SUI. Non-animal hyaluronic acid/dextranomer gel (NASHA/Dx) was previously available and marketed with an Implacer device as Zuidex™;⁶ however, concerns were raised regarding its efficacy and development of sterile abscesses with this product, and it was not approved in the U.S. It was subsequently removed from the Canadian market by the distributor. Another NASHA/Dx product, Deflux™, is available in Canada for management of vesicoureteral reflux, and it has been used off-label for intraurethral injection in SUI.⁷ Coverage for periurethral bulking agents varies amongst jurisdictions, with some provinces requiring patients to pay for the injectables.

Efficacy

Clinical data on bulking agents is limited and heterogeneous. An updated Cochrane review in 2012 found insufficient data to allow for meta-analysis or support clinical decision-making.⁸ Bulking agents have been demonstrated to be more effective than pelvic floor muscle therapy, but less effective than surgical management for SUI. Gluteraldehyde cross-linked bovine collagen (Contigen™) has often been used as an established comparison agent in clinical trials of novel bulking agents, but was removed from the market in 2010.⁸ The efficacy of collagen for SUI has been reported at 48% at 12 months, with a decline to 32% at 34–47 months.⁹ PAHG (Bulkamid™),¹⁰ calcium hydroxyapatite (Coaptite™),¹¹ pyrolytic carbon (Durasphere™),¹² and polydimethylsiloxane (Macroplastique™)¹³ have demonstrated non-inferiority to collagen in randomized, controlled studies.

In a randomized trial of 345 women with SUI, PAHG was found to be non-inferior to collagen.¹⁰ At 12 months, 53.2% of women in the PAHG group and 55.4% in the collagen

group experienced a 50% or greater improvement in SUI. Repeat treatment was required in 77% of patients treated with PAHG, with 35% requiring two repeat injections.

Safety

Potential adverse events associated with urethral bulking agents include transient urinary retention, hematuria, de novo urgency incontinence, bulking agent extrusion, immune reaction, and rare granuloma formation.³ The author has also consulted on patients previously treated with bulking agents who were misdiagnosed with urethral and/or vaginal masses on imaging and referred to the gynecological oncology service, leading to anxiety and unnecessary investigations.

In the PAHG study, adverse events occurred in 59.4% of women treated with PAHG and 54.3% treated with collagen.¹⁰ The most common adverse events were urinary tract infection and injection site pain. Over 95% of reported adverse events with both PAHG and collagen were classified as mild to moderate.¹⁰

Technical aspects of injection

Injection of urethral bulking agents is associated with low treatment morbidity and the procedure may be performed under local anesthetic in an outpatient setting. Intravenous sedation and/or narcotic may be required in select patients. Injection is most often performed through a transurethral approach with endoscopic visualization. Care should be taken to avoid or minimize passage of the cystoscope across the bulked urethra into the bladder once the material has been injected, and at the end of the case the bladder should be drained with a small caliber catheter. Periurethral injection of bulking agents with simultaneous endoscopy has also been described.

PAHG is marketed for use with a short disposable cystoscope (Bulkamid Injection System), a 0-degree lens, and a 23-gauge 120 mm needle. Three equally spaced injection

sites 0.5–1.0 cm distal to the bladder neck are used with deposition of ≤ 0.8 ml of PAHG at each site. Repeat injection after 1–2 months or later may be required if incontinence persists.¹⁴

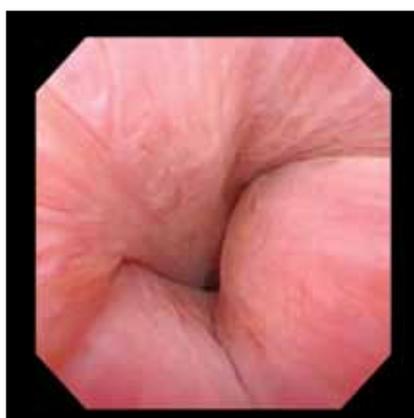


Fig. 1. Endoscopic view of augmented proximal urethra following bulking procedure.

Patient selection and counselling

As with other interventions for SUI, careful selection of patients for urethral bulking is the key to optimizing treatment outcomes and patient satisfaction. The efficacy and durability of bulking agents is inferior to surgical treatment for SUI and repeat injections may be required.¹ The lower efficacy and durability of bulking agents is balanced by low treatment morbidity and a favourable adverse event profile when compared to surgical management.

Treatment is indicated for patients who desire to undergo minimally invasive treatment at the potential cost of decreased efficacy and durability (Table 1). Bulking is more suited to low- to moderate-volume SUI and persistent SUI after prior anti-incontinence procedures. Patients with advanced age, high anesthetic risk, or inability to interrupt anticoagulation may benefit from bulking if other interventions are not feasible. Other indications include young patients who may desire future pregnancy or patients with a combination of SUI and poor bladder-emptying.¹⁵ Contraindications to urethral bulking agents include a history of hypersensitivity to the bulking agent and active urinary tract infection.

Conclusion

Urethral bulking agents offer a valuable alternative to surgical intervention for women with SUI. While the clinical effectiveness and durability are not equivalent to surgery, urethral bulking is associated with low treatment morbidity and a low risk of serious adverse events. Clear communication regarding the advantages and disadvantages of bulking as applied to each individual patient is essential to maximize patient satisfaction. The need for repeat injection should be explained and may be necessary for optimized continence. With proper patient selection and counselling, urethral bulking agents are a valuable option in the urologist's armamentarium for management of female SUI.

Table 1. Indications for periurethral bulking for female stress urinary incontinence (SUI)

Indication	Key points
Patient choice	<ul style="list-style-type: none"> • Low to moderate volume SUI • Accepts lower likelihood of success versus surgery
Young patient who desires future pregnancy	As above
Poor bladder emptying	Lower risk of permanent urinary retention vs. surgery
Poor candidate for surgical intervention	<ul style="list-style-type: none"> • High anesthetic risk • Stenotic introitus • Advanced age • Severe obesity • Anticoagulated

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References

1. Bettez M, Le Mai Tu KC, Corcos J, et al. 2012 update: Guidelines for adult urinary incontinence collaborative consensus document for the Canadian Urological Association. *Can Urol Assoc J* 2012;6:354-63. <https://doi.org/10.5489/cuaj.12248>
2. Herschorn S. Current use of injectable agents for female stress urinary incontinence. *Rev Urol* 2005;7: S12.
3. Herschorn S. Injection therapy for urinary incontinence. Wein A, Kavoussi LR, Novick AC, et al. Campbell-Walsh urology. 11th ed. 2013. Saunders Philadelphia 2049-69.
4. Kotb AF, Campeau L, Corcos J. Urethral bulking agents: Techniques and outcomes. *Curr Urol Rep* 2009;10:396-400. <https://doi.org/10.1007/s11934-009-0062-3>
5. Mutsuoka PK, Locali RF, Pacetta AM, et al. The efficacy and safety of urethral injection therapy for urinary incontinence in women: A systematic review. *Clinics* 2016;71:94-100. [https://doi.org/10.6061/clinics/2016\(02\)08](https://doi.org/10.6061/clinics/2016(02)08)
6. Lightner D, Rovner E, Corcos J, et al. Randomized, controlled multisite trial of injected bulking agents for women with intrinsic sphincter deficiency: Midurethral injection of Zuidex via the Implacer vs. proximal urethral injection of Contigen cystoscopically. *Urology* 2009;74: 771-5. <https://doi.org/10.1016/j.urology.2009.05.034>
7. Kaba R, Birnie A, Turney B. The use of Deflux to treat stress urinary incontinence: Three-year results. Paper presented at: International Continence Society annual meeting; Aug 29–Sept 2 2011; Glasgow Scotland.
8. Kirchin V, Page T, Keegan PE, et al. Urethral injection therapy for urinary incontinence in women. *Cochrane Database of Syst Rev* 2012: CD003881. <https://doi.org/10.1002/14651858.CD003881.pub3>
9. Appell RA, Dmochowski RR, Blaivas JM. Guideline for the surgical management of female stress urinary incontinence: 2009 update. AUA Guidelines Office, Clinical Practice Guidelines, American Urological Association, Inc (2009):1-45.
10. Sokol ER, Karram MM, Dmochowski RR. Efficacy and safety of polyacrylamide hydrogel for the treatment of female stress incontinence: A randomized, prospective, multicentre North American study. *J Urol* 2014;192:843-9. <https://doi.org/10.1016/j.juro.2014.03.109>
11. Mayer RD, Dmochowski RR, Appell RA, et al. Multicentre, prospective, randomized, 52-week trial of calcium hydroxylapatite vs. bovine dermal collagen for treatment of stress urinary incontinence. *Urology* 2007;69:876-80. <https://doi.org/10.1016/j.urology.2007.01.050>
12. Lightner D, Calvosa C, Andersen R, et al. A new injectable bulking agent for treatment of stress urinary incontinence: Results of a multicentre, randomized, controlled, double-blind study of Durasphere. *Urology* 2001;58:12-5. [https://doi.org/10.1016/S0090-4295\(01\)01148-7](https://doi.org/10.1016/S0090-4295(01)01148-7)
13. Ghoniem G, Corcos J, Comiter C, et al. Cross-linked polydimethylsiloxane injection for female stress urinary incontinence: Results of a multicentre, randomized, controlled, single-blind study. *J Urol* 2009;181:204-10. <https://doi.org/10.1016/j.juro.2008.09.032>
14. Toozs-Hobson P, Al-Singary W, Fynes, M, et al. Two-year followup of an open-label multicentre study of polyacrylamide hydrogel (Bulkamid®) for female stress and stress-predominant mixed incontinence. *Int Urogyn J* 2012;23:1373-8. <https://doi.org/10.1007/s00192-012-1761-8>
15. Cespedes RD, Serkin FB. Is injection therapy for stress urinary incontinence dead? No. *Urology* 2009;73:11-3. <https://doi.org/10.1016/j.urology.2008.05.048>

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