Use of Alternative Techniques and Grafts in Urethroplasty

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KEYWORDS

• Urethral stricture • Urethroplasty • Urethral reconstruction • Injectable antifibrotic treatment
• Augmentation urethroplasty • Lingual mucosa graft • Colonic mucosa graft
• Tissue-engineered graft

KEY POINTS

- Injectable antifibrotic agents may improve rates of recurrence compared with direct vision internal urethrotomy for short urethral strictures.
- Lingual mucosa has similar physiologic and anatomic characteristics to buccal mucosa with promising outcomes from initial clinical trials.
- Colonic mucosa can be harvested in a minimally invasive fashion, thereby increasing its potential use as a graft in complex cases of urethral reconstruction.
- Acellular matrices and tissue-engineered grafts have begun small clinical trials and may eventually provide an off-the-shelf option for urethral reconstruction.

INTRODUCTION

The repair of urethral stricture is approached with multiple different techniques, ranging from endoscopic incision to graft placement for open reconstruction, in an attempt to open and maintain a normal urethral lumen. All causes of stricture, including trauma, iatrogenic injury, lichen sclerosus, or prior urethral surgery, have the potential to form long, complex strictures that necessitate extensive reconstruction. Treatment selection ultimately depends on the cause of the stricture, location, length, and the surgeon's preference and experience level. Shorter strictures are amenable to endoscopic treatment or excision and anastomosis, whereas longer defects require augmentation with oral mucosa grafts or fasciocutaneous flaps. However, clinical scenarios exist whereby the typical buccal mucosa graft or fasciocutaneous flap is insufficient for urethral reconstruction.

Current practice of urethral reconstruction places a premium on buccal mucosa grafts, but additional grafts are available to use as an alternative or adjunct in complex cases, particularly panurethral strictures, recurrent strictures when buccal mucosa has been previously harvested, or in patients in whom retrieval of oral mucosa in contraindicated. Buccal mucosa has enjoyed such success that many of the original grafts for urethroplasty, such as extragenital skin, have fallen out of favor. Despite the decreased utilization of skin grafts, the principles of this technique should be continually revisited for inspiration and innovation toward new approaches. Furthermore, tissue engineering and stem cell therapies are promising opportunities to provide off-the-shelf grafts that would preclude the invasiveness and morbidity of tissue harvest for urethral reconstruction.

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INJECTABLES

Although open urethroplasty is the gold standard for treatment of anterior urethral strictures, endoscopic management offers options that are less invasive and can be effective in highly selected patients. Current endoscopic treatments achieve inferior outcomes to open repair,[1,2] so any improvements in endoscopic platforms that could open this treatment to a broader patient base are intriguing. In addition to stricture incision, multiple antifibrotic medications have been used in attempt to reduce scar formation and inhibit tissue contraction.

Combination of the traditional direct vision internal urethrotomy (DVIU) with topical application or injection of an antiproliferative agent has been evaluated for minimally invasive stricture treatment. Antifibrotic agents, including steroids (triamcinolone), mitomycin C (MMC), and hyaluronidase, have all been used to reduce stricture recurrence. The antifibrotic and anticollagen properties of steroids are well documented, and injectable forms are used in treatment of various fibrosis-induced pathologies. MMC has been shown to inhibit cellular proliferation and collagen deposition during scar formation in both in vitro and animal studies.[3,4] Additionally, MMC has been used clinically for pathologies ranging from nasolacrimal duct obstruction and to vaginal and anal stenosis.[5–10] Hyaluronidase also possesses antifibrotic properties and has shown benefits in treatment of pulmonary fibrosis, hypertrophic scars, and keloids. Its function is achieved by suppression of fibroblast synthesis of collagen and glycosaminoglycan, which are necessary building blocks for scar formation.[11] Although these agents have a clear theoretic and clinical role for scar management, there are few high-quality studies examining the efficacy of injected antiproliferative agents for anterior urethral strictures.

Triamcinolone has the most published experience, with trials of injected and catheter-coated topical administration dating back to the 1960s.[12] Urethrotomy followed by triamcinolone injection has been shown to be safe and moderately effective. Two small randomized controlled trials evaluated the effect of triamcinolone following urethrotomy for short bulbar strictures (<1.5 cm).[13,14] Mazdak and colleagues[14] reported stricture recurrence in 21.7% of the triamcinolone group versus 50.0% of the control cohort at a follow-up of 14 months. Meanwhile, Tavakkoli and colleagues[13] reported a lower number of recurrences in the triamcinolone group, but this finding was not statistically significant. A meta-analysis of 8 studies covering 203 patients showed no benefit for catheter-introduced steroids following DVIU, but steroid injection prolonged the time to stricture recurrence.[15]

MMC is also gaining attention as an injectable antiscar agent. The first randomized controlled trial to study MMC following DVIU in short bulbar urethral strictures found a recurrence rate of 10% in the MMC group compared with 50% for DVIU alone. Of note, this study only included 40 total patients and had relatively short follow-up (range 6–24 months).[16] These findings were supported by a recent randomized controlled trial that compared DVIU with MMC to DVIU alone in 151 patients with traumatic anterior urethral strictures measuring up to 2 cm in length. The patients were then followed with retrograde urethrography at 3-month intervals for 18 months. Stricture recurrence was identified in 14% of the MMC group compared with 37% of the control group ($P = .002$), and the time to recurrence was 3 months longer in patients treated with MMC ($P = .002$).[17]

Although hyaluronic acid has shown antifibrotic effects in animal models,[18] there has been minimal experience in humans. One randomized controlled trial examined the effect of hyaluronic acid and carboxymethylcellulose urethral instillation after DVIU. The experimental group had a significantly lower recurrence rate than controls (9.4% vs 22.9%).[19] These patients were only followed for 6 months, and more data are needed before definitive conclusions can be made for this treatment.

Injection of all 3 drugs simultaneously has also been proposed to reduce stricture recurrence following DVIU. A mixture of 40 mg triamcinolone, 2 mg MMC, and 3000 units of hyaluronic acid were injected into 103 patients with bulbar and penile urethral strictures with no control group. Following one procedure, strictures recurred in 19.4% of cases at a median follow-up of 14 months (range 3–18 months).[20] However, the validity of this study is in question as the lack of a control group precludes any definitive evaluation of this technique.

Other injectable therapies for anterior urethral stricture are in the nascent phase of investigation. Medications that have proven safe and effective for other urologic pathologies are being trialed for urethral stricture. Botox injection following DVIU was reported with modest improvement in short follow-up on 3 patients.[21] Additionally, collagenase *Clostridium histolyticum*, an injectable therapy for dissolution of Peyronie disease plaques, showed reduction in collagen expression and fibrosis in a rat model of urethral stricture.[22] Animal models have also tested the treatment of urethral strictures with topical bevacizumab, 5-fluorouracil, and halofuginone with promising early results.[23,24]