

URETHRAL STRICTURE REPAIR WITH AN OFF-THE-SHELF COLLAGEN MATRIX

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ABSTRACT

Purpose: In select patients with urethral strictures in whom genital skin is insufficient alternative tissues are needed for urethral reconstruction. We explored the feasibility of using a bladder submucosa collagen based inert matrix as a free graft substitute for urethral stricture repair.

Materials and Methods: A total of 28 patients 22 to 61 years old with a diagnosis of urethral stricture underwent reconstructive surgery using a collagen based inert matrix for urethral repair. The inert collagen matrix was trimmed to size as needed for each patient and the neourethra was created by anastomosing the matrix in an onlay fashion to the urethral plate with continuous 6-zero absorbable sutures. The size of the created neourethra ranged from 1.5 to 16 cm. A voiding history, physical examination, retrograde urethrography, uroflowmetry and cystoscopic examinations were performed preoperatively and postoperatively. Random urethral biopsies were also performed.

Results: After a 36 to 48-month followup (mean 37) 24 of the 28 patients had a successful outcome. The remaining 4 patients had a slight caliber decrease at the anastomotic sites on urethrography. A subcoronal fistula developed in 1 patient which closed spontaneously 1 year after repair. Mean maximum urine flow rate increased from the preoperative value of 9 ± 1.29 to 19.7 ± 3.07 ml. per second postoperatively. Cystoscopic studies revealed adequate caliber conduits and normal appearing urethral tissues. Histological examination of the biopsy specimens showed the typical urethral stratified epithelium.

Conclusions: Use of an off-the-shelf collagen inert matrix appears to be beneficial for patients with urethral strictures and obviates the need for obtaining an autologous graft, thus eliminating donor site morbidity.

KEY WORDS: cystoscopy, urethral stricture, tissues, collagen, transplants

Patients with urethral strictures often require additional tissues for repair.¹ Autologous nonurethral tissue grafts or flaps from genital and extragenital skin, bladder, rectal and buccal mucosa, tunica vaginalis and peritoneum have been used.^{2–4} However, use of nonurethral tissues often requires additional procedures for graft retrieval, and may be associated with prolonged hospitalization and donor site morbidity. Synthetic non-degradable materials, such as silicone, polytetrafluoroethylene and polyester, have been tried previously for urethral reconstruction but these materials have not been optimal substitutes due to associated problems, such as erosion and dislodgement.^{5,6} Biodegradable synthetic polymers and naturally derived collagen based matrices have been proposed recently as materials that may guide and promote urethral tissue regeneration.^{7–11}

We previously reported on the use of naturally derived bladder based acellular collagen matrices as biomaterials for urethral reconstruction experimentally in an animal model and clinically in children with hypospadias.^{10–12} The acellular collagen matrix served as a guide for urethral tissue regeneration. In this study we explored the feasibility of using the inert collagen matrix as a free graft substitute for urethral stricture repair.

MATERIALS AND METHODS

Acellular collagen matrix. Cadaveric human bladder tissue was aseptically obtained and processed in strict compliance

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with state and federal guidelines. The donors were comprehensively screened according to tissue bank guidelines (New England Organ Bank, Newton, Massachusetts). The tissue was held in quarantine until donor screening information and laboratory evaluation were approved by the tissue bank.

The bladder tissue was processed as described previously.^{9–11} Briefly, the bladder tissue was rinsed with phosphate buffered saline. The submucosa was microdissected and isolated from the adjacent muscular and serosal layers. The isolated submucosa was washed and treated with distilled water under continuous agitation for 48 hours. The submucosa was successively treated with 0.5% Triton-X 100 and 0.05% ammonium hydroxide for 72 hours. The cyclic washing and chemical treatment were repeated until decellularization was confirmed. Random samples of the matrix were obtained between each cycle for histological evaluation to ensure the acellular nature of the matrix. The tissue matrix was treated with 10% povidone solution for sterilization followed by repeated rinses in phosphate buffered saline containing 10% cefazolin. The acellular collagen matrix was further sterilized with ultraviolet light exposure for 24 hours before use.

Patient selection. A total of 28 patients with a diagnosis of urethral stricture were enrolled at our institutions from October 1998 to September 1999 under the guidelines approved by the clinical investigation review board. The criteria for study inclusion involved any patient with an anterior urethral stricture. Penile strictures with circumferential fibrosis who were candidates for a tubularized repair were excluded from the study. Patient age ranged from 22 to 61 years (average 40.4). The length of the strictured segments, as determined during surgery, ranged from 1.5 to 16 cm. The

strictures were due to trauma and instrumentation in 16 cases, idiopathic causes in 8, and infection and inflammation in 4. The sites involved were penile in 3 cases, bulbar in 11, and bulbar and penile in 14.

Surgical repair. Individual inert collagen based matrices were removed from their sterile containers and trimmed to fit the strictured segments for each patient (fig. 1). The strictures were exposed and the fibrotic ventral urethral tissues were excised with preservation of the healthy dorsal urethral plates. The neourethras, with a caliber similar to that of the healthy urethral segments (35 to 40Fr), were created by anastomosing the matrices in an onlay fashion to the urethral plates with continuous 6-zero absorbable monofilament sutures (fig. 2, B). Single graft strips were used in all cases. The size of the created neourethras ranged from 1.5 to 16 cm. Grafts in the pendulous urethra were covered with intact skin and dartos fascia, whereas grafts in the bulbous urethra were covered with the existing tissues, including bulbospongiosus muscle, periurethral tissue, dartos fascia and skin. Urethral catheters were placed across the repaired areas and were removed 4 to 6 weeks postoperatively, depending on the severity of the stricture. Four patients had indwelling catheters for 6 weeks postoperatively and the remaining 24 patients had catheter drainage for approximately 4 weeks.

In 3 patients the strictures involved the penile urethra and these were managed with a collagen onlay graft. In 1 patient a glandular stricture was managed by a lateral based subcoronal skin flap. Long bulbar urethral strictures ranging from 4 to 7 cm., in 11 patients were managed by excision of the fibrosed ventral urethral segments and replacement with the collagen grafts.

Bulbar and penile urethral strictures were present in 14

patients. In 5 patients double strictures were corrected at the same sitting. In 3 patients excision and end-to-end spatulated anastomoses were performed in the bulbar region, while the penile urethras were repaired with the collagen onlay grafts. In 2 patients strictures were managed with separate collagen patch grafts. Single strictures in the bulbar and penile urethra ranging from 3 to 16 cm. in 9 patients were treated with collagen onlay grafts.

Evaluation. The urethral strictures were assessed preoperatively by history, physical examination, retrograde urethrography, cystoscopy and uroflowmetry. Retrograde urethrography was performed routinely 4 months after the repair. Voiding patterns were assessed by uroflowmetry. Average flow rate, maximum flow rate and urine volume were calculated in each patient. A voided urine volume greater than 150 ml. was considered acceptable for evaluation. Cystoscopic visualization of the entire urethral lumen was performed approximately 4 months after surgery. Endoscopic urethral biopsies were obtained from the repaired segment of the urethra during followup in 4 cases. Five μ . sections of formalin fixed paraffin embedded tissues were processed and stained with hematoxylin and eosin. Statistical analysis was performed using Student's *t* test (InStat, Graphpad Software Inc., San Diego, California) with $p < 0.05$ considered statistically significant.

RESULTS

Surgical outcome was successful in 24 patients (see table). Radiographic retrograde urethrography postoperatively demonstrated a wide patent urethra in all 24 (fig. 2, A and C). A slight caliber decrease of the anastomotic sites was noted on urethrography in the remaining 4 patients, including 1 with a penile stricture and 3 with a bulbar and penile stricture. All 4 patients were treated with visual internal urethrotomies and were able to void through the wide patent urethras without the need for additional procedures. One patient had a subcoronal fistula postoperatively, which spontaneously resolved after 1 year without other complications. All patients were able to void without any further problems. Followup ranged from 36 to 48 months (mean 37).

Uroflowmetry was performed preoperatively and postoperatively. The average flow rate before repair was 6 ± 1.57 ml. per second with a mean maximum flow rate of 9 ± 1.29 ml. per second. Postoperative uroflowmetry showed an average flow rate of 13.57 ± 2.21 ml. per second with a mean maximum flow rate of 19.7 ± 3.07 ml. per second. Cystoscopic examination was performed to confirm the patency of the entire length of the urethra in each patient (fig. 2, D). Patients with a successful outcome had wide caliber urethras endoscopically. Histologically, the tissue biopsies confirmed the presence of normal urethral tissue.

DISCUSSION

Urethral stricture disease due to trauma, iatrogenic injury, infection, inflammation and idiopathic causes require surgical repair. Although an end-to-end anastomosis following resection of the diseased tissue is feasible for short localized strictures, additional tissue is often necessary for longer segments.¹ Autologous tissue from other sources has been used for urethral repair, including genital and extragenital skin flaps or grafts, mucosal grafts from the bladder or buccal regions, tunica vaginalis and peritoneal grafts. However, complications may occur, such as hair growth, graft shrinkage, recurrent strictures, stone formation and diverticuli.¹³⁻¹⁶ Nondegradable synthetic grafts have been proposed previously for urethral reconstruction but these materials have been associated with erosion, dislodgement, fistula, stenosis, extravasation and calcification.^{5,6} Biodegradable matrices have served as scaffolds which can guide urothelial and connective tissue regeneration experimentally.⁷

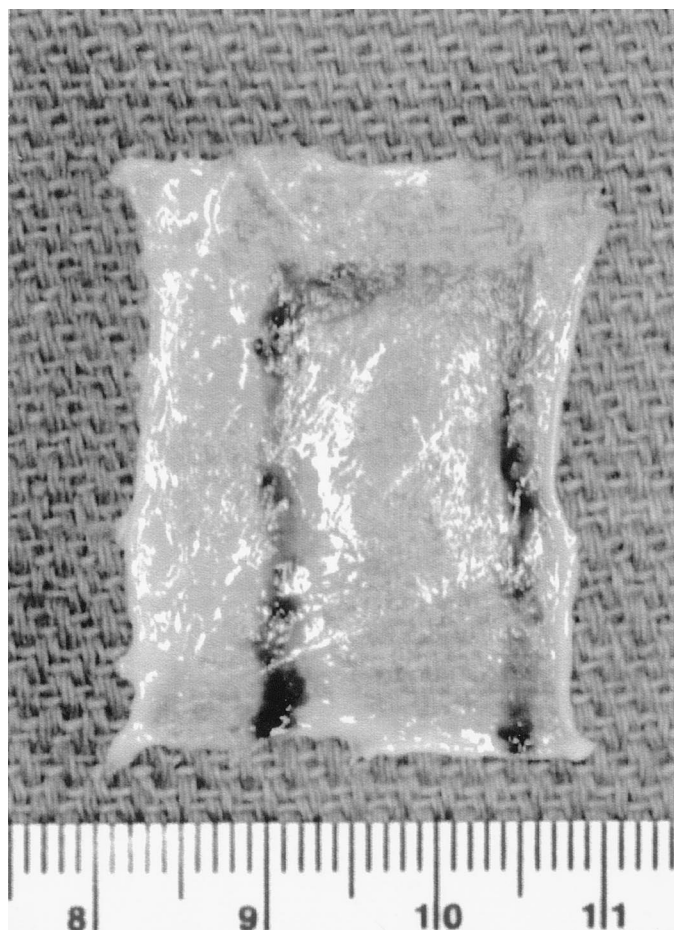


FIG. 1. Inert collagen matrix is trimmed to size as needed for each patient.

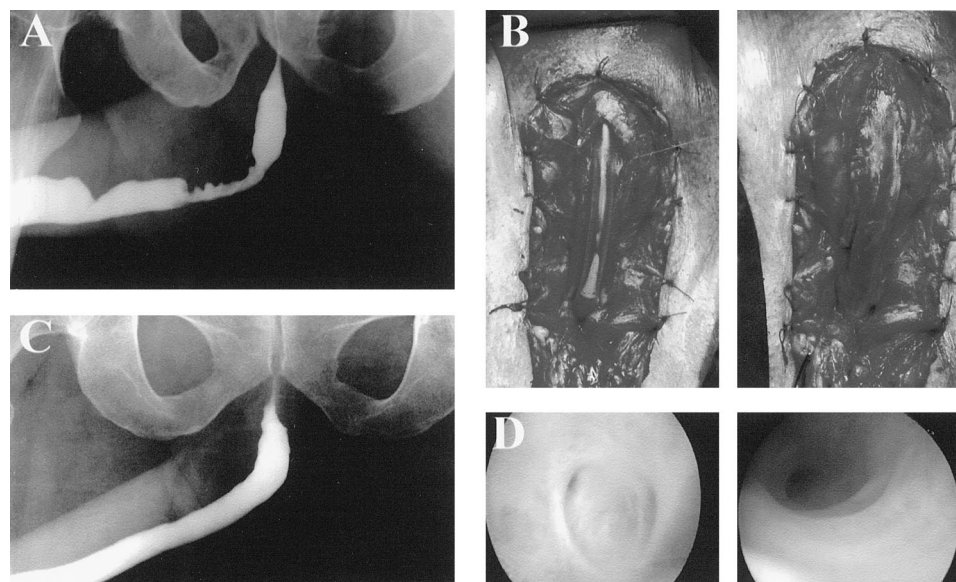


FIG. 2. Representative case of bulbar stricture. A, preoperative urethrogram. B, urethral repair. Strictured tissue is excised, preserving urethral plate on left side and matrix is anastomosed to urethral plate in an onlay fashion on right side. C, urethrogram 6 months after repair. D, cystoscopic view of urethra preoperatively on left side and 4 months after repair on right side.

Urethral stricture repair with collagen matrix

Site	No. Successful Outcome/ Total No.
Penile	2/3
Bulbar	11/11
Penile, bulbar	11/14

We previously reported that acellular collagen based matrices derived from donor bladders are biocompatible and can be used for urethral repair experimentally and clinically.^{9-12, 17-19} Clinically, the collagen based matrix has been used to repair hypospadias for more than 6 years. Neourethras ranging from 5 to 15 cm. long have been created in an onlay fashion with a successful outcome in regard to cosmetic appearance and function. The urethral segments reconstructed with acellular matrices showed normal cellular organization, which was indistinguishable from that of the native urethral tissue. No graft contractures or strictures have occurred to date.

In this study we expanded our application of the acellular collagen matrix for the repair of urethral stricture in 28 patients. The acellular collagen matrix, being an off-the-shelf material, was readily used after trimming to the appropriate defect size. After resection of the diseased fibrotic stricture segment, the matrix was anastomosed to the urethral plate in an onlay fashion. Of 28 patients 24 had a successful outcome after a single repair procedure, and 4 had an anastomotic caliber decrease postoperatively which was treated with visual internal urethrotomies. All patients had anatomically and functionally patent urethras as demonstrated by retrograde urethrography and uroflowmetry. In addition, the repaired segments showed regeneration of the urethral tissue histologically.

The acellular collagen matrix used in this study was obtained from cadaveric bladder tissue. Serological screening of the donors for infectious agents was performed before initiation of the decellularization process to ensure safety. The cellular components were removed, leaving only the collagen based matrix. Like donor corneas, which are also acellular, the bladder submucosa matrix can be implanted without fear of rejection. Other collagen based tissues, such as porcine heart valves have been processed and used clinically with wide acceptance.²⁰

The bladder based collagen matrix appears to be an excel-

lent biomaterial for urethral repair, since it can be safely obtained and processed easily, and has good characteristics for tissue handling and the advantage of being off-the-shelf. Use of the acellular collagen matrix as a graft material eliminates the need for harvesting other tissues, thus decreasing operative time and morbidity. In this study all patients withstood the repair procedures without any problems.

CONCLUSIONS

This study confirms the feasibility of using acellular bladder based inert collagen matrices as free graft substitutes for patients with urethral stricture disease. The collagen matrix patch can be used as an off-the-shelf material in an onlay fashion.

The New England Organ Bank and its organ procuring team members provided and tested the safety of the donor bladders.

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EDITORIAL COMMENTS

Reconstructive surgeons are always looking for an improved way to perform urethroplasty. Other than excision and primary anastomosis for short strictures, all substitution techniques have advantages and disadvantages. At the present time collagen matrix appears to be the same. A review of the results suggests that it works quite well in the bulbar urethra but not as well in the penile urethra. Therefore, how does it compare to other available tissues? How should it be used currently?

Without longer followup, collagen matrix should be reserved for unique cases when other tissues are not available. For penile strictures the gold standard remains the penile island flap when available. When penile skin is not available as in Lichen Sclerosus Atrophicus or adult hypospadias strictures, many surgeons proceed with a staged approach with extragenital skin or buccal mucosa. The authors would add considerably to our reconstructive options if the matrix were successful in these patients as a strip of urethra can be preserved. A larger study of these patients would be well received.

Bulbar strictures of moderate length can be repaired by many techniques with essentially equal success rates. Grafts of penile skin and buccal mucosa, or flaps of penile skin or hairless scrotal skin all appear to work but have their unique applications based on patient issues and surgeon preference. When should collagen matrix be considered? Longer followup and more studies are needed before it can replace many of these techniques but it certainly appears to have promise.

Finally, at a technical level, the authors have left the catheter in a week longer than after most other repairs which may negate donor site issues. In addition, most reconstructive surgeons are unlikely to excise a significant portion of the bulbar urethra. Strictures rarely involve the ventral corpus spongiosum. Therefore, a dorsal, dorso-lateral or ventral patch with spongioplasty might be considered. In summary, this study would suggest that collagen matrix be further investigated in select patients in a controlled setting before more widespread use is advocated.

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The potential for an off-the-shelf collagen matrix graft to allow urethral reconstruction without autologous graft harvesting is an intriguing concept, and the authors present a pilot study to assess the safety and initial efficacy of such a biomaterial. The group from Children's Hospital in Boston has previously used an acellular human bladder collagen matrix for 1-stage hypospadias repairs and have now extended this strategy to male urethral stricture.

The authors have demonstrated apparent biocompatibility, safety and preliminary evidence that the use of this off-the-shelf matrix can provide long-term resolution of urethral stricture disease. The study design is commendable, including the minimum 3-year followup. Retrograde urethrography and cystoscopy performed approximately 4 months after surgery are excellent short-term end points for determining outcomes of urethral stricture surgery.

Nevertheless, there are certain flaws which make it difficult to determine how successful this approach is and how it would compare to other more accepted grafting techniques. The length of the strictures is well documented in the study but the width of the remaining dorsal plate and the graft strips are not specified. Thus we do not really know whether these were tight strictures with a narrow residual dorsal plate or there was a wide dorsal plate and, thus, only a narrow strip of graft was required. The uroflow results postoperatively showed a significant increase compared to preoperative values but the authors do not inform us whether these were performed 4 months or 3 years after surgery. The retrograde urethrography and cystoscopy findings are of little value given the short interval between surgery and testing.

The current gold standard for long urethral strictures of the bulbar urethra that cannot be treated with excision and end-to-end anastomosis is buccal mucosa onlay grafting. The morbidity from the donor site in the mouth is minimal, catheters are required in the urethra for a maximum of 3 weeks and successful outcomes exceed 95% in most contemporary series. Thus, before this off-the-shelf collagen matrix can be considered a suitable substitute for buccal mucosa, more detailed studies, preferably with comparison through randomization between buccal mucosa and collagen matrix grafts, are advisable.

One of the exciting findings of this study was that the matrix performed extremely well on the penile urethra. This portion of the urethra is difficult to graft with full thickness grafts and many have adopted a staged approach to these strictures. Therefore, if the initial findings presented in this study can be duplicated by others, and it has been demonstrated that the severity of strictures is similar to those for which current practice dictates a free graft, then widespread and enthusiastic use of this biomaterial can be expected.

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REPLY BY AUTHORS

We have not used the collagen matrices in patients with Lichen Sclerosus Atrophicus or adult hypospadias strictures, but plan to do so in the near future. The types of donor tissues used for urethroplasty, such as buccal mucosa and skin, have not changed considerably during the last several decades, but the surgical techniques (use of dorsal patches) and postoperative management (shorter catheter drainage) have continued to evolve. In our study dorsal patches were not performed and the catheters were left for 4 weeks because that was our standard protocol for all patients undergoing stricture repair at the time of the study. Currently we advocate use of dorsolateral patches as well as shorter catheter drainage. The width of graft strips varied according to the severity of the stricture. We encountered tight strictures with a narrow residual dorsal plate and wide residual plates, requiring a range of wide to narrow strips of grafts, respectively.

In addition to the 4-month postoperative analysis with uroflow studies, cystoscopy and retrograde urethrography, many patients also had long-term followup studies performed up to 4 years after surgery. We have been satisfied to date with the long-term results in those patients treated for stricture disease (currently with up to a 4.5-year followup) and those treated for hypospadias (currently with up to a 7-year followup, reference 11 in article). Nonetheless, we agree that more studies are needed before more widespread use of the collagen matrix is advocated for urethroplasty. Additional studies are currently being conducted at our center.