Randomized Comparative Study Between Buccal Mucosal and Acellular Bladder Matrix Grafts in Complex Anterior Urethral Strictures

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Purpose: Urethral strictures have been a reconstructive dilemma for many years due to the limited availability of tissue substitutes and incidence of recurrence. Buccal mucosal grafts have been a favored material in instances where penile skin is unavailable due to its durability and excellent graft survival. Recently collagen based matrices derived from the bladder have been used successfully in patients with stricture disease and hypospadias. We performed a randomized comparative study to assess the outcome of the acellular bladder matrix compared to buccal mucosa in patients with complex urethral strictures.

Materials and Methods: Human demineralized bone matrix, obtained from cadaveric donors, was processed and prepared for use as an off-the-shelf material. Thirty patients with stricture 21 to 59 years old (mean 36.2) were enrolled and assessed using a standard protocol. The stricture length ranged from 2 to 18 cm (mean 6.9), of which 11 patients had bulbar, 7 had pendulous and 12 had combined bulbopendulous strictures. Of the 30 patients 7 had received no previous intervention while the remaining 23 had undergone 1 to 7 procedures (mean 1.9). All patients were randomized and alternatively assigned to receive either buccal mucosa or demineralized bone matrix and underwent an onlay procedure.

Results: All patients except 2 who were lost during followup were followed for 18 to 36 months (mean 25). In patients with a healthy urethral bed (less than 2 prior operations) the success rate of buccal mucosa grafts (10 of 10) was similar to the bladder matrix grafts (8 of 9) in terms of patency. In patients with an unhealthy urethral bed (more than 2 prior operations) only 2 of 6 patients with a bladder matrix graft were successful, whereas all 5 patients with a buccal mucosa graft had a patent urethra. Postoperative uroflowmetry showed significant voiding improvement in both groups. Histology of the graft biopsies showed normal urethral tissue characteristics.

Conclusions: This study demonstrates that the use of acellular bladder matrix is a viable option for urethral repair. Demineralized bone matrix as an off-the-shelf biomaterial achieves the best results in patients with a healthy urethral bed, no spongiofibrosis and good urethral mucosa.

Key Words: urethra, urethral stricture, reconstructive surgical procedures

Multiple techniques have been practiced to treat anterior urethral strictures using a penile skin flap for urethral reconstruction.[1,2] However, penile skin is not always available in instances where the penile skin is insufficient or diseased, which prevents its use for reconstruction.[3] In such circumstances, surgeons have used grafts as an alternative measure for urethral repair. The graft materials that have been used include skin grafts,[4] bladder epithelium,[5] buccal mucosa,[6–9] tunica vaginalis,[10–14] small intestinal submucosa[15–17] and tissue engineered buccal mucosa[18,19] with various degrees of success. Of these, the buccal mucosa has been widely accepted as the gold standard for graft procedures in the anterior urethra due to its durability and excellent graft take.[20]

Recently an off-the-shelf matrix derived from the bladder has been introduced as an acellular matrix material for urethral repair. This biomaterial is obtained from donor bladders and prepared through a multiple step process that results in the removal of cellular components, leaving a tissue matrix consisting of collagen and elastin, growth factors and macromolecules.[21] Acellular bladder matrix has been shown to be biocompatible and is able to guide urethral tissue growth in several experimental and clinical studies involving urethral pathologies.[22–24] However, it is uncertain whether ABM could serve as a universal graft material for all urethral stricture diseases. In this study we conducted a randomized comparative study using ABM and buccal mucosal grafts to determine specific applications of urethral stricture conditions through evaluating the outcome of repair.

PATIENTS AND METHODS

Patients

Between January 2002 and January 2004, 30 male patients 21 to 59 years old (average 36.2) and fulfilling the inclusion

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criteria were enrolled in this study (see table). All patients had an anterior urethral stricture, scarce or diseased penile skin (balanitis xerotica obliterans), and a stricture length greater than that amenable for end-to-end anastomosis (2 cm or greater). These patients were candidates for an onlay procedure and not a tubularized graft.

The length of the strictures ranged from 2 to 18 cm (average 6.9 cm). A total of 11 patients had bulbar strictures, 7 had pendulous strictures and 12 had combined bulbopendulous strictures. None of the patients had a stricture extending to the distal penile or meatal segments.

A total of 19 patients had received 1 or no previous interventions, while the other 11 had received 2 to 7 interventions (average 2.7), whether endoscopic or previous trials of reconstruction by other methods. The cause of the stricture was posttraumatic in 9 patients, idiopathic in 1, previous catheterization in 8, iatrogenic in 5, infectious in 5 (after urethritis) and following failed hypospadias repair in 2.

The inert acellular bladder matrix used in the study was obtained and processed in strict compliance with state and federal guidelines in a manner described in previous publications.[23] Briefly the mucosa (urothelium/suburothelium) of the bladder was grossly removed by surgical delamination. The dissected tissue was crosssectioned, and using hematoxylin and eosin stain bladder submucosa was confirmed. The BSM was rinsed with water in a stirring flask (200 rpm) for 2 days at 4 1C, and subsequently treated with 0.03% trypsin for 1 hour followed by rinsing in 10% FBS with PBS overnight at 4 1C and finally treated with Triton X-100 (0.5%) and ammonium hydroxide (0.05%) in distilled water for 72 hours at 4 1C. The solution was changed every day. After this washing step a small piece of tissue was sampled for histology to confirm the levels of decellularization. The tissue was washed with distilled water for 2 days at 4 1C, frozen, lyophilized and sterilized using Gamma irradiation (800 Rads) for subsequent use.[21]

Patients

Pt No.—Pt Age	Etiology	No. Previous Interventions	Length (cm)	Position	Surgery Performed	Outcome
1—30	Postcatheterization	1	5–6	Pendulous	Primary end-to-end anastomosis in posterior part+ buccal mucosal graft on floor of anterior part	Success
2—42	Postcatheterization	2	16–18	Bulbopendulous	ABM patch graft in posterior part + Monsieur urethroplasty in anterior part	Success
3—28	MCA	1	3–4	Bulbar	Buccal mucosal patch graft on floor	Success
4—31	Postcatheterization	1	5–6	Bulbar	ABM patch on floor	Failed
5—59	After endoscopy for transurethral prostate resection	1	13–15	Pendulous	Russell's on bulbar part + augmentation by buccal mucosa on rest of stricture (11 cm)	Success
6—35	Penoscrotal hypospadias	2	10	Pendulous	ABM patch graft on floor of urethral plate	Failed
7—39	Blunt trauma to perineum	1	3–4	Bulbar	Russell's procedure on roof + buccal mucosa on floor	Success
8—42	Idiopathic	0	5–6	Bulbar	Russell's on roof + ABM patch graft on floor	Success
9—56	After endoscopy for bladder stone	7	5–7	Bulbopendulous	Buccal mucosa patch on roof	Success
10—36	Postinfectious (urethritis)	2	5–7	Bulbopendulous	ABM patch graft	Failed
11—41	MCA	3	5–6	Bulbar	Russell's procedure on roof + buccal mucosa on floor	Success
12—38	Postinfectious (urethritis)	3	7–8	Bulbopendulous	ABM patch graft	Failed
13—21	After hypospadiac correction	1	4–5	Pendulous	Buccal mucosal patch graft on strictured part	Success
14—27	Postcatheterization	0	7–8	Bulbopendulous	ABM patch graft	Success
15—46	Postcatheterization	2	5–6 Bulbar + 2–3 pendulous	Bulbopendulous	Russell's procedure on roof of bulbar urethra + buccal mucosal patch graft on whole urethra joining 2 strictures	Success
16—36	Postcatheterization	2	5–7	Bulbar	Russell's procedure on roof + ABM patch graft on floor	Success
17—28	Blunt trauma to perineum	1	2–3	Bulbopendulous	Buccal mucosal patch graft	Success
18—34	Postinfectious (urethritis)	0	9–10	Pendulous	ABM patch graft	Success
19—44	MCA	2	6–7	Bulbar	Russell's procedure + buccal mucosal patch graft	Success
20—29	Postcatheterization	1	5–6	Bulbar	Russell's procedure + ABM patch graft	Success
21—43	Blunt trauma to perineum	0	4	Bulbar	Roofing urethroplasty with buccal mucosal patch graft	Success
22—29	After endoscopy for bladder stone	1	6–7	Bulbopendulous	ABM patch graft	Success
23—36	After endoscopy for ureteral stones	1	5–6	Bulbar	Buccal mucosal patch graft	Success
24—35	Postinfectious (urethritis)	0	8–9	Bulbopendulous	ABM patch graft + Russell's procedure on roof	Success
25—26	MCA	1	4–5	Bulbopendulous	Russell's procedure on roof + buccal mucosal patch graft on floor	Success
26—27	Postinfectious (urethritis)	0	3–4	Pendulous	ABM patch graft	Success
27—32	Blunt trauma to perineum	1	3–4	Bulbopendulous	Buccal mucosal patch graft on roof	Success
28—38	Post catheterization	0	5–6	Bulbar	Russell's procedure on roof + ABM patch graft on floor	Success
29—35	Blunt trauma to perineum	2	6–7	Pendulous	Buccal mucosal patch graft	Success
30—36	Postinfectious (urethritis)	2	5–6	Bulbopendulous	ABM patch graft	Failed

Assessment

All patients were assessed preoperatively by thorough medical history taken with emphasis on etiology of stricture and of associated medical disease or sexual dysfunction, physical examination, and laboratory evaluation including complete blood count, renal functions, liver functions, blood glucose and urinalysis. If urinary tract infection were present, culture and sensitivity testing was performed followed by appropriate treatment. Retrograde and voiding urethrography were performed to visualize the extent and site of the stricture. Uroflowmetry was performed preoperatively to obtain baseline voiding pattern and to determine the extent of urinary obstruction. Sonourethrography was performed in the 11 patients who had 2 or more prior procedures to visualize the extent of spongiofibrosis and the true length of stricture.

Randomization

After diagnostic assessment, the patients were randomized 1 for 1 between the buccal mucosal graft and the acellular bladder matrix, regardless of their previous interventions. Each group was subsequently subdivided and analyzed after surgery.

Surgical Repair

All patients were subjected to general anesthesia. Nasal intubation was used in those who were planned to undergo a buccal mucosal graft. Patients with only pendulous strictures were positioned in the supine position, while all others were positioned in the lithotomy position. After sterilization and drappings the penis was slung by a 3-zero silk suture which was attached to a small artery forceps. A 20 ch Nelaton catheter was inserted through the urethra to identify the starting point of the stricture. A degloving subcoronal incision was used in cases of purely pendulous strictures, while an inverted Y incision in the perineum was used in patients with bulbar and bulbopendulous strictures. The urethra was exposed and opened longitudinally on the ventral side of pendulous strictures, while it had to be slung and completely dissected from the surrounding fibrous tissues in bulbar and bulbopendulous strictures. It was still opened along its ventral aspect, and the 20 ch Nelaton catheter was inserted to the bladder through the healthy proximal urethra to ensure exposure of the entire stricture. In cases of strictured segments longer than 5 to 6 cm or heavily fibrotic areas a Russell's (end-to-end anastomosis on the roof) procedure was performed to shorten the length of the required graft and to remove extensive fibrosis.[25,26] A total of 11 patients were treated with the Russell's procedure, 6 patients from the buccal mucosal group and 5 patients from the ABM group.

Subsequently, the graft was obtained either from the sterile container or from the oral cavity through a routine buccal mucosa harvest technique.[8] The graft was then trimmed to fit the length and width of the stricture followed by anastomosis using 5-zero polyglycolic acid absorbable sutures in a continuous fashion starting from the proximal angle forward. On average, the width of the buccal mucosal graft was 1 cm while the width of ABM was 1.5 cm to allow for matrix shrinkage. The anastomosis was performed over a 26 ch urethral catheter. The graft integrity was tested by injecting sterile saline from the penile meatus to ensure watertightness. Spongioplasty was performed in the bulbar region and the urethra was closed in a routine manner. In the pendulous portion the graft was only covered by the dartos fascia and intact skin. An indwelling silicone urethral catheter 18 to 22 ch was placed in the urethra and was left in place for 3 to 4 weeks. No suprapubic catheters were inserted except in 2 cases where complete obstruction was present. The wound was covered with soft permeable dressing which allowed absorption of any minor bleeding from the wound site. The dressing was left in place for 3 days postoperatively followed by a routine dressing change.

The repair was evaluated routinely by ascending and voiding urethrography 3 months after the repair, every 3 months for the first year, and every 6 months for the second year. Uroflowmetry was performed at 3 months postoperatively. The average and maximum flow rates were compared to the preoperative baseline values. The patients were followed for up to 32 months with a mean period of 25 months (range 3 to 32).

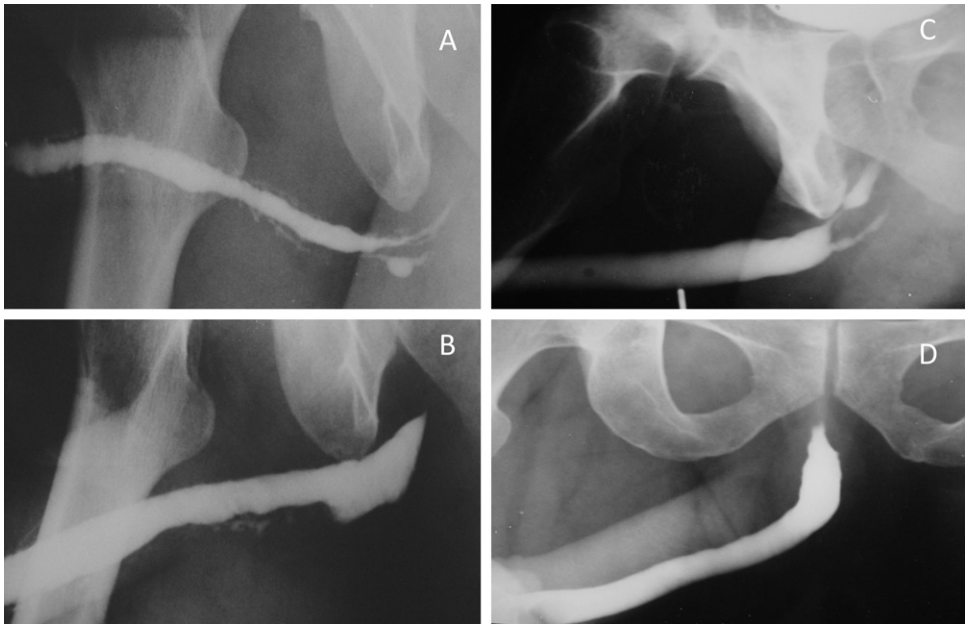
RESULTS

All patients were assessed postoperatively as previously described. If the patients maintained a voiding pattern with a steady stream without weakening over time and required no further intervention, the outcome was considered as successful. There was no evidence in any patient that the duration or etiology of the stricture had a role in the outcome. There was also no evidence that the length or location of the stricture had any role in the success or failure of the procedure as well. All patients with different etiologies were successfully treated and the outcome was only dependant on the quality of the urethral bed during the repair. The urethral bed was considered healthy when the urethral mucosa was fresh and vascular and there was no signs of spongiofibrosis, these features were mostly found in patient with 1 or no previous interventions.

We divided our patients into 2 groups, the first with 1 or no previous interventions and the second with 2 or more previous operations. In the first group treated with buccal mucosal grafts, all 10 patients (100%) had a successful outcome according to our assessment throughout the followup period. At the same time 8 of the 9 patients (89%) in the first group treated with ABM were also successful (see figure). The patient who did not have successful outcome needed a simple end-to-end anastomosis 3 months after the procedure due to an anastomotic stricture.

However, in the second group all 5 patients (100%) treated with a buccal mucosal graft showed successful outcome during followup, while only 2 (33.3%) of the 6 patients treated with ABM showed the same result. The other 4 patients needed an alternative intervention for repair after the initial re-stricture.

Uroflowmetry, performed at 3 months postoperatively, showed a significant improvement in patients who received a buccal mucosal graft. The mean preoperative Qavg was 5.7 ml per second and the mean Qmax was 9.4 ml per second. These values were improved to 10.3 and 16.5 ml per second, respectively, 3 months after repair. In the ABM group the preoperative means were 5.5 ml per second for the Qavg and 9.7 ml per second for the Qmax. At 3 months after repair these values changed to 9.7 ml per



Preoperative and postoperative urethrograms at 6 months showing successful treatment outcome using both graft techniques. *A* and *B*, ABM. *C* and *D*, buccal mucosa.

second and 16.4 ml per second, respectively in the successful cases.

None of our successfully treated patients required an endoscopic procedure postoperatively. Only the patients needing a second repair after the ABM reconstruction were subjected to a partial urethral retrieval and histological examination, which showed normal urethral tissue findings with a stricture formation at the site of repair due to poor condition of the residual unhealthy mucosa.

DISCUSSION

Various surgical techniques have been introduced over the years for repairing anterior urethral strictures that use flaps and/or grafts.[1–5,27,28] A general consensus indicates that a graft is preferred for the bulbar urethral repair, while a flap has been frequently used in the pendulous region of the urethra. In this study we compared the efficacy of ABM to a well established graft material that has been the gold standard in urethral grafting, namely the buccal mucosa. It is well-known that the buccal mucosa has the advantage of being a true substitute for urethral tissues, while the ABM is known to serve as a scaffold for promoting tissue regeneration. In this study we considered the quality of the urethral bed on which the graft was anastomosed as 1 of the criteria for assessing the outcome.

We randomized our patients in a 1:1 manner between repairs using buccal mucosa and ABM. The same inclusion criteria were used for both and the evaluation of outcome was performed in a similar manner. In our series the site of the stricture did not seem to affect the outcome. Some previous studies have suggested that bulbar strictures are more amenable for repair with acellular matrices than pendulous or bulbopendulous strictures.[7,29] Our results did not show a difference in this aspect.

The only major difference shown to have an impact on the outcome of the procedures in our series was the history of previous interventions which correlated directly to the quality of the urethral mucosa and the lack or presence of spongiofibrosis.

The 30 patients enrolled in this study were further subdivided by the condition of mucosal bed, which seemed to have a large impact on the outcome of the procedure. In the buccal mucosal group condition of the urethral bed did not seem to have any impact and all patients had a successful outcome after a meticulous surgical repair. However, in the ABM group the condition of the urethral bed had a definite role in the outcome. We had a successful outcome in 8 of 9 patients who had a history of 1 or less previous interventions (89%). However, we had 2 successful repairs in the 6 patients with 2 or more previous interventions (33.3%). These results are not entirely surprising based on the characteristics of grafting materials, which depend mostly on the quality of the urethral mucosal bed and the ability of the native urethra to regenerate along the scaffold material.

All successful cases were followed for a mean period of 25 ($\pm$2) months with excellent results in both groups. In all failed cases that received an alternative procedure, histological analysis was performed on the excised segment of stricture, which showed a complete urethral regeneration yet with new stricture formation in the repaired segments.

CONCLUSIONS

These results show that ABM is a viable option for urethral repair despite the lower success rate as compared to the buccal mucosa group in recurrent and complicated strictures. However, the ABM would be a preferred material for early strictures with an apparently healthy urethral bed and minimal spongiofibrosis due to the material being an off-the-shelf nature, which eliminates a tissue harvest procedure normally practiced for buccal mucosa derived repair. A Russell's procedure on the roof is also recommended whenever possible to decrease the length of the stricture which should improve the outcome of the surgery.

Abbreviations and Acronyms

ABM	=	acellular bladder matrix
BSM	=	bladder submucosa
MCA	=	motor car accident
Qavg	=	average flow rate
Qmax	=	maximum flow rate

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