Long-term Results of Small Intestinal Submucosa Graft in Bulbar Urethral Reconstruction

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OBJECTIVE To retrospectively report the long-term results of the use of a small intestinal submucosa (SIS) graft in bulbar urethral repair.

METHODS From 2003 to 2007, 25 men (mean age 40.5 years) with bulbar strictures underwent patch graft urethroplasty using SIS placed on the dorsal or ventral or dorsal plus ventral surface of the urethra. The mean follow-up period was 71 months (range 52-100). The clinical outcome was considered a failure when any postoperative instrumentation, including dilation, was needed.

RESULTS Of the 25 cases, 19 (76%) were successful and 6 (24%) were failures. No postoperative complications were related to the use of heterologous graft material, such as infection or rejection. The failure rate was 14% for strictures <4 cm and 100% for strictures >4 cm.

CONCLUSION At long-term follow-up, in bulbar stricture repair, SIS grafts showed similar results to penile skin grafts but were less effective than buccal mucosa grafts. The use of SIS as graft material should not be the first choice but represents an alternative option for patients with bulbar strictures that are not long and who refuse the harvesting or are not ideal candidates for buccal mucosa or penile skin grafts. Larger series of patients with longer follow-up are needed before widespread use can be advocated. UROLOGY 79: 695–701, 2012. © 2012 Elsevier Inc.

Despite developments in the surgical techniques, the type of substitutive material for use in the repair of urethral strictures remains 1 of the most challenging problems in urethral reconstructive surgery. Various autologous grafts or flaps from the skin or mucosa have been proposed for urethral stricture repairs; however, currently, the buccal mucosa (BM) is considered the best tissue for urethral substitution.[1]

Urethral tissue engineering is an emerging field in which the main aim is the development of an ideal material for urethral substitution, avoiding the problems related to the use of autologous tissue such as donor site morbidity and time-consuming harvesting. Various heterologous materials have been used but with poor results in the long term. Biodegradable organic matrices have been proposed as scaffolds promoting urethral regeneration but with potential risks of infection or antigenic complications. Several collagen matrices have already been applied for urethroplasty.[2]

Promising results have been reported with the use of small intestinal submucosa (SIS) as a urethral substitute material in animals.[3] Finally, SIS has also been tested in the urethra of human patients for the repair of urethral strictures. However, the published data reported only a few studies with results varying from 25% to 100% success and with short follow-up.[4-8] Moreover, these series were nonhomogeneous regarding the site of urethral reconstruction, because they included both penile or bulbar or penile-bulbar urethral repairs.[5,6]

The aim of the present study was to extend our previously published short-term follow-up,[6] by reporting a long-term follow-up in a homogeneous series of 25 patients with urethral stricture localized only in the bulbar tract who underwent patch graft urethroplasty using SIS. To our knowledge, this is the study on SIS graft bulbar urethroplasty with the longest follow-up.

MATERIAL AND METHODS

Patient Population

We retrospectively evaluated 25 men (mean age 40.5 years, range 23 to 66) with nonobliterative bulbar strictures who underwent graft urethroplasty using SIS from 2003 to 2007. Patients with penile, penobulbar, and obliterative bulbar stricture were excluded.

After the recent trends that aimed to reduce sexual complications,[9,10] in all nonobliterative strictures, we planned to

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perform patch graft urethroplasty without urethral transection instead of traditional end-to-end anastomosis transecting the urethra. All patients were informed of this and of the good results using the BM as the graft material, but they chose SIS to reduce the eventual donor site discomfort. Patients were also informed about the lack of long-term results using the SIS. All patients were interviewed to exclude sensitivity to porcine material.

The preoperative evaluation included clinical history, uroflowmetry, urethrography, and urethroscopy. Stricture etiology was unknown in 16 patients, iatrogenic in 8, and traumatic in 1. Of the 25 patients, 21 (84%) had undergone previous stricture treatment, including urethral dilation in 3, internal urethrotomy in 11, dilation plus internal urethrotomy in 5, and dilation plus urethroplasty in 2.

The stricture length ranged from 1.5 to 6 cm (mean 3.3). The grafts ranged from 4 to 7 cm (mean 4.7).

Surgical Techniques

In all patients, we performed urethroplasty using SIS as patch grafts for the urethral augmentation. To augment the urethra, the graft was placed dorsally in 11 patients (using Asopa's procedure in 8 patients and Barbagli's procedure in 3), ventrally as the McAninch group suggested in 6 and ventrally plus dorsally using Palminteri's technique in 8 (Fig. 1).[11-14]

The techniques were selected according to the site of the stricture within the bulbar urethra and according to the urethral plate quality. We used the dorsal graft in strictures located in the distal or middle bulbar urethra, where it is easy to expose the corpora and splay the graft. The ventral graft was preferred in strictures located in the proximal bulbar urethra, where it is difficult to work dorsally and the split of the corpora causes the lack of adequate support for the graft. Furthermore, the abundant ventral spongiosum provides adequate vascularization and support for the graft.[13] The dorsal plus ventral double graft was used in tight strictures with a narrow residual urethral plate (<5 mm) in which a single patch seemed to be insufficient to make a wide enough lumen.[14]

In all patients, after ventral or dorsal opening of the stricture, fibrotic urethral tissues were partially excised while preserving the remaining urethral plate. Neourethras were created by anastomosis of the matrices in an on-lay patch fashion to the mucosal urethral plate.

In all patients, we used SIS® (Cook Urological, Spencer, IN) grafts, size 2 × 10 cm, in 4 layers. After being opened, the material was rehydrated with saline solution. The sheet was trimmed to fit the urethral defect size, providing small allowance for overlap. SIS is nonelastic; thus, it is advisable to work with larger patches than the urethral defect. A 18F Silicon Foley catheter was left in place.

All surgical procedures were performed by the same surgeon (E.P.).

Postoperative Course and Follow-Up Criteria

The patients were discharged home 3 days after surgery. Voiding cystourethrography was done at catheter removal 3 weeks after surgery. All patients received perioperative broad-spectrum antibiotics followed by nitrofurantoin for 3 weeks until catheter removal.

We used the same follow-up and success criteria already used by other leading investigators.[1,12] Uroflowmetry and urine cultures were repeated every 4 months in the first year and annually thereafter. When obstructive symptoms developed or the peak flow rate deteriorated <14 mL/s, urethrography and urethroscopy were repeated. The clinical outcome was considered a failure when any postoperative instrumentation, including dilation, was needed.

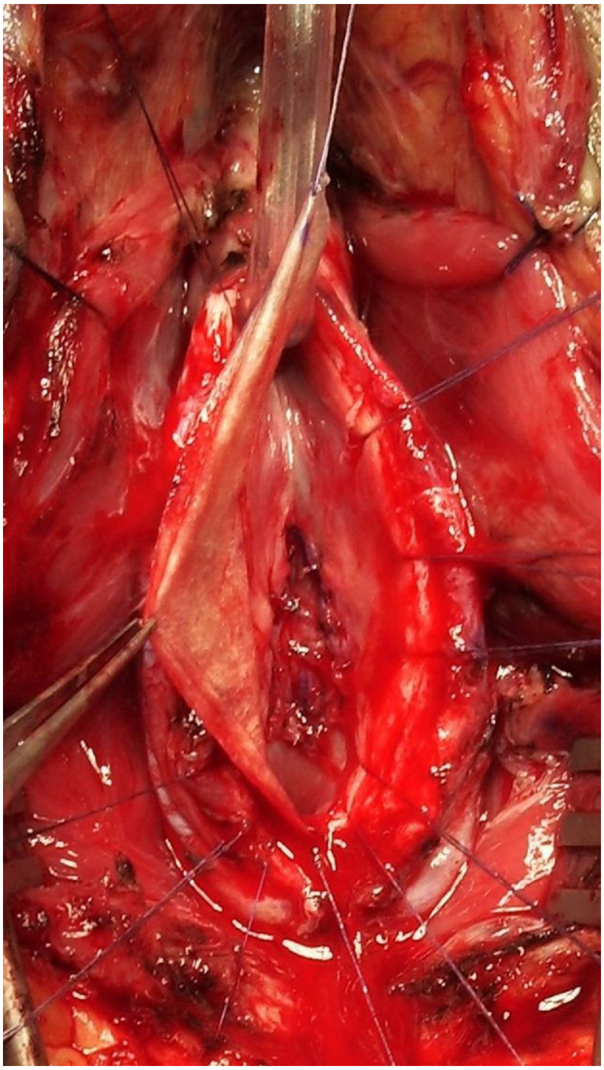

Figure 1. Dorsal plus ventral SIS grafts by Palminteri's technique. Urethra is opened ventrally; the urethral plate is graft augmented dorsally by Asopa procedure and subsequently, the lumen is also graft enlarged ventrally by McAninch's procedure.

The mean follow-up in the entire series was 71 months (range 52-100).

RESULTS

Of 25 cases, 19 (76%) were successful and 6 (24%) were failures (Table 1).

No postoperative complications were related to the use of heterologous material such as infection, an allergic reaction, or rejection. No fistulas were evident on voiding urethrography after catheter removal.

Of the 19 successful cases, the mean stricture length was 3 cm (range 1.5-4), and the mean graft length was

Table 1. Results

Pt. No.	Age (y)	Etiology	Previous Treatment	Stricture Length (cm)	Stricture Location	Repair Type	Mean Follow-Up (mo)	Follow-Up Methods (Result)	Outcome	Secondary Procedures
1	24	Iatrogenic	1 IOU	1.5	Mid	Dorsal	100	Qmax 5 mL/s Urethrography: restricture Urethroscopy: lumen <15Ch	Failure	2 IOU
2	66	Iatrogenic	Dilation	1.5	Mid	Dorsal	100	Qmax 23 mL/s Urethrography: no restricture Urethroscopy: lumen >15Ch	Success	
3	36	Iatrogenic	Dilation	2	Mid	Dorsal	73	Qmax 21 mL/s	Success	
4	38	Iatrogenic	2 IOU	2	Proximal	Dorsal/ventral*	69	Qmax 30 mL/s Urethrography: no restricture Urethroscopy: lumen >15Ch	Success	
5	35	Unknown	Dilations and 1 urethroplasty	2.5	Mid	Dorsal	74	Qmax 19 mL/s Urethrography: no restricture Urethroscopy: lumen >15Ch	Success	
6	27	Unknown	1 IOU and dilations	2.5	Proximal	Ventral	52	Qmax 25 mL/s	Success	
7	23	Unknown	1 IOU	3	Mid	Dorsal	98	Qmax 16 mL/s Urethrography: no restricture Urethroscopy: lumen >15Ch	Success	
8	50	Unknown	—	3	Proximal	Dorsal	75	Qmax 28 mL/s	Success	
9	54	Iatrogenic	Dilations and 1 urethroplasty	3	Mid	Dorsal	73	Qmax 14 mL/s Urethrography: no restricture Urethroscopy: lumen >15Ch	Success	
10	47	Unknown	1 IOU	3	Proximal	Dorsal/ventral	61	Qmax 31 mL/s	Success	
11	47	Unknown	—	3	Proximal	Dorsal/ventral	61	Qmax 26 mL/s	Success	
12	49	Unknown	4 IOUs and dilations	3	Proximal	Dorsal/ventral	67	Qmax 8 mL/s Urethrography: restricture Urethroscopy: lumen <15Ch	Failure	1 IOU
13	29	Unknown	1 IOU	3	Proximal	Ventral	60	Qmax 18 mL/s	Success	
14	38	Unknown	7 IOUs	3	Proximal	Ventral	64	Qmax 29 mL/s	Success	

Table 1. *Continued*

Pt. No.	Age (y)	Etiology	Previous Treatment	Stricture Length (cm)	Stricture Location	Repair Type	Mean Follow-Up (mo)	Follow-Up Methods (Result)	Outcome	Secondary Procedures
15	30	Iatrogenic	1 IOU	3	Proximal	Ventral	68	Qmax 20 mL/s Urethrography: no restricture Urethroscopy: lumen >15Ch	Success	
16	23	Trauma	—	3,5	Mid	Dorsal	70	Qmax 32 mL/s	Success	
17	51	Unknown	1 IOU	4	Mid	Dorsal	68	Qmax 18 mL/s Urethrography: no restricture Urethroscopy: lumen >15Ch	Success	
18	42	Unknown	Dilation	4	Mid	Dorsal	75	Qmax 21 mL/s	Success	
19	41	Unknown	1 IOU and dilations	4	Proximal	Dorsal	73	Qmax 15 mL/s Urethrography: no restricture Urethroscopy: lumen >15Ch	Success	
20	64	Iatrogenic	1 IOU and dilations	4	Mid	Dorsal/ventral	68	Qmax 5 mL/s Urethrography: restricture Urethroscopy: lumen <15Ch	Failure	1 IOU and perineostomy
21	35	Unknown	3 IOUs and dilations	4	Proximal	Dorsal/ventral	72	Qmax 25 mL/s Urethrography: no restricture Urethroscopy: lumen >15Ch	Success	
22	44	Unknown	—	4	Proximal	Ventral	61	Qmax 34 mL/s	Success	
23	29	Unknown	4 IOU	5	Proximal	Dorsal/ventral	69	Qmax 10 mL/s Urethrography: restricture Urethroscopy: lumen <15Ch	Failure	1 IOU
24	44	Unknown	4 IOUs	5	Mid	Dorsal/ventral	60	Qmax 6 mL/s Urethrography: restricture Urethroscopy: lumen <15Ch	Failure	1 IOU and perineostomy
25	47	Iatrogenic	2 IOUs	6	Mid	Ventral	60	Qmax 6 mL/s Urethrography: restricture Urethroscopy: lumen <15Ch	Failure	Perineostomy

Pt. No., patient number; Qmax, peak urinary flow rate; IOU, internal optical urethrotomy.

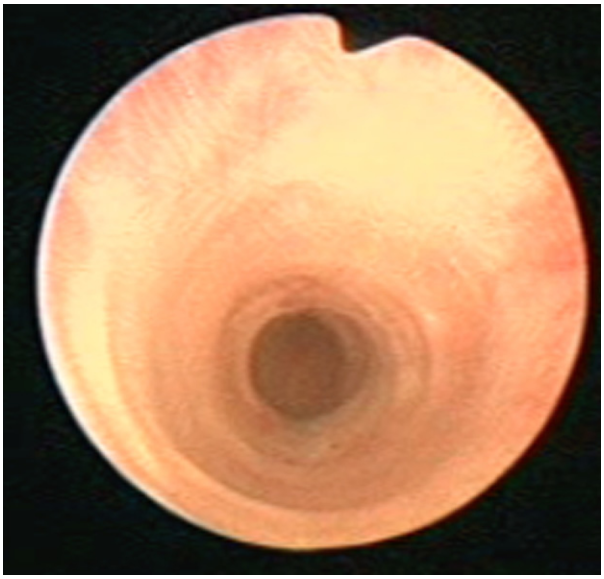

Figure 2. Postoperative endoluminal picture of urethral mucosal appearance after SIS graft.

4.6 cm. Of the 6 failed cases, the mean stricture length was 4.1 cm (range 1.5-6), and the mean graft length was 5.2 cm. In particular, the failure rate was 14% for strictures <4 cm and 100% for strictures >4 cm.

The postoperative mean peak urinary flow of the patients with successful treatment was 26.9 mL/s versus a preoperative mean peak urinary flow of 10.5 mL/s.

Of the patients with successful treatment, 9 (47%) agreed to undergo urethrography and urethroscopy 1 year after surgery. In all patients, these examinations revealed adequate-caliber lumens (no restricture on urethrography and lumen calibrate to a 15Ch cystoscope), and the SIS grafted area seemed to be replaced by urothelium (Fig. 2). Failures developed within 18 months after surgery. In 3 cases, the recurrence was only a slight fibrotic ring that was managed by a single successful endoscopic urethrotomy in 2 patients, and 1 patient required 3 urethrotomies. In 3 cases, the fibrosis involved the entire grafted area. In these patients, the fibrotic urethra was laid open leaving a urethrostomy proximal to the stricture. At the last follow-up, the patients were awaiting staged solutions.

COMMENT

BM and Penile Skin Graft Urethroplasties

A new trend has provided the use of urethral enlargement techniques through grafts even in short bulbar strictures instead of an anastomotic technique in which the section of the urethra and its shortening can cause sexual problems.[9,10] Regarding the grafting techniques, at present, BM is considered the reference standard for graft material. Previously, penile skin (PS) was the preferred tissue used for urethroplasty. Other types of autologous and heterologous material were tested but with uncertain results. Graft urethroplasty steadily deteriorates with time; thus, the question that reconstructive surgeons are asking is: which is truly the best urethral replacement tissue at long-term follow-up?

With regard to the BM, a recent wide review showed an overall 90% success rate at a medium follow-up of 3 years and with different techniques.[1] However, some studies with the longest follow-up showed that the success rate had decreased to 83% with a follow-up of 58 months[15] or 77% with a follow-up of 41 months).[16] Thus, even if today, BM is considered the reference standard, we have to wait for more studies to know the true result with even longer follow-up.

With regard to the PS, its long-term success rate showed a decrease to 73% with a follow-up of 71 months[17] and to 66% with a (follow-up of 111 months.[16]

SIS Graft Urethroplasty

Similar to the previously reported studies, in our study, with a mean follow-up of 71 months, longer than that of our previous study (mean 21 months),[6] we observed a reduction in the success rate of the SIS from 100% to 76%. At present, our study represents the largest series of bulbar SIS graft urethroplasty with the longest follow-up (Table 2). The published data on SIS urethral repair are scarce. In particular, only a few reports have focused on bulbar urethral repair but with small series of patients and short-term follow-up.[4-8,18]

We selected a homogeneous series of patients with only bulbar strictures, although we are conscious that the limitation of our study is that the series was heterogeneous with respect to the different techniques used. This makes it difficult to assess whether the surgical outcome resulted from the surgical technique or the "graft take" of the SIS. Another limitation was that only 15 patients (60%) agreed to undergo urethrography and urethroscopy during the follow-up period, and 10 patients (40%) rejected the invasive investigations because they were fine after years of suffering and/or urethral manipulation. Therefore, even if the criteria for urinary outcomes and follow-up were comparable to those used in many other studies,[1,16] we realize that a stronger follow-up method could detect unrecognized repeat strictures.

SIS Properties

SIS appears to have the properties of a valid heterologous substitutive tissue. It is thin but strong, easy to handle, and immediately ready for grafting. Prefabricated in different sizes, it has no limit to the length of graft that can be used. It is an acellular, nonimmunogenic, biocompatible, collagen matrix manufactured from porcine intestinal submucosa. Animal tests showed SIS to induce native tissue regeneration in various organs. Regarding its application in the urethra of animals, SIS was demonstrated to promote success-

Table 2. Outcomes of SIS graft bulbar urethroplasty

Investigator	Treated (n)	Follow-Up (mo)	Success Rate (%)
Donkov et al,[7] 2006	9	18	89
Farahat et al,[8] 2009	10	18	80
Palminteri et al,[6] 2007	16	21	100
Le Roux et al,[4] 2005	8	24	25
Fiala et al,[5] 2007	10	31	90
Present series	25	71	76

ful urethral regeneration.[3,19] In contrast, in men with urethral strictures, SIS has been used in graft urethroplasties with conflicting results.[4,7,18]

As all collagen matrices, SIS provides a scaffold for the regeneration of host tissues. It has tissue-specific regeneration properties associated with low risk of infection and no risk of rejection, because it is acellular.[20] It has never been shown to cause host immunogenic responses in cross-species transplantation. Matrix graft relies on angiogenesis of host tissue, and the grafted area is vascularized and epithelialized. When SIS is grafted in healthy tissues, healing seems to occur by tissue regeneration and not by scar tissue formation. Otherwise, the regenerative process could be adversely affected by scarring associated with strictures, explaining the poor results of SIS in urethras considerably compromised by spongiofibrosis.[4] Similar to that of other investigators,[18] in our previous experience with SIS,[6] we had failure in repairing long penile or penile-bulbar strictures characterized by extensive spongiofibrosis. In contrast, SIS appeared to work well in short/medium bulbar strictures. In the present study, we had a 100% failure rate in bulbar strictures >4 cm, confirming the belief that SIS patch grafts are successful only in short-medium bulbar strictures with mild spongiofibrosis when a strip of healthy urethra can be preserved and the remaining healthy spongiosum promotes urethral regeneration over the collagen scaffold. However, SIS does not seem appropriate in penile or penile-bulbar strictures with extensive spongiofibrosis (eg, lichen sclerosus and failed hypospadias strictures), and post-traumatic bulbar strictures or pelvic fracture urethral injuries with wide scarring.[4]

Current and Future Role of SIS

Finally, it is necessary to emphasize that to make a valid comparative evaluation between different materials, we need wide homogeneous series of patients who underwent the same surgical technique with a long follow-up period.

Our long-term follow-up data seem to show that SIS has similar results to the PS graft but less effective than BM graft in the repair of bulbar strictures. Furthermore, SIS seems unsuitable in long strictures, thus representing not the first choice but only an alternative option for patients with short or medium (<4 cm) bulbar strictures who refuse harvesting or are not ideal candidates for BM or PS graft.

CONCLUSIONS

We found that at long-term follow-up, SIS grafts seemed to show similar results to PS grafts but were less effective than BM grafts in the repair of bulbar strictures.

The use of SIS graft might represent not the first choice but only an alternative option in patients with short-to-medium bulbar strictures who refuse harvesting or are not ideal candidates for BM or PS grafts.

It is mandatory to perform additional long-term follow-up with larger series of patients to better evaluate these results and our conclusions.

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