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ORIGINAL ARTICLE

Long-term follow-up of neurogenic bladder patients after bladder augmentation with small intestinal submucosa

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Abstract

Purpose To evaluate the long-term effect of using small intestinal submucosa (SIS) for bladder augmentation in patients with neurogenic bladder.

Materials and methods A total of 15 patients (age range 14–65 years; mean age 29.6 years) were enrolled in our study. The patients had poor bladder capacity and compliance caused by a neurogenic disorder requiring bladder augmentation. A small intestinal submucosa (SIS) cystoplasty was performed alone or in combination with ureter reimplantation. We prospectively followed the cohort to assess the urodynamics parameters, morphologic changes and patient satisfaction and evaluate the clinical benefit of the SIS procedure in long term. The surgical indications and complications were analyzed.

Results The duration of follow-up ranged from 4.5 to 8.3 years (mean 6.3 years). Nine patients had expected long-term benefit, leading to an overall success rate of 60%. Two patients experienced immediate failure, and four patients slowed decrease in bladder capacity over time. Compared with the baseline data, there were significant increases in bladder capacity (163.5 ± 80.90–275.6 ± 159.5 ml, $p < 0.05$) and a significant decrease in maximum detrusor pressure (45.07 ± 29.03–17.60 ± 10.34 cmH_2O, $p < 0.05$). Histologic examinations showed a complete conversion of SIS, leaving the urothelial lining and bladder wall containing muscular, vascular, and relatively thick connective tissue. Major complications included vesicoureteral reflux in five patients, bladder stone formation in one patient, and bladder perforation in one patient.

Conclusion Bladder augmentation with an SIS graft offers a partial long-term success rate in neurogenic bladder patients. This procedure cannot be recommended as a substitute for enterocystoplasty, especially in patients with severe upper urinary tract deterioration and/or bladder fibrosis.

Keywords Small intestinal submucosa · Tissue engineering · Bladder augmentation · Neurogenic bladder · Long-term follow-up

Abbreviations

SIS	Small intestinal submucosa
TE	Tissue engineering
BA	Bladder augmentation
VUDS	Video-urodynamics
MBC	Maximum bladder capacity
MDP	Maximum detrusor pressure
BC	Bladder compliance
VUR	Vesicoureteric reflux
IC	Intermittent catheterization
DO	Detrusor overactivity
URI	Ureter reimplantation
UTIs	Urinary tract infections
UUT	Upper urinary tract

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Introduction

Regenerative medicine and tissue engineering (TE) techniques hold great promise for bladder reconstruction in patients with neurogenic bladder (NB), interstitial cystitis, bladder cancer, and other inflammatory bladder diseases by simplifying the surgical procedures and avoiding bowel-related complications when compared with conventional

enterocystoplasty. Previous studies have generally reported the preclinical and clinical experience on TE bladder augmentation (BA) using natural or synthetic scaffolds alone or seeded with different categories of cell sources [1–4]. Unfortunately, the promising outcome in animal models has not been substantiated in all clinical trials, revealing dissimilar outcomes in patients with different clinical/disease backgrounds. Based on the different follow-up outcomes and reports of side effects, including graft shrinkage, fibrosis, infection, and calculi formation, the current clinical applications of TE BA are controversial. The pertinent issues involve the status of the native bladder, the scaffold characteristics and mechanical properties, the implantation technique, and the post-implantation environment [5–7].

Small intestinal submucosa (SIS), an acellular matrix, provides a substantial opportunity for urinary reconstruction in experimental or clinical settings [2, 8, 9]. SIS relies on the body's natural ability to regenerate the new tissue growth with the proper orientation and direction. SIS-based bladder tissue regenerative medicine allows for regeneration of three vascularized bladder-like layers together with expression of purinergic, muscarinic, and β-adrenergic receptors. SIS has proven efficacy for BA in normal animal models [2, 8, 10, 11]. Previous clinical reports have demonstrated a high incidence of adverse events that result in significant morbidity and the need for secondary surgery [12, 13]. Long-term follow-up is required to confirm the practicability and effect of an SIS scaffold for bladder regeneration in humans with dysfunctional/diseased bladders.

With regard to our previously published pilot clinical experience, assertion had been arisen on the limited ability of SIS-grafted surface for bladder expansion [14]. We are encouraged to continue the SIS BA produce and prospectively follow this cohort to determine if the mid-term results are maintained [8, 9]. Herein, we report the ongoing clinical experience in SIS-mediated bladder reconstruction based on our long-term follow-up data.

Materials and methods

Subjects

The ethics committee of our institution approved the study. Between December 2010 and January 2015, a total of 15 patients (8 males and 7 females; mean age, 29.6 years; age range 14–65 years) with poor bladder capacity and compliance underwent SIS BA. The underlying causes for poor bladder capacity and compliance were meningomyeloceles (MMS) in 9 patients and spinal cord injury (SCI) in 6 patients.

All patients were evaluated pre-operatively with the following: serum creatinine (Scr) level; renal ultrasound; magnetic resonance urography (MRU); radioactive nephrography; and video-urodynamics (VUDS). VUDS variables were defined according to the standards recommended by the International Continence Society (ICS). During the urodynamic assessments, special attention was given to the following key parameters: (1) the maximum detrusor pressure (MDP) during the filling phase (2) the bladder compliance (BC), which was defined as the relationship between the change in bladder volume and the change in detrusor pressure (calculated by dividing the volume change by the change in detrusor pressure during the change in bladder volume) and (3) the maximum bladder capacity (MBC), which was defined as the infused volume during involuntary voiding/leakage or the volume when the investigator decided to stop filling (usually at 500 ml). Upper tract imaging and serum biochemistry testing confirmed that none of our patients had severe renal impairment [15, 16]. Poor bladder compliance existed in 14 patients pre-operatively based on urodynamic studies. The mean pre-operative MBC was 163.5 ml (range 73–352 ml) and the mean amplitude of MDP was 45 cm/H_2O (range 12–121 cm/H_2O). Seven patients were also shown to have grade 3–4 vesicoureteric reflux (VUR), and five patients had grade 3–4 upper urinary tract (UUT) dilation (Table 1).

All patients were refractory to conventional anti-cholinergic treatment and were interested in surgical treatment options. Patients were informed about the BTX-A injection therapy and advised of the possibility of repeated administration of BTX-A due to a decreasing effect. Patients were not receptive to the conventional enterocystoplasty. SIS BA was offered as an alternative to conventional enterocystoplasty. Patients were counselled about the relative novelty of the procedure and the need for long-term follow-up evaluations. The possible need for intermittent catheterization (IC) and the likelihood of further surgery were discussed pre-operatively.

The indications for surgery are described in our previous study, as follows [9]: (1) high bladder storage pressure (>40 cmH_2O) or decreased bladder capacity with or without UUT dilation/deterioration; (2) socially unacceptable urinary incontinence (UI) due to detrusor overactivity (DO) or decreased BC (<10 ml/cmH_2O); and (3) high-grade and/or low-pressure VUR with mild-to-moderate UUT deterioration. The indications for concomitant ureter reimplantation (URI) were greater than grade III VUR during storage or a lower grade of VUR starting at a low bladder pressure (<10 cmH_2O). Ureters were re-implanted into the native bladder.

Procedures

In our series, procedures were carried out following a standard technique, as previously reported [9]. A Pfannenstiel incision was used. The bladder was per-distended with

Table 1 Patient characteristics, urodynamic results, complications, and current status

Pt no.-sex-age-etiologty	Preop. UUTD-degree/VUR	Patch size (num.)	Urodynamic data: MBC (ml), MDP (cmH_2O), BC (ml/cmH_2O)				Postop. UUTD-degree/VUR (latest)	Complications/solution	Current status
			Preop	1st year	2–3 years	4–5 years			
1-M-21-SCI	B-2 VUR(R)	7*10(1)	218/15/14.5	289/28/10.3	350/22/15.9	300/25/12	B-1	_	IC/self voiding
2-M-23-MMS	B-1	7*10(1)	255/55/4.6	140/44/3.2	119/7/17	100/3/33.3	B-1	VUR(L)	Indwelling catheter
3-F-20-MMS	B-2 VUR(L)	7*10(2)	74/15/4.9	230/22/10.5	280/13/21.5	200/19/10.5	–	_	IC
4-F-22-MMS	B-1 VUR(R)	7*10(2)	90/18/5	230/9/25.6	400/14/28.6	370/12/30.8	N.A	_	IC
5-M-54-MMS	B-1 VUR(R)	7*10(1)	235/56/4.2	352/22/16	54/2/27	65/6/10.8	B-1 VUR(R)	VUR(R)	Indwelling catheter
6-M-14-MMS	B-2 VUR(B)	4*7(2)	79/121/0.7	250/27/9.3	300/25/12	350/22/15.9	N.A	_	IC
7-M-23-SCI	R-2 VUR(R)	7*10(2)	207/33/6.3	400/13/30.8	360/7/51.4	124/6/20.7	R-1 VUR(R)	VUR(R)	Self voiding
8-M-26-MMS	L-4	4*7(2)	203/28/7.3	500/5/100	510/3/170	530/8/66.3	–	_	IC
9-F-29-SCI	B-3 VUR(L)	7*10(2)	113/60/1.9	400/16/25	450/20/22.5	450/18/25	–	_	IC
10-F-14-MMS	L-2	7*10(2)	73/77/0.9	300/30/10	400/16/25	450/25/18	L-1	Bladder stone/lithotriptoscopy	IC
11-M-40-SCI	L-4	7*10(2)	123/48/2.6	350/38/9.2	500/28/17.9	500/25/20	–	_	IC
12-F-22-SCI	B-2	7*10(2)	132/54/2.5	300/38/7.9	450/26/17.3	200/27/7.4	R-2 VUR(R)	Bladder rupture/safety drainage-VUR(R)/BTX-A	IC
13-F-39-MMS	B-3	7*10(2)	180/28/6.4	250/16/15.6	200/24/8.3	240/29/8.3	L-1	_	IC
14-M-65-SCI	B-2	7*10(2)	119/56/2.1	300/41/7.3	200/38/5.3	200/35/5.7	N.A	_	IC
15-F-32-MMS	B-4	7*10(2)	352/12/29.3	340/4/85	304/6/50.7	200/4/50	L3 VUR(R)	VUR(R)/BTX-A	IC

UUTD upper urinary tract dilation, *R* right side, *L* left side, *B* bilateral side, *N.A.* not available (missing values)

saline and then exposed extraperitoneally. The urachus was identified and excised away from the extraperitoneal tissue with a combination of sharp and blunt dissection. The bladder dome was incised in a cranio-caudal direction. Seven patients with grade 1 to 3 VUR underwent simultaneous URI. The SIS membrane graft (Surgisis®ES, 4-layer tissue graft; COOK®, West Lafayette, IN, USA) was fashioned into a strap shape, rehydrated, and sewn to the mucous membrane of the bladder wall opening using 3-zero polyglycolic acid suture. The size of the patch chosen was in accordance with the pre-existing bladder capacity (generally two pieces of SLH-4S, 7×10 cm or 4×7 cm for < 100 ml [two pieces of SIS were sewn together]; and one piece of SLH-4S, 7×10 cm for > 100 ml). The correct orientation of the SIS membrane was internal to the luminal surface and external to the serosal surface. To ensure a watertight anastomosis, the SIS-grafted bladder was covered with soft perivesical tissue.

A transurethral catheter was inserted and left in place for 4 weeks, a suprapubic catheter was left for two weeks post-operatively, and a perivesical safety drain was left for 5–7 days. Antibiotics were administered during the first week post-operatively and continued as needed. The patients remained hospitalized 15–20 days as a precautionary measure. A full-dose anti-cholinergic agent (5 mg of solifenacin twice daily and 4 mg of tolterodine once daily) was given in the first 2 weeks and then a relatively low-dose

Table 2 Comparison of pre- and post-operative urodynamics results in patients who underwent the SIS procedure

Total urodynamic data	Preoperative	1st year follow-up	2–3-year follow-up	4–5-year follow-up
MBC (ml)	163.5 ± 80.90	308.7 ± 87.09*	315.1 ± 127.6*	275.6 ± 159.5*
MDP (cmH_2O)	45.07 ± 29.03	23.53 ± 13.04$^{\#}$	17.47 ± 11.70$^{\#}$	17.60 ± 10.34$^{\#}$
BC (ml/cmH_2O)	6.21 ± 7.25	24.37 ± 28.85	32.70 ± 40.19$^{\&}$	22.32 ± 16.99

Compared to the pre-operative status, there was a significant increase in the MBC ($^{*}p < 0.05$) and a significant decrease in the MDP profile ($^{\#}p < 0.05$) at 1, 2–3, and 4–5 years post-operatively. There was a significant increase in the BC ($^{\&}p < 0.01$) 2–3 years post-operatively

MBC maximum bladder capacity, *MDP* maximum detrusor pressure, *BC* bladder compliance

was administered for 3 months. Intermittent bladder cycling was begun 2 days post-operatively by timely clamping and opening of the bladder drainage catheters (usually at 1–2 h intervals). The clamping schedule was gradually extended to expand and remodel the augmented bladder. A VUDS evaluation was performed and IC regimen instructions were given before hospital discharge. The mean duration of hospital stay was 3 weeks and ranged from 21 to 28 days. All patients in our series initiated IC as daily micturition management.

Outcome measures

Follow-up evaluations included a serum creatinine level, renal ultrasonography, and MRU and VUDS assessments every 3–6 months, then yearly after the procedure. Bladder specimens were taken for histology from four patients during endoscopy from the middle portion of the regenerated wall. Hydronephrosis and ureter dilation were graded according to the Liao UUT dilation grading system [15, 16]. Complications were documented based on the medical record review or telephone interview. Patient satisfaction was assessed via a questionnaire with overall satisfaction on a scale of 1–10 (1 least satisfied, 10 most satisfied).

Statistical analysis

Results are reported as the mean ± SD. Statistical analysis was performed using SPSS (version 19.0; SPSS, Inc., Chicago, IL, USA). Student's t test and analysis of variance were used to compare the cystometric parameters and the patient reported outcomes before and after surgery. A $p < 0.05$ was considered to be statistically significant.

Results

The duration of follow-up ranged from 4.5 to 8.3 years (mean 6.3 years). A total of 9 patients had stable improvement, leading to the overall success rate of 60%. Four patients had a gradually decrease in incontinence episodes. Two patients had no symptomatic benefit. Compared with the pre-operative status, there were significant increases in MBC ($^{*}p < 0.05$) and a significant decrease in the MDP profile ($^{*}p < 0.05$) at 1, 2–3, and 4–5 years post-operatively. There was a significant increase in BC ($^{*}p < 0.01$) at 2–3 years post-operatively (Table 2). The results of patients with successful and unsuccessful procedures were reported separately. There were no significant differences between groups with successful and unsuccessful procedures in pre-operative VUDS parameters (Fig. 1).

During the post-operative surveillance period, one patient (#12) experienced a bladder perforation that occurred within 3 weeks post-operatively. Perforation was treated conservatively (bladder drainage with broad spectrum antibiotics) and the augmented bladder healed in 2 weeks. One patient (#10) had a bladder calculus formation and underwent a cystoscopic extraction at the 6-month follow-up evaluation. In spite of the early complication, this patient (#10) had a continuing amelioration in VUDS parameters and UUT dilation (Figs. 2, 3).

At the 12-month follow-up evaluations, 14 patients had increased bladder capacity and 13 patients had increased bladder compliance. VUR occurred in 5 patients during 1–2 years of follow-up, including 2 patients with recurrent VUR (#5 and #7) and 3 patients with new onset VUR (#2, #12 and #15). At the 2–3 years follow-up evaluations, 10 patients had progressively increased in bladder volume without deterioration in compliance or immunologic or urologic complications. Two patients (#12 and #15) required a BTX-A detrusor injection for reduced IC volume owing to DO with decreased compliance. When combined with IC and a low dose of anticholinergic medications (six of 15 patients as indicated), most patients were able to achieve continence consistently with preservation of renal function.

At the latest follow-up evaluation, 13 patients had continued with the post-operative IC regimen for adequate bladder drainage. Two patients (#1 and #7) switched to reflex voiding due to a gradually reduced bladder capacity and recurrence of incontinence after 3 years of follow-up. A total of 9 patients (60%) had a stable improvement in urodynamic parameters and UUT dilation (Table 1, Figs. 1, 2, 3). Four patients (27%) had an increased IC volume in the first 2 years post-operatively; however, they had a decrease in the continence interval thereafter due to reduced BC

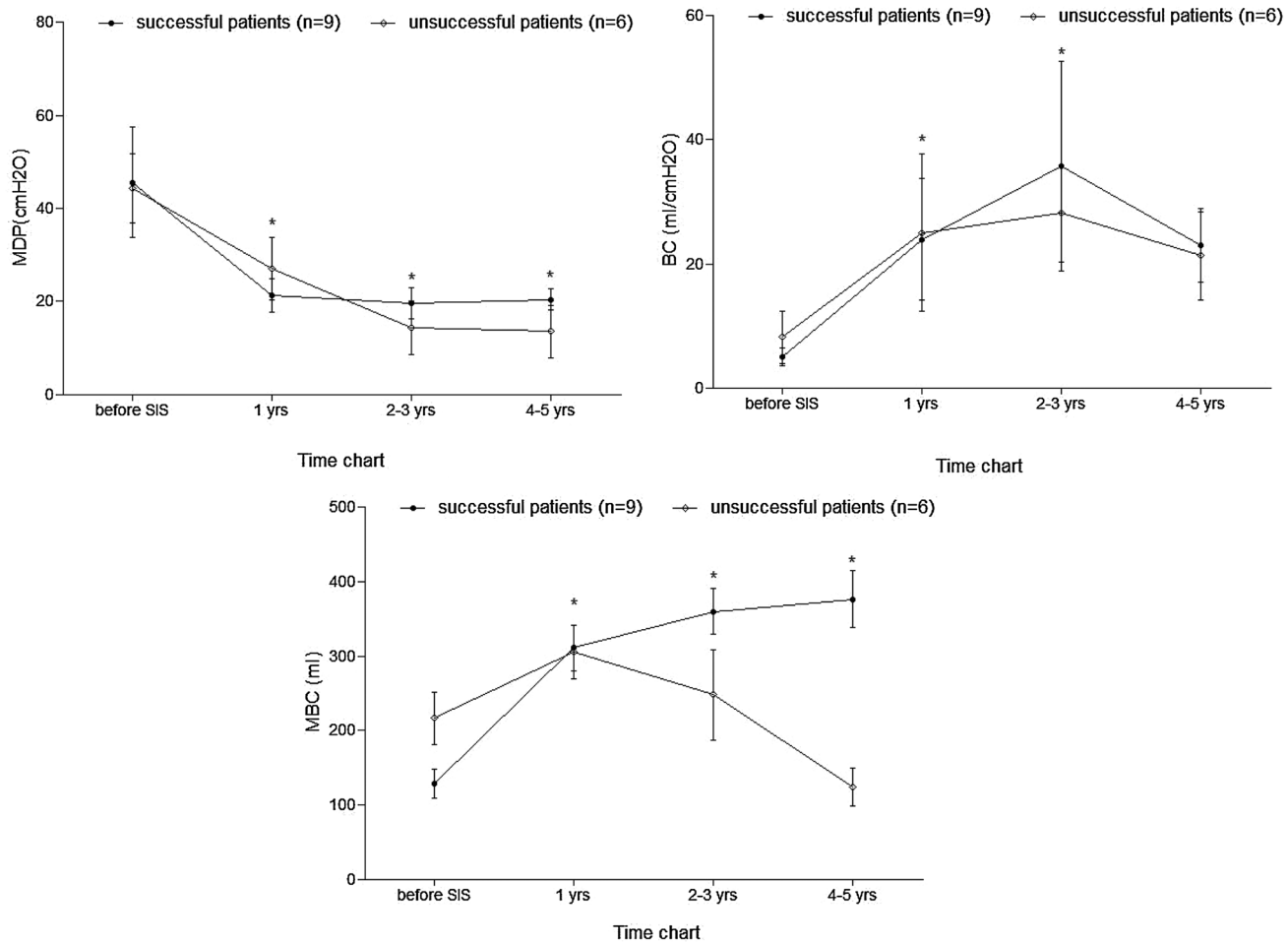

Fig. 1 The VUDS parameters layout in groups with successful and unsuccessful procedures during pre- and post-operative findings. *MBC* maximum bladder capacity, *MDP* maximum detrusor pressure, *BC* bladder compliance

and recurrent VUR. Two patients (#7 and #14) reported no symptomatic benefit from the procedure with an unchanged UUT dilation grade, but desired no further intervention. The overall average satisfaction score was 6.5 (Table3).

Macroscopic examination showed that the regenerated bladder wall was not distinguishable from the native bladder based on ultrasound, cystogram, and endoscopy (Figs. 2, 4). Cystoscopy showed that the regenerated bladder was fully lined by normal appearing urothelium. It was difficult to delineate the junction between the native bladder and the regenerated area. At 3–5 years, the regenerated area could not be distinguished from the native bladder. Re-vascularization was noted from the original bladder to the patched area (Fig. 4a, b). Histologic examination showed a complete conversion of SIS, leaving the bladder wall containing smooth muscle, vessels, and relatively thick connective tissue. At 4–5 years, the regenerated transitional multilayer epithelium was similar to native bladder, without evidence of the grafted acellular membrane. Furthermore, small vessels were present in the lamina propria (Fig. 4c). The muscular layer was characterized by smooth muscle bundles separated by abundant collagen tissue. The smooth muscle fiber proliferation was distributed into the connective tissue, either isolated or in parallel sheets (Fig. 4d).

Discussion

The goal of the BA procedure is to improve the functionality of diseased bladders by decreasing the intravesical pressures, improving BC and continence, avoiding violation of the bowel and peritoneal cavity, and preventing progressive renal disease. The ideal outcome should be stable over time, with a minimal complication rate and no increased oncologic risk [17]. Enterocystoplasty is described as beneficial in patients with underlying neurological disorders with an overall success rate of 77% (range 55–88%) [17–19]. Our study demonstrated that BA with an SIS graft can achieve a roughly 60% success rate during long-term follow-up. This technique helps increase bladder volume and alleviate UUT

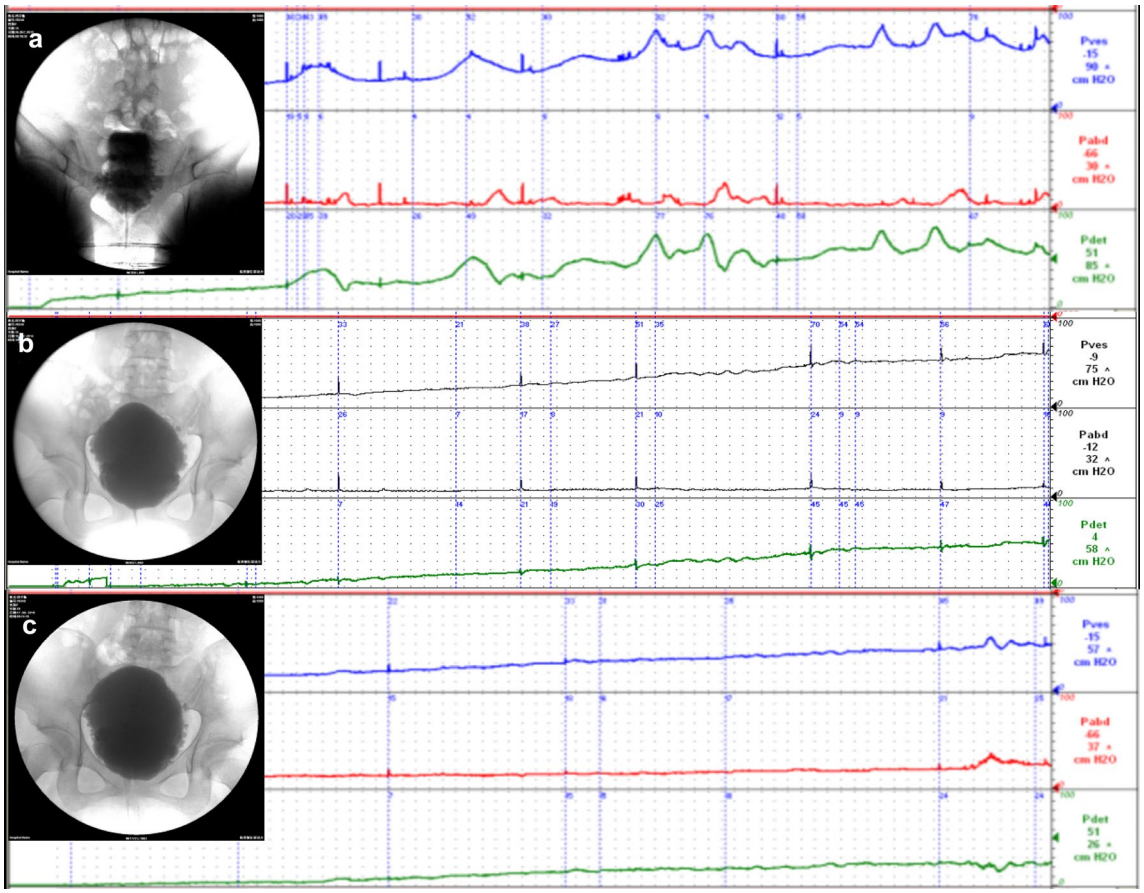

Fig. 2 **a** Pre-operative, **b** 2-year post-operative, and **c** 5-year post-operative video-urodynamic findings in patient #10 with SIS bladder augmentation

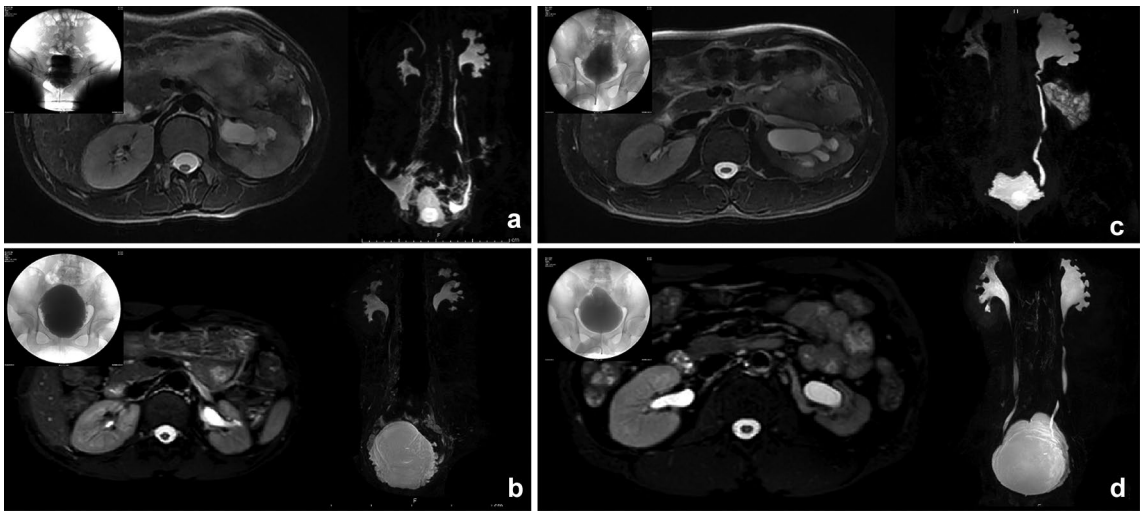

Fig. 3 **a**, **b** MRU and cystogram (upper left) of patient #10. **a** Before surgery. **b** 5-year follow-up; **c**, **d** MRU and cystogram (upper left) of patient #8. **c** Before surgery. **d** 5-year follow-up

dilation, therefore, offering relatively safe conditions for IC during long-term follow-up in some patients. Despite known complications and a relatively low success rate, SIS BA has the advantage of a simpler surgical procedure and avoidance

Table 3 Patient satisfaction score on the bladder condition before and after operation

Score data	Preoperative	1st year follow-up	2–3-year follow-up	4–5-year follow-up
Successful group	2.67 ± 0.50	$6.44 \pm 1.33^{*}$	$7.11 \pm 0.78^{*}$	$7.78 \pm 1.30^{*}$
Unsuccessful group	3.17 ± 0.41	$6.50 \pm 1.05^{\#}$	5.33 ± 0.82	4.67 ± 0.82
overall	2.87 ± 0.52	$6.47 \pm 1.19^{\&}$	$6.40 \pm 1.18^{\&}$	$6.53 \pm 1.92^{\&}$

The overall patient satisfaction of bladder condition on the quality of life measured by the visual analogue scale increased from 2.87 ± 0.52 to 6.53 ± 1.92 ($^{\&}p < 0.001$)

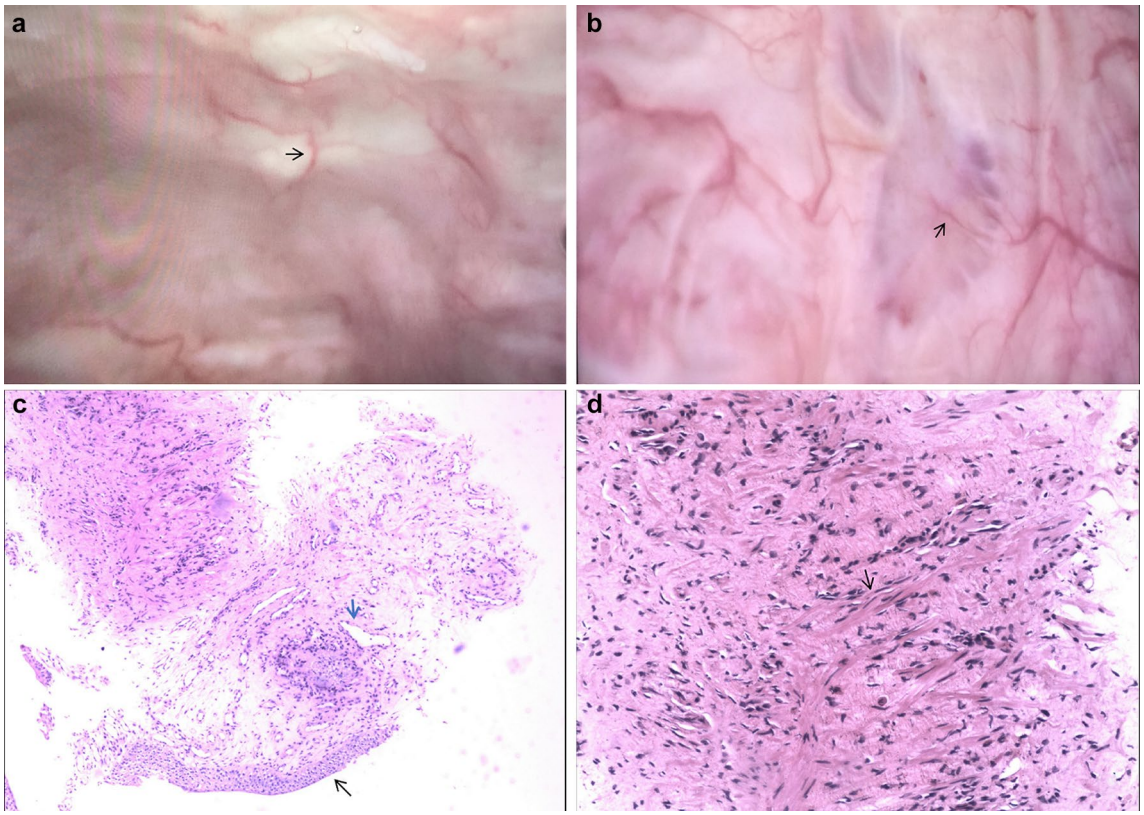

Fig. 4 **a**, **b** cystoscopy at 5-year follow-up shows that the patch edges are replaced by host connective tissues that are differentiated similar to native bladder tissue structures. Re-vascularization (dark arrow) is noted from the original bladder. **c** The regenerated transitional multilayer epithelium was similar to native bladder (dark arrow), and small vessels were present in the lamina propria (blue arrow; magnification × 40). **d** The smooth muscle fiber proliferation was distributed into the connective tissue, as isolated or in parallel sheets (dark arrow; magnification × 100)

of bowel-based complications compared with enterocystoplasty. Several notable findings merit further discussion.

With development of TE technology, numerous natural and synthetic biomaterials have been used for urinary bladder reconstruction with a wide range of outcomes. The validated approaches consist of augmentation cystoplasty in patients with poorly compliant neurogenic/neuropathic bladders using autologous cells seeded onto nature/synthetic materials or adopting naturally derived acellular tissue matrices as a scaffold [1, 9, 12–20]. Seeded strategy requires secondary surgical procedures for tissue isolation and propagation of in vitro cultures, thereby requiring substantial laboratory resources [1, 20, 21]. The unseeded technique is more convenient to perform clinically; in which native cells can regenerate organs when the tissues/organs are in direct contact with the scaffold. Unfortunately, many research challenges remain owing to unstable functional results over time. Currently, the clinical applications for bladder TE have not been established. Permanent synthetic materials have been associated with mechanical failure and calculus formation. Natural materials usually resorb with time and have been associated with marked graft contracture [5–7]. The acellular matrix (SIS) permits the regeneration of native epithelium acting as a scaffold, allowing cross-healing of the edges and promoting angiogenesis and growth of smooth muscle bundles [2, 3, 8]. This approach relies on the ability

of the intrinsic structure to interact with the host because the implanted material is rapidly degraded from the original architecture and is replaced by host connective tissue.

A concern about the clinical use of SIS for bladder reconstruction arises from the risk of the regenerated bladder wall repeating the histopathologic abnormality of the native bladder, such as an NB or a poorly compliant fibrotic wall [12, 13]. Because the morphology and innervation of the neurologically impaired bladder are different from those of a normal bladder, the potential for regeneration of the bladder may be different from healthy tissue. The healing process from in-growth of the surrounding fibrosis tissue may generally lead to more scarring than a grafted surface. We previously reported our experience with in vivo bladder regeneration using SIS in a healthy rabbit model. At the 24-week follow-up evaluation, the regenerated bladder showed no significant shrinkage and was completely lined by normal urothelium with neoangiogenesis [8]. However, the current study included two patients who had no symptomatic benefit from the procedure with an unchanged UUT dilation grade and four patients experiencing decreasing capacity and compliance over time. This finding may be attributed to the severe fibrosis of the native bladder with limited regeneration ability. Another important insight involves the use of SIS in a subtotal cystectomy (90%) model, which does not induce the same quality and quantity of bladder regeneration that occurs in the 35–45% partial cystectomy model [3, 11]. This finding indicates that the process of regeneration in a severely damaged bladder can be more difficult than a partial capacity preserved model, because the remaining small bladder template cannot provide strong enough structural support to prevent large patches from collapsing. In our opinion, when grafted on native bladder tissue, completion of the matrix epithelization process requires a few days. During this period, the matrix remains in contact with urine and undergoes phlogosis and tissue structural changes precluding fibrosis or graft shrinkage. The inflammatory response toward the matrix may contribute to resorption of the collagen matrix and scarring process may also inhibit sufficient bladder wall regeneration and the limited increase in capacity over time.

A pilot study reported on five patients with bladder exstrophy (3 with grade 3–4 VUR) who underwent BA using an SIS scaffold with concomitant URI. No VUR recurred in 7–19 months of follow-up [12]. It was shown that URI during cystoplasty in children with NB might be required because VUR can persist after BA without reimplantation and be associated with febrile urinary tract infections (UTIs) and UUT scarring [22]. The ICI in 2012 stated that BA might resolve low-grade VUR, while URI was recommended in patients with grade 4 or 5 VUR (grade C level) [23]. In the current study, seven patients with grade 1–3 VUR had simultaneous URIs; however, VUR occurred in five patients during 1–2 years of follow-up, including three new onsets of VUR and two recurrent VUR. In the two recurrent VURs, one (#7) showed that the VUR healed at 1 year post-operatively and then reappeared in 2-year follow-up, while one (#5) had a persistent VUR. We considered mild urine outflow resistance and bladder cycling as important factors for promoting bladder regeneration, which stimulated a capacity increase over time. In our series, patients were instructed to maintain a distended bladder for 1–3 weeks after surgery allowing coaptation of the SIS graft to the surrounding urothelium and perivesical tissues. Nevertheless, increased intravesical pressure with timed bladder distention may aggravate the native or reconstructed anti-reflux system. A sufficient dose of anti-cholinergic agents is needed to maintain low bladder pressure during the post-operative period, especially in patients with a previous VUR. Thus, it may be wise to select patients with no VUR or low-grade UUT deterioration for SIS BA. Two patients with postoperative VUR had BTX-A injection followed by anti-cholinergic agent. It is reported that BTX-A injections partially prevent the re-epithelialized gastric flap contraction in canine SIS BA model, indicating that BTX-A could have clinical potential during TE bladder reconstruction [24]. However, long-term follow-up is needed to further demonstrate the combination effect.

A previous study stated that IC was not routinely performed and that most patients should be encouraged to initiate self-voiding post-operatively. IC is only necessary when presenting afebrile urinary infection episodes due to significant residual urine [12, 13]. It should be kept in mind that the purpose of BA in NB patients is to provide a capacious, low-pressure reservoir to maintain renal integrity and allow the patient to be dry emptying the bladder periodically by IC. Spontaneous voiding after BA can be achieved in neurologically intact patients, but this is the exception rather than the rule. Thus, SIS augmentation in NB patients may only function as a low-pressure reservoir, but does not confer functional contractile activity to the bladder tissue. We assumed that the IC regimen may help expand and maintain the capacity and compliance of an augmented bladder, while spontaneous voiding could progressively induce bladder shrinkage and affect the upper urinary tract in the long term.

Severe complications associated with SIS grafts include the development of struvite bladder stones and bladder rupture. One patient had a bladder perforation 2 weeks post-operatively, probably due to poor bladder drainage and improper bladder cycling. We assumed that the drainage catheter was inadvertently positioned adjacent to the bladder wall and floccule formation during the scaffold degradation process could also blocked the drainage tube. Floccule accumulation can predispose patients to UTIs and stone formation, and can occasionally contributes to bladder perforation. The other patients underwent bladder stone removal at the 6-month follow-up visit. Stone

analysis showed a mixture of cellulose, collagen fibers, magnesium phosphate, and calcium phosphate carbonate. Because an intermittent floccule was usually discovered from the bladder drainage catheter during the first month post-operatively, we presumed that the scaffold degradation process induced lower calcium oxalate stone formation. Some studies have shown that naturally implanted grafts remain susceptible to inflammatory reactions, a low muscle-to-collagen ratio, interstitial fibrosis, and UTIs, which may result in atrophy of the graft, accompanied by stone formation, decreased bladder capacity, and urinary leakage. Thus, safe catheter drainage and a timed bladder irrigation protocol are essential during the bladder remodeling process [9].

In our study, different SIS patches were used (4 × 7 cm and 7 × 10 cm). Regardless of the size of the patch, there was no difference in total bladder capacity, maximum detrusor pressure, or compliance. Despite the larger size, complete regeneration of the bladder wall was possible, but some patients showed an insufficient increase in bladder compliance and recurrence of VUR. It remains unclear which patients are the most appropriate candidates for SIS BA. These results demonstrated that six of the nine patients (66.7%) with previous DO had stable improvement, and most patients with poor preoperative compliance and high-grade VUR did not have long-term success and required further intervention. The use of an SIS graft does not appear to increase the capacity and compliance more than the classic technique, especially in those patients with a small initial bladder capacity and poor BC [25]. We suggest that patients with pre-operative bladder capacity of < 100 ml and/or compliance of < 5 ml/cmH_2O should not be directly offered SIS BA as the first-line option. Because some patients had an initial improvement, followed by gradual deterioration, we recommend lifelong annual follow-up for these patients.

This study had numerous limitations. A potential weakness was the relatively small sample, leading to a lack of power to detect subtle associations. Immunohistochemical analysis may be needed in histological evaluation between groups with successful and unsuccessful procedures [26]. However, it is an exploratory research with continuing follow-up surveillance. The relatively higher rates of complications in the initial few patients may be a reflection of the learning curve for the surgical techniques and perioperative management needed to perfect. Cautious enrollment criteria were important factors for increasing the success rate. Conventional enterocystoplasty can still be used if SIS BA fails.

Conclusions

Our study demonstrated that BA with an SIS graft increased bladder volume and alleviated UUT dilation in some patients. This technique simplifies the surgical procedure while potentially avoiding the bowel-based complications compared with the conventional procedure. Nevertheless, the partial success outcome in current study does not necessarily translate to others with different diseased background. Careful patient selection remains of the utmost importance and patients need to be motivated to perform IC. Moreover, this procedure cannot be routinely recommended as a substitute for enterocystoplasty, especially in patients with seriously damaged bladder, high-grade VUR, severe UUT deterioration, and/or detrusor fibrosis. Furthermore, the possibility of malignancy for the regenerated bladder should be monitored out of safety concerns. Additional studies and continued follow-up evaluations are needed for TE BA to achieve significant consistent success.

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Author contributions LL: project development, manuscript editing. FZ: data collection, data analysis, manuscript writing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All protocols involving human participants in this study were approved by the Ethics Committee of Capital Medical University, China and had informed consent.

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