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Original Article

Tissue engineered indigenous pericardial patch urethroplasty: A promising solution to a nagging problem

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KEYWORDS
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Bovine pericardial patch;
Tissue engineering;
Long segment

Abstract *Objective:* Urethral stricture is a highly prevalent disease and has a continued rising incidence. The global burden of disease keeps rising as there are significant rates of recurrence with the existing management options with the need for additional repeat procedures. Moreover, the existing treatment options are associated with significant morbidity in the patient. Long segment urethral strictures are most commonly managed by augmentation urethroplasty. We explored the potential for the application of an acellular tissue engineered bovine pericardial patch in augmentation urethroplasty in a series of our patients suffering from urethral stricture disease. The decreased morbidity due to the avoidance of harvest of buccal mucosa, decreased operative time and satisfactory postoperative results make it a promising option for augmentation urethroplasty.

Methods: Nine patients with long segment anterior urethral strictures (involving penile and/or bulbar urethra and stricture length >4 cm) were included in the study after proper informed consent was obtained. Acellular tissue engineered indigenous bovine pericardial patch was used for urethroplasty using dorsal onlay technique.

Results: A total of nine patients underwent tissue engineered indigenous pericardial patch urethroplasty for long segment urethral strictures, mostly catheter injury induced or associated with balanitis xerotica obliterans. Median follow-up was 8 months (range: 2—12 months). Out of nine patients, eight (88.9%) were classified as success and one (11.1%) was classified as failure.

Conclusion: Our study brings a product of tissue engineering, already being used in the cardiovascular surgery domain, into the urological surgery operating room with satisfactory results achieved using standard operating techniques of one stage urethroplasty.

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1. Introduction

Urethral stricture is a disease that is highly prevalent and has a continued rising incidence. Various management options available at present include urethral dilatation, urethral stenting, urethrotomy, anastomotic and substitution urethroplasty. The global burden of disease keeps rising as there are significant rates of recurrence with the existing management options with the need for additional repeat procedures. Moreover, the existing treatment options are associated with significant morbidity in the patient.

Long segment urethral strictures are currently managed by augmentation urethroplasty. Various grafts and flaps have been described including buccal mucosal graft, lingual graft, scrotal skin, tunica vaginalis flap, extragenital skin, bladder epithelium and colonic mucosa. Chapple et al. [1] have made an observation that in contemporary practise, genital skin and oral mucosa are most commonly used, although there is interest in the potential for tissue engineering in the future. Buccal mucosal graft harvesting causes considerable morbidity in some patients. Moreover in countries like India where the practise of chewing tobacco and betel nut is very common, the buccal mucosa in such patients is already significantly fibrosed and of poor quality.

At present, in the literature only seven reports, concerning the clinical application of different tissue engineered materials for urethral reconstruction, are available with a total of 140 patients. Moon et al. [2] have reported a case of bladder reconstruction using bovine pericardium in a case of enterovesical fistula. Chee et al. [3] used the pericardial patch as a partial bladder wall substitute to close a defect in the bladder wall that occurred during adhesiolysis resulting in inadvertent injury in a patient of colorectal cancer who had received radiation therapy. A cystoscopy performed later in that patient revealed that the patch was *in situ* and had integrated into native tissue [3]. Bovine pericardium being a fixed tissue is cheap and relatively easily available [4]. It is elastic, has a high tensile strength and flexibility and is extremely durable [5]. A tissue-engineered urethra can be constructed with a limited amount of material without harvesting a mass of autologous healthy tissue [6]. In a study five patients with urethral stricture secondary to lichen sclerosus (LS) awaiting substantial substitution urethroplasty underwent urethroplasty using tissue engineered buccal mucosa and three of them had satisfactory results [7].

We explored the potential for the application of an acellular tissue engineered bovine pericardial patch in augmentation urethroplasty in a series of our patients suffering from urethral stricture disease. The decreased morbidity due to the avoidance of harvest of buccal mucosa, decreased operative time and satisfactory postoperative results make it a promising option for augmentation urethroplasty.

2. Patients and methods

Nine patients with long segment anterior urethral strictures (involving penile and/or bulbar urethra and stricture length >4 cm) (Fig. 1) were included in the study after proper informed consent was obtained. Patients with short segment strictures, those with local infection and those with underlying urological co-morbidities like urothelial malignancy or neurovesical dysfunction were excluded from the study.

Acellular tissue engineered indigenous bovine pericardial patch was used for urethroplasty using dorsal inlay technique. Approval was obtained from the Institutional Ethics Committee at N.R.S. Medical College & Hospital.

In all patients medical history was taken and physical examination performed. All patients underwent urological evaluation including uroflowmetry, ultrasonogram of kidney ureter bladder (KUB) region including post void residual urine, retrograde urethrogram, voiding cystourethrogram and urethroscopy.

Acellular tissue engineered pericardial patch (Synkroscaff® manufactured by SynkroMax Biotech Private

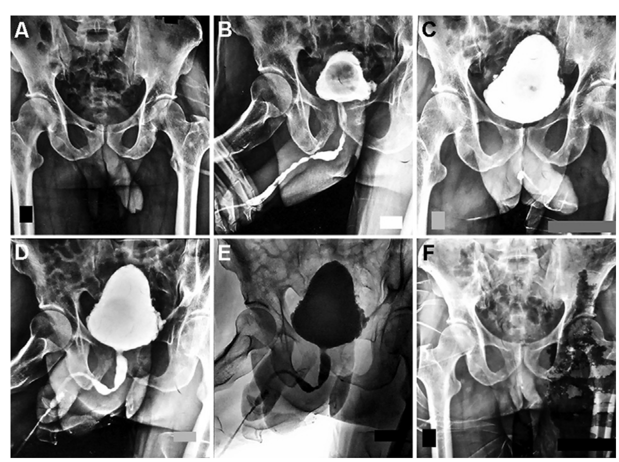

Figure 1 Preoperative retrograde urethrogram and voiding cystourethrogram. (A) Control film; (B) Retrograde urethrogram; (C) Cystogram of full bladder; (D) Voiding cystourethrogram; (E) Voiding cystourethrogram of invert mode image; (F) Post void image.

Limited, India) available in dimensions of 4 cm×4 cm and 6 cm×6 cm was used. It has a thickness ranging from 2 mm to 5 mm. Its quality is standardised and it is available in a sterile packaging that is ready to use and contains non glutaraldehyde solution.

After it was ensured that the urine culture of the patients was sterile, urethroplasty was carried out in the lithotomy position through perineal approach. After dorsolateral mobilisation of bulbar urethra on one side keeping the other side intact, the affected segment of urethra was opened dorsally (Fig. 2A). The patches were cut into appropriate dimensions (Fig. 2B) depending on the length of the stricture and the width of the native urethral plate with the intention to make the lumen of 20 Fr calibre. Tissue engineered pericardial patch was placed as a dorsal inlay patch. In stricture of length more than 4–5 cm, multiple patches (2–3 patches) were placed sequentially along the length of the urethra. The patch was fixed with 4-0 polydioxanone sutures (Fig. 2C) while quilting with the underlying corpora cavernosa was done with 4-0 vicryl rapide sutures in two rows (Fig. 2D, E). Tubularisation was completed over a silicon Foley's catheter of 16 Fr size (Fig. 2F). Suprapubic cystostomy (SPC) was maintained in all cases with a 14 Fr Foley's catheter *in situ*. Perineal wound was closed in layers after placement of a suction drain which was removed on 3rd postoperative day. Perioperative and postoperative antibiotics and analgesics were given up to 7th post-operative day.

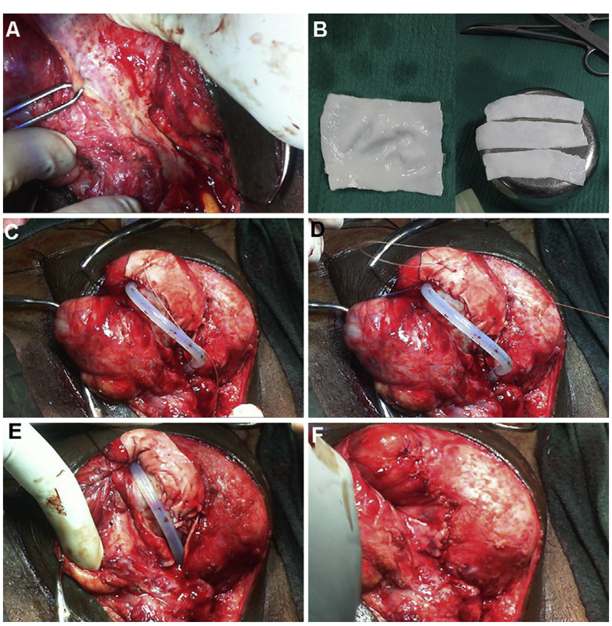

Figure 2 Intraoperative images. (A) Stricture urethral plate; (B) Bovine pericardial patch; (C) Pericardial patch placed dorsally; (D) Quilting of patch to underlying corpora cavernosa; (E) Another row of quilting of patch; (F) Tubularization of urethra.

Urethral Foley's catheter was removed on 8th post-operative day after the SPC Foley's catheter had been clamped. Patients underwent uroflowmetry on 8th post-operative day followed by discharge and advice to follow up after 3 weeks, 3 months, 6 months and 1 year. Urethral assessment by cystoscopy was performed at 3 weeks, 3 months and 6 months.

3. Results

A total of nine patients underwent tissue engineered indigenous pericardial patch urethroplasty for long segment urethral strictures, all of them being associated with balanitis xerotica obliterans. All patients were properly counselled regarding the procedure and informed consent was obtained.

Age of the patients ranged from 20 years to 58 years with an average of 43.22 years. Six out of nine patients had a history of chewing tobacco or betel nut and had poor oral hygiene and buccal mucosa. One patient had a history of undergoing buccal mucosal graft urethroplasty 4 years back, and had a fibrosed oral mucosa on bilateral cheek. The location of the stricture was Peno-bulbar in seven cases and penile in two cases. Stricture length varied from 5 cm to 18 cm (average: 10.44 cm). Width of the native urethral plate at the site of stricture ranged from 5 mm to 6 mm with an average of 5.55 mm.

Preoperative maximal flow on uroflowmetry was between 3 mL/s to 7 mL/s with a median value of 5 mL/s. All patients underwent urethroplasty via perineal approach using dorsal inlay technique.

Median follow-up was 8 months (range 2–12 months). Out of nine patients, eight (88.9%) were classified as success and one (11.1%) was classified as failure (Table 1). Postoperative maximal flow on uroflowmetry (Q_{max}) ranged from 10 mL/s to 30 mL/s with a median of 24 mL/s (Table 2). Failure was defined as a Q_{max} of less than 12 mL/s on uroflowmetry. One patient had a Q_{max} of 10 mL/s at three months follow-up. He underwent endoscopic urethral

Table 1 Stricture characteristics.

Patients	N	Success, *n* (%)	Failure, *n* (%)
Overall	9	8 (88.9)	1 (11.1)
Stricture site			
Penile	2	2 (100)	0 (0)
Peno-bulbar	7	6 (85.7)	1 (14.3)
Stricture length			
5–7 cm	2	2 (100)	0 (0)
>7–10 cm	3	3 (100)	0 (0)
>10–13 cm	2	2 (100)	0 (0)
>13 cm	2	1 (50)	1 (50)
Native urethral plate			
5 mm	4	4 (100)	0 (0)
6 mm	5	4 (80)	1 (20)

Table 2 Maximal flow on uroflowmetry.

Patients Serial No.	Preoperative Q_{max} on uroflowmetry (mL/s)	Postoperative Q_{max} on uroflowmetry (mL/s)		
		8th day	3 months	6 months
1	3	20	20	19
2	4	24	25	22
3	3	14	10	15
4	6	30	24	24
5	5	24	23	24
6	4	28	23	22
7	7	14	15	15
8	6	26	25	22
9	6	20	19	19

Q_{max}, maximal flow on uroflowmetry.

assessment which revealed a narrowing at the proximal anastomotic end of the patch and also at the junction between two patches. Gentle dilatation was carried out using soft endoscopic serial dilators and a silicon Foley's catheter was placed for a period of 1 month. His Q_{max} at 9 months follow-up was 15 mL/s.

One patient had local wound infection in the post-operative period, which was managed conservatively with antibiotics. No patients had any adverse events.

4. Discussion

Our initial experience with indigenous tissue engineered pericardial patch urethroplasty (TEPP Urethroplasty) showed that it is a potential feasible option in the treatment of long segment urethral strictures. The technique of application and success rate in our limited study are similar to the conventional buccal mucosal graft urethroplasty. Native buccal mucosa is known to be an appropriate tissue for urethroplasty but its excision is associated with complications like postoperative pain, perioral numbness, difficulty in opening mouth and some degree of difficulty in eating and chewing. In addition, a large number of people in India, especially Eastern India are addicted to chewing tobacco or betel nut. Both lead to fibrosis and hyperkeratosis of the buccal mucosa and submucosa making it unsuitable for being used as a graft. Two-thirds (66%) of the patients in our study had such a history.

Various centres across the world have been making efforts to develop a new tissue or patch for urethroplasty to avoid excision of the buccal mucosa. Our study with the pericardial patch represents a potential solution in this direction. It brings a tissue engineered pericardial patch which is being successfully used in various cardiovascular surgeries, to be applied to urethral reconstruction using the existing technique of urethroplasty. The success rate is comparable to that of buccal mucosal graft urethroplasty. No local or systemic side effects were noted, and complications of graft harvesting from the buccal mucosa were completely avoided.

The acellular pericardial patch acts as a scaffold for the regeneration of urothelium in the urethra, while it gets completely impregnated into the native tissue without any adverse effects. The future of urethral reconstructive surgery lies in the successful application of tissue engineering in the surgical field. Most of the research work in this field has been *in vitro* or in animal models. Very few studies have demonstrated the application of bovine pericardial patch in the urothelium in human patients.

Our study has a limitation of having a small sample size and a limited follow-up period. Nevertheless, it can prove to be a significant step towards application of new technology in the field of urethral reconstructive surgery. The study is continuing to include more patients and a longer follow-up period and we have reported our interim results here.

We have successfully shown that we could perform a safe and effective urethroplasty in long segment anterior urethral stricture using an indigenous tissue engineered bovine pericardial patch, with the standard dorsal inlay technique of one stage augmentation urethroplasty.

5. Conclusion

Our study brings a product of tissue engineering, already being used in the cardiovascular surgery domain, into the urological surgery operating room with satisfactory results achieved using standard operating techniques of one stage urethroplasty.

Author contributions

Study concept and design: Tapan K. Mandal, Shashanka Dhanuka, Tapas K. Majhi, Sunirmal Choudhury.
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Critical revision of manuscript: Tapan K. Mandal, Sunirmal Choudhury, Tapas K. Majhi.

Conflicts of interest

The authors declare no conflict of interest.

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