

Single-Layer Acellular Porcine Bladder Matrix as Graft in Corporoplasty for Ventral Curvature in Pediatric Proximal Hypospadias Repair: An Initial Experience



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BACKGROUND Single-layer ACell Cytal matrix (ACell Inc, Columbia, MD) is a commercially available, acellular scaffold derived from porcine bladder epithelial basement membrane and tunica propria. We describe our initial experience using Cytal as corporal graft in pediatric patients who underwent correction of ventral curvature in proximal hypospadias repair.

METHODS A retrospective review of a single-institution, 4 surgeon hypospadias database was performed between January 2020 and December 2021. Outcomes assessed were postoperative recurrent ventral curvature, corporal diverticulum, scarring on corporoplasty site on physical exam, and parental reports of atypical adverse effects.

RESULTS Ten males underwent correction of ventral curvature with Cytal as corporal graft for correction of ventral curvature were identified. All completed planned operations. Median age was 18.6 months (IQR 14.6-27.0). Median follow up was 14.1 months (IQR 8.9-16.5). Mean ventral curvature after degloving was 80 ± 50 degrees. All patients had straight erections. Nine of the 10 patients had straight erections verified at a subsequent artificial erection test at least 6 months from the corporoplasty (90%). The remaining patient underwent a double face onlay-tube-onlay transverse island preputial flap as a single-stage hypospadias repair and did not require any additional procedures. He had straight erections per parental history. None developed corporal diverticulum or demonstrated induration at site of corporoplasty on physical exam. There were no parental reports of atypical adverse systemic effects.

CONCLUSION In the short term, single-layer Cytal is effective as corporal graft for correction of ventral curvature in proximal hypospadias repairs without incurring additional donor site morbidity. UROLOGY 169: 196–201, 2022. © 2022 Elsevier Inc.

Tissue availability for grafts and flaps for corporoplasty can pose a challenge during the correction of ventral curvature in proximal hypospadias.

Interposition flaps and grafts have been reported with various materials, including tunica vaginalis, dermis, small intestine submucosa (SIS; Cook Biotech, West Lafayette IN), pericardium, or dura.¹ Tunica vaginalis, due to its ease of harvest and lack of donor site morbidity, continues to be the substrate of choice for corporoplasty for many pediatric urologists when correcting ventral curvature. However, the search for easily accessible and similarly effective graft material continues, stemming from the inefficiency of graft harvest, morbidity of donor harvest site, and unavailability of autologous tissue in certain circumstances.¹ SIS has demonstrated variable success as a pre-packaged graft,^{2,3} while the use of Alloderm in pediatric hypospadias is in its nascency.¹

Single-layer Cytal wound matrix (ACell Inc, Columbia, MD) is the sheet form of a commercially available,

Abbreviation: SIS, small intestine submucosa; UBM, urinary bladder matrix; DTITA, deep transverse incision of tunica albuginea; USD, United States dollars; UDT, undescended testis; IHR, inguinal hernia repair; HTN, hypertension; ESRD, end stage renal disease

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acellular, non-crosslinked wound management scaffold derived from porcine bladder epithelial basement membrane and tunica propria, termed MatriStem “Urinary Bladder Matrix (UBM)”. After grafting, ACell MatriStem UBM induces a host-derived tissue remodeling response.⁴ It stimulates neovascularization through a number of growth factors and functional proteins such as collagen, laminin, and elastin.⁵ Inflammatory reactions are uncommon, given the acellular, inert nature of UBM.⁴

ACell MatriStem UBM has been used successfully in various disciplines: as graft material in trauma and burn wounds for regeneration of muscle and dermis,^{6,7} as reinforcement of soft tissues in ventral, hiatal, and parastomal hernia repairs,^{8,9} and as a salvage option for failed local and regional flaps in head and neck surgery.¹⁰ However, scant studies on its clinical application exist in the urological literature. Pearlman et al describe the use of the ACell MatriStem UBM as substitution for buccal mucosal graft in a case series of 8 adult patients with urethral strictures. Although the specific form, thickness and size of the wound matrix was not described, the authors demonstrated similar graft take and contraction rates following staged repair when compared to buccal mucosal graft.¹¹ Case series involving use of ACell MatriStem UBM for female urethral reconstructions and closures of vesicovaginal fistulae have also been reported.^{12,13} A pinned search with MeSH terms in PubMed demonstrates no published reports using Cytal in the pediatric urological literature.

We aim to describe our initial experience and short-term postsurgical outcomes using Cytal as corporal graft in pediatric patients undergoing ventral penile lengthening for correction of severe ventral curvature in proximal hypospadias repair.

MATERIALS AND METHODS

A single-institution 4-surgeon database of hypospadias repairs at our institution has been maintained since 2008 (IRB#190105). Beginning July 2020, the authors began use of Cytal in hypospadias repairs after the successful use in a patient with bladder exstrophy who had a wound breakdown after discussion with the

pediatric plastic surgery. A retrospective review of the database to identify males with proximal hypospadias who underwent corporotomy with Cytal as corporal graft for correction of ventral curvature was performed, querying between July 2020 and December 2021. Patients were excluded if staged procedures were not completed, or if Cytal was used in other contexts. Clinical and operative characteristics of each patient were recorded. Data were summarized using SAS Statistical Software version 9.4 (SAS Institute, Cary, NC, USA).

Cytal as Corporal Graft After Corporotomy

Preoperative intramuscular testosterone was administered in the outpatient setting according to surgeon preference. Cefazolin was administered in all cases prior to incision. The penis was degloved down to the tunica albuginea after excising tethering bands on the ventral aspect. Lifting of the urethral plate and of the underlying divergent corpus spongiosum was performed. Artificial erection tests were performed, and ventral curvature was measured with a goniometer. If curvature was over 45°, the urethral plate was transected at point of maximum curvature. The divided urethral plate was mobilized proximally and distally. The erection test was repeated, and if curvature persisted, a corporoplasty was performed. A tourniquet was placed prior to corporotomy to minimize bleeding. Corporotomy was performed transversely on the ventral aspect for 180° at point of maximum curvature (Fig. 1A). The authors' preference is to perform a transverse corporotomy to lengthen the penis, rather than perform a dorsal plication for curvature greater than 45°. The tunica albuginea was lifted off the erectile tissues meticulously to avoid injury to the vascular erectile tissue.

A 3 × 3.5 cm single-layer Cytal was prepared as directed with soaking in sterile normal saline at room temperature for 10 minutes. It has 2 fenestrations (Fig. 2A). The single layer does not have a hydrophilic or hydrophobic side. Cytal was then trimmed to fit the resulting defect, typically in between the fenestrations. Approximately 25% redundancy was left on the edges of the graft to account for overlap on the underlying tissue when suturing. Cytal grafts were secured to the edges of the tunica albuginea with running locking suture of 5-0 or 6-0 polydioxanone suture (PDS) (Fig. 1B). Tisseel fibrin sealant (Baxter Healthcare Corporation, Deerfield, IL) was typically then applied to the entire graft, including sutured edges, while the tourniquet remained. A Coban pressure dressing (3M Medical, Saint Paul, MN) over the corporoplasty was applied, the tourniquet removed, and the surgeon proceeded with other portions of

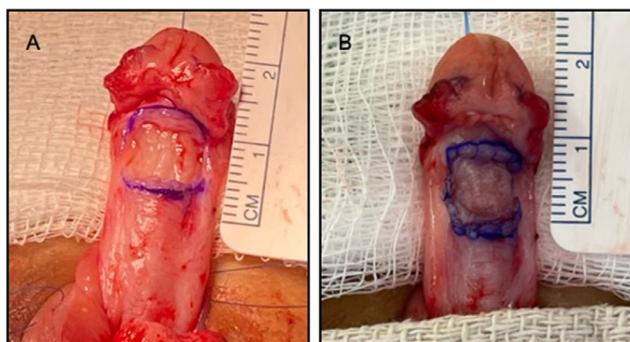


Figure 1. (A) Transverse corporotomy performed at point of maximal curvature on the ventral aspect of the penile shaft. (B) Cytal that has been trimmed and secured to the edges of the tunica albuginea with a running locking absorbable suture. (Color version available online.)

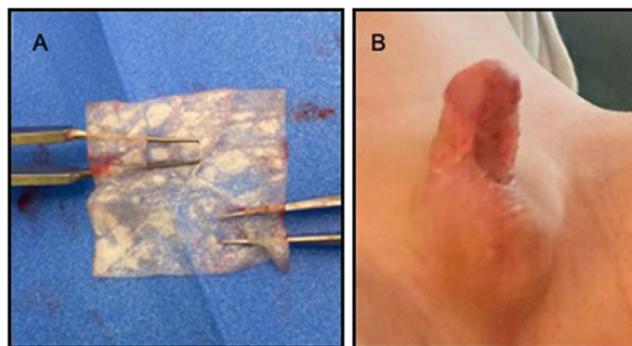


Figure 2. (A) Intraoperative hydrated 3 × 3.5cm single layer Cytal. There are two preplaced fenestrations; the graft that is used for corporotomy is typically taken in between fenestrations as to maximize the available graft surface area. (B) Ten-month postoperative spontaneous straight erection after first stage hypospadias repair with Cytal as graft for corporoplasty for perineal hypospadias, prior to second stage hypospadias repair. (Color version available online.)

the case. After 15-25 minutes, the Coban dressing was removed, and hemostasis was re-assessed. A repeat artificial erection test was not performed after corporotomies. In select patients, multiple deep transverse incisions of tunica albuginea (DTITA), where only partial transection of the tunica albuginea is completed and the erectile vascular tissue is not exposed, was performed. Cytal was placed over the DTITA in those cases.

A transverse island preputial flap rotated from dorsum to ventrum was used as coverage of the Cytal graft and skin coverage. If the surgeon proceeded with the first stage of a 2-stage repair, the flap was laid as a flat rectangle. The second stage repair proceeded at least 6 months after the first stage repair and has been previously described.¹⁴ If the surgeon proceeded with a single stage repair, the epithelium of the preputial flap was split and used as a double-faced onlay-tube-onlay transverse island preputial flap, previously described.¹⁵ Patients were all placed on weight-based prophylactic oral antibiotics post operatively with indwelling catheters or urethral stents for urinary drainage.

Outcomes

The primary outcome was the presence of postoperative recurrent ventral curvature. This was assessed primarily by artificial erection test with curvature measured by a goniometer if the patient underwent a subsequent hypospadias-related procedure, frequently a second-stage hypospadias repair. In follow up visits, families were instructed to take photographs of the penis with a lateral view during an erection, which was then brought to the clinic for review by the clinician (Fig. 2B). If the patient had a one-stage hypospadias repair without the need for subsequent procedures, recurrent ventral curvature was assessed by photographs taken by families, when available, or by parental history. Secondary outcomes included presence of corporal diverticulum, the presence of scarring on physical exam by the clinician, and parental reports of atypical systemic effects. Corporal diverticulum was defined as an outpouching of the corpora cavernosa ventrally or laterally observed on artificial erection test, photograph of erections, or parental history. Presence of scarring on physical exam was defined as induration or scarring palpated in area of corporoplasty at the last follow up visit; for patients who underwent a subsequent operation after corporoplasty with Cytal, documented scarring was performed in the visit prior to the staged operation. Adverse systemic effects were defined as

fevers, nausea or emesis or other systemic symptoms that do not typically accompany hypospadias repairs.

RESULTS

Of the 967 patients in the database, 312 had proximal hypospadias. Twenty patients had Cytal used during the hypospadias operations; 6 had Cytal used for indications other than corporal graft (eg, dorsal inlay graft in glans, waterproofing layer, and wound healing scaffold), and were excluded from analysis. Of the remaining 14 males who had Cytal used as corporal graft, 4 were still awaiting their second stage urethroplasty, and were thus excluded. Ten boys were identified who underwent correction of ventral curvature with Cytal as corporal graft who had completed planned operations. Median age was 18.6 months (IQR 14.6-27.0). Median follow up was 14.1 months (IQR 8.9-16.5). Three patients had prior hypospadias repairs before undergoing corporoplasty with Cytal (30%). Nine of 10 males (90%) had staged operations following the first operation with Cytal graft corporoplasty.

Individual clinical and operative characteristics are detailed in Table 1. Patient number 8 had Cytal laid over DTITA; all other individuals had a single transverse corporotomy with subsequent corporoplasty. Preoperative testosterone was used in 50% (5/10) of boys. All 5 boys had 3 doses of 25 mg testosterone intramuscularly monthly leading up to 1-2 months prior to operation. Mean ventral curvature after degloving was 80 ± 50 degrees.

All patients had straight erections postoperatively. Nine of the 10 patients (90%) had straight erections verified at a subsequent artificial erection test at least 6 months from the corporoplasty. The remaining patient underwent a double face onlay-tube-onlay transverse island preputial flap as a single-stage hypospadias repair and did not require any additional procedures. He had straight erections postoperatively per parental history. No corporal diverticulum developed in any patients. None of the patients demonstrated induration at site of corporoplasty on physical exam. There were no parental reports of atypical adverse systemic effects.

DISCUSSION

This is the first published report of the use of the ACell Cytal as corporal graft for correction of ventral curvature

Table 1. Clinical and operative characteristics of patients who underwent Cytal graft placement for corporoplasty for correction of ventral curvature

Patient#	Age at Operation (months)	Number of Prior Hypospadias Surgeries	Meatal Location other Indications for surgery	Ventral Curvature (degrees)	Concomitant Conditions	First Operation (all with concurrent corporoplasty with Cytal)	Second Operation	Assessment Method of Residual Curvature
1	27	0	Penoscrotal	60	Bilateral UDT, Wolff Hirschhorn	Double-face onlay-tube-onlay transverse island preputial flap, R orchiopexy, RIHR	Second stage, L orchiopexy, L IHR	Artificial erection test
2	14	0	Penoscrotal	180	Bilateral UDT (R testis brought down previously), Denys Drash, HTN, ESRD	First stage, laparoscopic L 1-stage orchiopexy, laparoscopic Mullerian remnant removal	Second stage, L orchiectomy	Artificial erection test
3	38	1	Penoscrotal, RVC after prior first stage	35	Bilateral UDT	Urethroplasty, chordee correction, R orchiopexy, R IHR	Double-face onlay flap from previous rotated transverse island preputial flap	Artificial erection test
4	11	0	Penoscrotal	90	None	First stage	Second stage, L tunica vaginalis flap harvest, L orchiopexy	Artificial erection test
5	14	0	Perineal	145	VSD	First stage	Second stage	Artificial erection test
6	17	0	Penoscrotal	45	None	Double-face onlay-tube-onlay transverse island preputial flap	None	Parental history
7	25	1	Perineal, RVC after prior First stage	Missing	Bilateral UDT	Re-do First stage, bilateral laparoscopic First stage Fowler Stephens orchiopexy	Second stage, laparoscopic Second stage Fowler Stephens orchiopexy	Artificial erection test
8	15	0	Penoscrotal	45	Mixed gonadal dysgenesis	Double-face onlay-tube-onlay	Second stage	Artificial erection test

Continued

Table 1. Continued

Patient#	Age at Operation (months)	Number of Prior Hypospadias Surgeries	Meatal Location other Indications for surgery	Ventral Curvature (degrees)	Concomitant Conditions (descended gonads)	First Operation (all with concurrent corporoplasty with Cytal)	Second Operation	Assessment Method of Residual Curvature
9	209 (17 years)	4	Coronal, RVC at puberty	60	None	transverse island preputial flap, L testis biopsy Chordee correction, skin Z-plasty for penile shaft coverage First stage	Buccal mucosal graft harvest and placement Second stage	Artificial erection test
10	20	0	Penoscrotal	60	None	First stage	Second stage	Artificial erection test

UDT, undescended testis; RVC, recurrent ventral curvature; IHR, inguinal hernia repair; R, right; L, left; VSD, ventricular septal defect; HTN, hypertension; ESRD, end stage renal disease; UCF, urethrocutaneous fistula.

in children with proximal hypospadias. All boys had straight erections, with the majority verified objectively in an artificial erection test in the subsequent operation. No corporal diverticula developed in the cohort, and all had supple corporoplasty sites on physical exam.

ACell, Inc. currently markets 3 structural configurations of its MatriStem UBM product. Cytal is the sheet form indicated for wounds; there are also micronized particulate forms and thicker sheet forms available for tissue reinforcement. This material is derived from acellularized basement membrane and tunica propria layers of the porcine bladder, and consists of extracellular matrix proteins that include collagens, glycosaminoglycans and growth factors.¹⁶ Currently commercially available prepackaged grafts reported for corporoplasty in the pediatric population include SIS (Cook Biotech, Lafayette IN) and Allo-derm (LifeCell Corporation, Branchburg NJ).¹ SIS is a collagen-based biomaterial harvested from porcine small bowel, while Allo-derm is a cadaveric-derived acellular human dermal collagen matrix. Autologous options include dermal grafts, tunica vaginalis grafts or tunica vaginalis flaps. Off-the-shelf grafts are attractive options when compared with dermal grafts, eliminating donor site morbidity associated with graft harvest. When able, it continues to be the authors' preference to use a well vascularized tunica vaginalis flap for as substrate for corporoplasties.¹⁷ However, prepackaged grafts do offer a reduction in operative time associated with eliminating tunica vaginalis harvest.¹

Available in 1-, 2-, 3- and 6-layers, Cytal Wound Matrix 1-Layer was our preferred choice given the suggested higher incidence of recurrent ventral curvature using multiple-layer SIS in the literature. Significant fibrosis and contracture of the corporal graft arising from 4-ply SIS when compared to use of 1-ply SIS has been reported, with similar surgical techniques from the same group of investigators.^{2,3} Although there are also reports where the number of layers of the graft did not alter the outcome of recurrent curvature,¹⁸ in a study involving rabbit models, Hafez *et al.* found a 25% contracture of the 4-ply SIS at 12 weeks compared with no contracture in the 1-ply group.¹⁹ On histological examination, the 4-ply SIS graft site was replaced by a dense fibrous tissue with patches of calcification, while the 1-layer SIS graft was completely replaced by well collagenized tissue, similar to that of tunica albuginea, without surrounding inflammatory infiltrate.¹⁹ Extrapolating from the SIS literature and the premise that both Cytal and SIS are extracellular matrices that serve as a scaffold for healing, designed to promote similar processes for tissue remodeling, our decision was to use 1-layer Cytal instead of multiple-layer Cytal.

The cost of graft material for institutions in the United States can differ based on contracted pricing. In our institution, the typical retail pricing of a single layer Cytal 3 × 3.5 cm is \$63 United States Dollars (USD). Using the sheet form of UBM over a median of 11 weeks with much larger dimensions, an institution calculated their average cost of ACell MatriStem UBM per week was \$152 USD.²⁰

In contrast, Alloderm, an acellular cadaveric dermal matrix that has been recently demonstrated by Palmer and Palmer in a preliminary case series as another commercial, off-the-shelf material that is safe for corporal grafting with positive initial outcomes, has a typical retail cost of \$500 USD.¹ SIS has a Medicare reimbursement of \$528 USD for outpatient physician application of the material.²¹ Based on our institution's pricing, we have found Cytal to be beneficial from a cost standpoint.

In our nascent experience with Cytal, we have found it to be effective for correction of ventral curvature without incurring donor site morbidity. However, our study has several limitations. First, follow up is relatively short at 14 months. Despite this shortcoming, all patients completed their planned surgeries with 90% having objectively verified straight erections through an artificial erection test in a subsequent procedure. Second, in contrast to typical operative steps with the use of grafts in corporoplasties, no repeat artificial erection test was performed immediately after Cytal corporoplasty. Third, our sample is small. As our experience in the use of Cytal as corporal graft in ventral penile lengthening in proximal hypospadias repair continues in the pediatric population, we aim to validate our results and report longer term outcomes.

CONCLUSIONS

In the short-term, single-layer Cytal is effective as corporal graft for correction of ventral curvature in children with proximal hypospadias without postoperative recurrent ventral curvature or induration.

FUNDING

None.

ETHICAL APPROVAL

The study was approved by the Institutional Review Board (IRB#190195).

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare. The authors have no financial interests in ACell Inc.

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