Short-term experience of porcine small intestinal submucosa patches in paediatric cardiovascular surgery

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Abstract

OBJECTIVES: Surgical reconstructions or palliations of congenital heart defects often require the utilization of patches, of which the ideal material has yet to be discovered. Recently, porcine small intestinal submucosa extracellular matrix (SIS-ECM) has been advocated as an alternative to conventional synthetic or biological patch material. Here, we present our initial experience with SIS-ECM in paediatric cardiovascular reconstructions.

METHODS: A retrospective review of all patients <18 years of age who had SIS-ECM implanted during surgery from July 2009 to September 2011 was performed. Chart review consisted of assessment of heart defect, operative procedures, implant location, echocardiograms, reinterventions and pathology studies related to any explanted SIS-ECM.

RESULTS: During the study period, 37 paediatric patients had SIS-ECM implanted during a cardiovascular reconstruction. Mean length of follow-up was 411 days (range 6–757 days). SIS-ECM was implanted in 48 cardiac locations as patches for septal defects (n = 26), outflow tract augmentation (n = 7) and valve reconstruction (n = 3). Eight of the patients required SIS-ECM patches in multiple locations. There was progressive stenosis in one RVOT patch requiring reoperation. Progressive stenosis in a near-circumferential pulmonary artery patch was present in 1 patient, requiring stent placement. All other patched structures remained patent.

CONCLUSIONS: SIS-ECM is suitable for the closure of septal defects. Use of SIS-ECM for the reconstructions of outflow tracts and great vessels carries a small risk of stenosis, especially in patches that form the majority of the vessel circumference. The long-term follow-up is needed to determine the risk of late stenosis.

Keywords: Congenital—cyanotic · Congenital—cyanotic · Great vessels · Vascular malformations

INTRODUCTION

The surgical repair of many congenital heart defects has improved over the past few decades and more patients are surviving into adulthood [1]. Despite improvements in congenital heart surgery procedural mortality, there remain a substantial number of patients who need multiple reinterventions [1]. The surgical repair of complex congenital heart defects frequently requires additional tissue in various forms, such as patches, conduits and valves that often require replacement over a patient’s lifetime because of degeneration, calcification or lack of growth. Current materials used in the reconstruction of complex congenital heart defects include processed allografts (pulmonary and aortic allograft), xenografts (bovine pericardium and porcine aortic valves) or synthetic materials (Gore-Tex, Dacron, mechanical valves).

The ideal patch material would be pliable, durable, inexpensive, non-immunogenic, easily handled and allow for growth rather than scar formation or calcification. Decellularized porcine small intestine submucosa extracellular matrix (SIS-ECM) patches have shown promising results in animal models of cardiovascular disease and have demonstrated patch remodelling and integration [2, 3]. Scholl et al. [4] demonstrated in their clinical study that in one case of explanted SIS-ECM augmentation of the tricuspid valve, there was replacement of the SIS-ECM with organized collagen and population of the former patch with endothelial-like cells. Large studies of the growth potential of the porcine SIS-ECM have not been conducted yet and there are no large comparative studies between porcine SIS-ECM and other implantable biomaterials used for cardiac reconstructions. Porcine SIS-ECM is currently approved by the Food and Drug Administration (FDA) for use in humans for a variety of reconstructions including cardiac patching, carotid artery repair, dural grafting, tendon repair and lower urinary tract reconstruction [5–8]. Only a few published studies exist that specifically evaluate...
the outcomes of SIS-ECM in congenital heart surgery for cardiac and vascular reconstructions [4, 9]. Here, we describe our experience using porcine SIS-ECM in congenital heart surgery.

MATERIALS AND METHODS

This study was conducted under an approved protocol from the University of California Davis Institutional Review Board. From 1 July 2009 to 1 September 2011, 37 patients underwent congenital cardiovascular reconstructions that utilized SIS-ECM (CorMatrix™, Alpharetta, GA, USA) in a non-randomized fashion at the discretion of the surgeon. The medical records of these patients were reviewed retrospectively. Patient demographic information, medical diagnosis, operative procedures, SIS-ECM placement location, clinical course including the need for reinterventions, echocardiograms and pathology studies related to any explanted SIS-ECM or surrounding tissues were noted.

Patients were divided into four groups based on implant location: septal defect patching, vascular patching, outflow tract patching or valve reconstruction. Echocardiograms that had been obtained as part of the routine paediatric cardiology follow-up were reviewed with specific attention to the areas where SIS-ECM patches were implanted. The presence of aneurysmal changes, recurrence of septal defects and pressure gradients in vessels or outflow tracts were recorded.

RESULTS

The SIS-ECM was used in various locations for multiple cardiac and vascular defects: atrial septum (n = 11), pulmonary artery (n = 12), superior cavopulmonary anastomosis (n = 7), right ventricular outflow tract (RVOT, n = 6), supravalvular aorta (n = 3), pulmonary root (n = 3), ventricular septum (n = 2), pulmonary valve (n = 2), superior vena cava–right atrial junction (n = 1) and left ventricular outflow tract (LVO, n = 1). Eight patients underwent implantation of SIS-ECM patches in >1 location. Location of implantation and fashioning of SIS-ECM were at the surgeon's discretion. Patches were sewn in using 6-0 or 7-0 Prolene sutures typically in a running fashion for good approximation of the SIS-ECM and native tissue. The mean age of patients at the time of surgery was 18.2 ± 47.7 months (median of 5.5 months, range 2 days – 7.5 years). The mean length of follow-up was 411 ± 225 days (range 62–757 days). Sixty five percent of patients were male (24/37). The frequency of follow-up echocardiograms was performed at the discretion of the patient's cardiologist.

All patients were evaluated by transthoracic echocardiograms at discharge following their operations. Subsequent echocardiograms were performed at intervals decided by the patient's cardiologist, with a mean echocardiogram follow-up length of 371 days (mean of 393 days). There were no cases of thrombosis, aneurysm, calcification or tearing of the patches identified during this follow-up period.

Mortality

There were a total of 4 deaths (10.8%), and none was believed to be related to the implanted SIS-ECM. There was 1 early death, Patient 17, due to low cardiac output syndrome after a repair of tetralogy of Fallot with absent pulmonary valve. Patient 32 died from recurrent supravalvular aortic stenosis and subsequent myocardial infarction 2 months after surgery secondary to progressive coronary ostial stenosis, which was not believed to be related to the remotely implanted SIS-ECM away from the coronary ostium. Patients 12 and 37 died of non-cardiac related issues over 8 months after the initial surgery involving SIS-ECM implantation. Patient 12 had multiple non-cardiac congenital abnormalities and suffered septic shock with anoxic brain injury and then treatment was transitioned to palliative care until eventual death at home. Patient 37's death was due to a perforated colon secondary to Clostridium difficile colitis.

Complications related to SIS-ECM

Two patients required reintervention related to the SIS-ECM implant (Table 1): Patient 18 with RVOT obstruction after SIS-ECM transannular patch placement and Patient 31 with early stenosis after left pulmonary artery reconstruction with SIS-ECM. Patient 4 required reoperation unrelated to SIS-ECM patch placement, but during the reoperation a portion of the previous patch was removed and then histologically examined.

Patient 18 underwent RVOT augmentation (transannular patch) for tetralogy of Fallot. After repair of the RVOT with an SIS-ECM patch, the patient developed progressive RVOT obstruction. The initial discharge echocardiogram demonstrated a pressure gradient of 34 mmHg at discharge 3 days following surgery and a peak pressure gradient of 101 mmHg at 467 days after surgery. Reoperation occurred 553 days after the original operation. During reoperation, the SIS-ECM patch was noted to be fibrotic and thickened, which was believed to be the cause of the elevated gradient across the RVOT. There were no signs of patch dehiscence or evidence that the obstruction was related to the sewing technique. The SIS-ECM was replaced with a Gore-Tex patch without any further complications. The explanted patch was shown to have signs of chronic inflammation and fibrosis (Figure 1A).

Patient 31 was diagnosed with hypoplastic left heart syndrome and underwent Stage II palliation with a superior cavopulmonary anastomosis and extensive left pulmonary artery reconstruction with a SIS-ECM patch comprising a significant portion of the total circumference of this vessel. The patient was discharged from the hospital 6 days after this procedure, but was readmitted 6 days later with pleural effusions. The patient's clinical course was notable for resolution and recurrence of the pleural effusions. During the patient's hospitalization, echocardiogram and cardiac catheterization demonstrated left pulmonary artery stenosis (2.2–2.6 mm in diameter) that was believed to be the cause of his recurrent pleural effusions. After balloon dilatation and stent placement, the pleural effusions resolved and the patient was discharged home in stable condition.

Patient 4 required reoperation for a residual ventricular septal defect unrelated to her initial SIS-ECM implantation as a transannular patch, unicusp pulmonary valve and primum atrial septal defect (ASD) patch. A small portion of the primum ASD patch was biopsied during the reoperation and sent for pathological studies, which demonstrated chronic inflammation, myxoid degeneration and numerous eosinophils (Figure 1B).

RVOT pressure gradients

Patients with SIS-ECM patches were evaluated for increased pressure gradients in the implanted regions. In a subgroup analysis, the 5 patients surviving to discharge with RVOT patches had an
average increase of 47.8 percent pressure gradient from immediately following discharge to the most recent echocardiogram with an average follow-up time of 541 ± 245 days (Figure 2). Aside from the previously described case of left pulmonary artery stenosis requiring stent placement, all other vascular patches (96%) remained patent with no need for intervention.

Unicus pulmonary valve creation with SIS-ECM

Three patients underwent unicus pulmonary valve creation as part of their congenital cardiac defect repair. Patients 14 and 17, both diagnosed with tetralogy of Fallot who had a unicus pulmonary valve creation with the SIS-ECM. In patient 14, the most recent echocardiogram at 699 days demonstrated severe to free pulmonary insufficiency. Patient 17 died of low cardiac output and it was not possible to evaluate their valve over a significant amount of time. Patient 4 was diagnosed with a complete AV canal defect and underwent SIS-ECM implantation at 32 months of age as a RVOT patch and pulmonary unicus valve creation. The patient underwent reoperation for LVOT obstruction unrelated to the SIS-ECM as described above. The most recent echocardiogram taken at 631 days showed mild to moderate pulmonary insufficiency with mild flow acceleration of 2.2 m/s across the unicus valve. None of the unicus pulmonary valve creations was noted to be stenotic, but both valves showed signs of insufficiency that may be indicative of valve shrinkage.

**DISCUSSION**

Allografts were first introduced in 1962 by Donald Ross [10] but were found to have problems maintaining patency due to calcification and rapid stenosis. Glutaraldehyde-treated porcine xenografts mounted in Dacron tubing were introduced thereafter but also suffered from similar complications. Cryopreserved allografts later came into favour due to the improved ease of handling relative to the Dacron mounted counterpart, but results in congenital heart surgery were similar with regard to graft failure requiring conduit exchange. To avoid conduit exchange and graft failure, an optimal requirement of cardiovascular patch material in congenital heart surgery would be the ability to become viable, grow, remodel and repair itself throughout the patient’s life.

SIS-ECM has shown promise in a few preclinical studies that have demonstrated minimal scar formation and eventual remodelling of the material following implantation [11, 12]. One study in rats demonstrated that RVOT reconstruction with SIS-ECM patches resulted in new cardiac tissue formation in the patched areas and ventricular dimensions near normal baseline values when compared with Dacron reconstructions of the RVOT that resulted in significant ventricular dilatation [13]. The newly formed cardiac tissue was disorganized in comparison with the native myocardium but demonstrated integration of the patch into the surrounding tissue.

Understandably, studies showing tissue remodelling have led to a great deal of optimism as decellularized SIS-ECM would represent a relatively inexpensive and easily implantable solution that could potentially decrease the rates of graft failure. The animal studies that demonstrate new native tissue formation during remodelling also suggest there may be a chance for growth and reconstitution of the native tissue, which is particularly desirable in the paediatric population. These two factors coupled with an easily handled, abundant and durable material make porcine SIS-ECM a very promising biomaterial.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age at surgery</th>
<th>Time until intervention</th>
<th>Patch use</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Tetralogy of Fallot</td>
<td>9 months</td>
<td>555 days</td>
<td>Right ventricular outflow tract patch</td>
<td>Right ventricular outflow tract obstruction</td>
</tr>
<tr>
<td>31</td>
<td>Hypoplastic left heart syndrome</td>
<td>6 months</td>
<td>23 days</td>
<td>Glenn augmentation and left pulmonary artery patch</td>
<td>Stenosis of left pulmonary artery, recurrent pleural effusions</td>
</tr>
</tbody>
</table>

SIS-ECM: small intestinal submucosa-extracellular matrix.

**Table 1: Complications associated with SIS-ECM patches requiring intervention**

Figure 1: (A) Explanted SIS-ECM RVOT patch (Day 555) in Patient 18, H&E staining demonstrates similar chronic inflammation and fibrous collagenous tissue (magnification ×20). (B) Biopsy of SIS-ECM ASD patch in Patient 4 taken 336 days after implantation (magnification ×40). H&E staining demonstrates chronic inflammation including eosinophils and diffuse myxoid degeneration.
However, optimism must be tempered with caution when applying porcine SIS-ECM to new applications outside of current FDA-approved indications. Porcine SIS-ECM patch marketed as Surgisis™ was evaluated in a clinical trial for carotid artery repair following endarterectomy [14]. Surgisis™ is produced differently but is similar to CorMatrix™ in that it does not have protein cross-linkage. In the study, 7 of 76 patients (9.2%) were found to have pseudoaneurysms within 10 weeks of endarterectomy and three required reoperation for stenosis. They concluded that the material required a minimum thickness for use in carotid artery repair to prevent aneurysm formation.

The CorMatrix™ SIS-ECM patches used in this study are currently FDA approved for pericardial closure, cardiac patching and recently, for carotid artery repair. In our study, there were no instances of aneurysms when using SIS-ECM material. In the patients who had material removed, there were no indications of patch thinning or failure, rather, in each case the material appeared to be thickened and fibrotic. In patches used in high-pressure areas, such as supravalvular aortic patches, there were no signs of aneurysm and they functioned well over the time-frame for which the patients were followed. CorMatrix™ has higher tensile tear strength on average than the Surgisis™ lot that developed the pseudoaneurysms in the abovementioned clinical trial (29.67 ± 6.09 vs 17.81 ± 3.59 N, normalized for cross-sectional area). However, as shown in the Surgisis™ trial, there can be great variability of the SIS-ECM biomechanical properties between different lots. It is difficult to speculate regarding the effectiveness of the Cormatrix™ SIS-ECM in high-pressure systems with such a limited number of patients receiving augmentation in the form of high-pressure vascular patches. In a high-pressure system, particularly the supravalvular aorta, the ideal biomaterial must have the tensile strength and durability to withstand high pressures without aneurysm formation but at the same time have a degree of elasticity that does not inappropriately raise cardiac afterload. There are most likely numerous other differences between the products that cannot allow for direct comparison such as the decellularization process and other manufacturing techniques. Our population is very different from that of the Surgisis™ trial and expectations of the patch implants are as well. The immune response in the elderly undergoes a proinflammatory cytokine shift [15] and can therefore result in a very significantly different response to foreign implanted materials in comparison with paediatric patients. As a result, it is impossible to generalize implantable biomaterial studies in adults to children. Also, the requirements of the ideal material differs significantly between adults and children, with materials used in children requiring substantial growth potential while for adults, durability is the most important factor. In theory, the process of remodelling, particularly the inflammatory aspect, followed by patch invasion by native cells and eventual degeneration, may leave tissue susceptible to aneurysm and rupture. One could imagine that even the ideal tissue would have to find a balance between fibrosis leading to stenosis, or remodelling with the potential of aneurysm formation with each patient having a varied response. These factors, including patient age, patch location and its hemodynamic environment, and patient’s immune response will all be factors in biomaterial selection. It remains unclear where current SIS-ECM is along that spectrum and further studies are warranted to find the ideal situation for patch use.

Decellularization itself has multiple techniques that can alter ECM three-dimensional structure. Typically, decellularization is achieved through a combination of physical, chemical and enzymatic methods [16]. Various decellularization techniques have led to the creation of multiple commercial products derived from diverse tissues with different physical properties and applications. Decellularization in theory would limit the immunogenic effect by stripping the ECM of cells and antigens that fuel the immune response. The ECM between species is well conserved and if well decellularized, should not elicit a strong immune response. Scar formation appears to be affected strongly by the modification of the ECM scaffolds following decellularization. Chemical cross-linking of proteins in the material allows for conditioning of the material for useful biomechanical properties, such as increased tensile strength [17], but the modification prevents degradation and tissue remodelling, resulting in increased scar formation.

It has been suggested by Badylak et al. [18] that the non-cross-linked SIS-ECM, such as the one used in this study,
incites an immunoregulatory and proangiogenic macrophage response instead or an inflammatory, scar-forming response. In our explanted and biopsy samples, there were continued inflammation and fibrosis as far as 555 days after implantation. This indicates that there was infiltration of the patch with host cells, primarily inflammatory cells as one would expect with any foreign material as well the formation of collagen, but at 555, the collagen formation was more consistent with scar formation than tissue integration. However, these samples were taken from patients who had obvious signs of clinical failure with patch augmentation and may not accurately represent the patients who did not have any clinical signs of patch failure. We suspect that other factors may play a role in the remodeling response and may include patch size (i.e. larger patches do not remodel completely before a scar response), implantation location, hemodynamic environment and patient age. The lack of aneurysm formation in our small number of patients with aortic patching may have been attributed to the relatively healthy adjacent vascular tissue of these younger patients when compared with the older patients with diseased vascular tissue in the abovementioned clinical trial of carotid artery patching with SIS-ECM.

One patient in our study suffered from RVOT obstruction following SIS-ECM augmentation for tetralogy of Fallot. Two institutional studies not employing the SIS-ECM have shown that reintervention specifically for RVOT obstruction occurs at a rate between 18 and 31% within 5 years [19, 20]. The rapid and progressive stenosis/scarring of the RVOT patch were only seen in this particular patient and suggest an early inflammatory/reactionary process; however, no markers of inflammation were obtained in the early postoperative course of this patient. In the 2 patients who had unicusp valves repaired, there was no indication of stenosis. However, one of the patients had severe insufficiency, indicating complete failure of the valve. Other studies evaluating porcine SIS-ECM for congenital cardiac surgery also had very few pulmonary valve reconstructions from unicusp valves [8, 9]. The study conducted by Scholl et al. [4] currently describes the greatest experience with four unicusp valve repairs. The results ranged from no insufficiency to severe insufficiency with almost equal distribution across the ranges. None of the valves reconstructed in any of the studies became stenotic, but each showed signs of insufficiency. With such little experience, it is difficult to make any conclusions on the efficacy of SIS-ECM in valve creation or reconstruction.

In our study, the majority of SIS-ECM patches performed well in paediatric cardiovascular reconstructions, particularly those with septal defects or vascular patch augmentation remote from the outflow tract. In patients with SIS-ECM ventricular outflow tract reconstructions, we noticed increases in their outflow tract gradients, but our sample size is too small to draw any major conclusions except that the close follow-up is needed in this group of patients. In vascular patch augmentation, the SIS-ECM patches maintained patency and only required balloon dilatation in 1 patient in which a large patch was used to reconstruct the majority of the circumference of a branch pulmonary artery. This result suggests that this situation should be avoided and that SIS-ECM circumferential conduits of substantial length may be prone to stenosis. Overall, SIS-ECM septal defect patching appears to be its safest and most durable application. Further longitudinal studies of greater magnitude are necessary to assess the performance of the SIS-ECM in congenital cardiac applications and to define better the limitations of this material.

Conflict of interest: none declared.

REFERENCES