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Repair of Nasal Septal Perforation with Porcine Small Intestinal Submucosa Xenograft

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**Repair of Nasal Septal Perforation with Porcine Small Intestinal
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ABSTRACT

Background:

Numerous techniques have been described for nasal septal perforation repair, with various degrees of success in achieving closure. Evidence supports the use of bilateral mucoperichondrial advancement flaps with interpositional grafting for greatest success. Many surgeons use autografts such as fascia, cartilage, bone, and pericranium, however, extracellular matrices have also become popular.

Objective:

We analyze factors determining the success of nasal septal perforations repaired using an acellular, freeze-dried interpositional xenograft derived from Porcine Small Intestinal Submucosa (PSIS).

Methods:

Patients with septal perforation repaired by the senior author from 1998 to 2006 were examined in a retrospective chart review with regard to perforation size, etiology, pre- and postoperative symptoms, follow-up, outcomes and complications.

Results:

Forty-seven PSIS repairs were performed on 46 patients. Two procedures were planned staged procedures. **Of the total 47 procedures, 41 (87.2%) continued to be closed at the site of repair during the follow up period.** Follow up ranged from 6 months to 4.9 years with a mean of 18.3 months. Two patients (4.3%) were found to have perforations at the site of closure in the immediate post-operative period. One patient (2.1%) perforated at the site of closure after the immediate post-operative period. Subjective symptom scores demonstrated improvement in crusting, epistaxis and obstruction postoperatively. Larger perforations correlated with poorer outcomes.

Conclusions:

The authors conclude that closure of nasal septal perforation with an interpositional xenograft derived from PSIS compares favorably to published results for autografts with advantages including absence of donor site morbidity, easy graft modification and manipulation, and shorter operative time.

Introduction:

Numerous techniques have been advocated for repair of nasal septal perforations [1-3]. For symptomatic patients who fail conservative management, the surgical goals can largely be agreed upon to include: 1) Restoration of normal function and physiology to the nose and 2) Reduction of symptoms [4]. However, a consensus on the ideal procedure to achieve complete closure of nasal septal perforations remains elusive. Reconstruction of the nasal septum in three distinct layers using bilateral mucoperichondrial flaps with interpositional grafting has gained widespread acceptance [1, 2, 4, 5]. This method consistently demonstrates closure rates greater than 70% and frequently higher than 90% in numerous series. These rates match favorably with respect to closure by mucoperichondrial advancement omitting the use of interposition grafting [1]. The mechanism for this greater success is theorized to include 1) improved mucosal cellular migration with the graft acting as a scaffold 2) the graft providing a barrier between the bilateral incision lines during healing and 3) the allowance of incomplete mucosal closure on one side of the septum where excessive tension would be required [1, 4]. Even amongst surgeons who employ this method to achieve closure of nasal septal perforations, there is considerable diversity in the choice of interpositional graft material.

Autologous grafts used for the repair of nasal septal perforations include temporalis fascia, septal cartilage and bone, pericranium, mastoid bone and perichondrium, tragal cartilage and perichondrium, ethmoid bone, iliac crest, conchal cartilage, and skin graft [2, 6]. Recently, use of manufactured allografts such as freeze-dried acellular human dermis, xenografts such porcine small intestinal submucosa (PSIS), and synthetic materials such as bioactive glass has been described [6-9]

Porcine small intestinal submucosa (“SurgiSIS”, Cook Biotech Inc, West Lafayette, IN) is a biologic, acellular, freeze-dried, soft tissue graft. It is purified, washed in solutions to eradicate viruses, and sterilized. Small intestinal submucosa mimics the extracellular matrix (ECM) environment. Fibrillar collagens and adhesive glycoproteins serve as a scaffold for cellular migration, and regulatory factors such as glycosaminoglycans, proteoglycans, and growth factors are reportedly retained following processing [10]. Following implantation, SIS encourages angiogenesis, epithelial and connective tissue growth and differentiation, and evolution of recipient site ECM. Porcine SIS has been used in a wide variety of surgical applications including hernia repair, urethral and ureteral reconstruction, pelvic floor reconstruction, and chronic wound dressing.

The senior author (EP) previously reported a case series of 10 patients with nasal septal perforations repaired using an external rhinoplasty approach, bilateral bipediced mucoperichondrial advancement flaps and interpositional graft consisting of porcine small intestinal submucosa [7]. A rate of closure of 100% was achieved in the early follow-up period. This article updates the series to include 46 patients repaired using this approach, and reviews the series demographics, etiology, outcomes, and risk factors for perforation and complications of repair.

Patients and Methods

Following approval from the Institutional Review Board at Thomas Jefferson University, a retrospective chart review was performed on all patients undergoing nasal septal perforations repair using porcine small intestinal submucosa as an interpositional

graft by the senior author (EP), during the time period from 1998-2006. Of a total of 53 patients undergoing septal perforation repair during this same time period, 46 patients underwent 47 repairs using PSIS interpositional graft and the surgical method. The remaining seven patients were closed using silicone sheeting, rib graft, or local advancement flaps alone because of large unstable defects or inadequate mucosa. Two patients in the series had tissue expanders placed, with the expanded mucosa employed at the time of septal perforation repair. One patient underwent revision septal perforation repair with repeated PSIS placement.

Patients with symptomatic nasal septal perforations were considered candidates for repair with PSIS graft. Patients with a history of cocaine abuse were required to abstain for at least 6 months prior to consideration of repair, as well as demonstrate a negative preoperative drug screen. Laboratory workup included screening for granulomatous diseases, rheumatologic diseases and syphilis.

Patients received perioperative antibiotics and corticosteroids. Nasal septal perforation closure was achieved using either an endonasal (n=6) or open rhinoplasty (n=41) approach with bilateral mucoperichondrial advancement flaps covering an interpositional PSIS graft [7]. The PSIS was rehydrated in a gentamicin-normal saline solution for 10 minutes, then shaped and trimmed to the appropriately sized interpositional graft [7]. Septal biopsies were performed intraoperatively. Patients had 0.25 mm silicone splints secured on either side of the repair, which were removed after 3 weeks.

A retrospective chart review abstracted presenting symptoms and an attempt was made to determine the general effect of surgical repair on these symptoms. Two authors (PSM and AAS) subjectively determined the severity of these symptoms both pre and post-operatively as described by office notes and symptom questionnaires. A 4-point scale was created, with "0" representing a lack of symptoms (e.g. for epistaxis, "0" means patient did not experience epistaxis), and scores of 1, 2, and 3 representing mild, moderate, and severe symptoms, respectively.

Results:

Twenty-four percent (11/46) of patients were male. Patient ages ranged from 17-69 years with a mean of 40.4 (stddev=11.4). 63% (29/46) were self-described lifetime nonsmokers, while 19.6% (9/46) were former smokers and 17.4% (8/46) current smokers. The size of perforations ranged from 0.5 cm to 4.7 cm in largest dimension, with a mean approximately 1.7 cm (stddev=0.8 cm). Patients were followed for an average of 18.3 months (stddev=14.2 months), with a range in follow up from 6 months to 4.9 years. See Table 1 for a summary of patient characteristics.

Table 1. Patient Characteristics		
Age (mean, std)	40.4	11.4
Gender (N=46)		
Male	11	23.9%
Female	35	78.3%
Smoking Status (N=46)		
Non-Smoker	29	63.0%
Former Smoker	9	19.6%
Current Smoker	8	17.4%
Perforation Sizes (N=47)		
<10 mm	5	10.6%
10-19 mm	29	61.7%
20-29 mm	7	14.9%
30-39 mm	4	8.5%
>=40 mm	1	2.1%
Largest Dimension of Perforation (mean, std)*	1.7 cm	0.8 cm
Follow Up (mean, std)	18.3 mos	14.2 mos

N=46 patients, or 47 procedures

Previous surgery, cocaine use, and previous trauma were the most common determined etiologies for these patients (Table 2).

Table 2. Contributing Etiology	N=47	%
Surgery	20	42.6%
Cocaine Use	13	27.7%
Trauma (i.e. fracture, picking, cautery)	11	23.4%
Idiopathic	5	10.6%
Infection/Septal Abscess	4	8.5%
Granulomatous/Systemic	3	6.4%
Sprays	2	4.3%
Occupational Exposure	1	2.1%

Some patients had more than one contributing etiology

The three most frequently reported presenting symptoms were, in descending order: nasal obstruction, crusting, and epistaxis (Table 3).

Table 3. Presenting Symptoms	N=47	%
Obstruction	38	80.9%
Crusting	27	57.4%
Epistaxis	21	44.7%
Chronic Sinusitis/Chronic Sinus Complaints	19	40.4%
PND	13	27.7%
Anosmia	6	12.8%
Whistling	3	6.4%
Rhinorrhea	3	6.4%

Some patients had more than one presenting symptom

Outcomes

Closure

Forty-seven PSIS repairs were performed on 46 patients. Of the total 47 procedures, 41 (87.2%) continued to be closed at the site of repair during the follow up period. Two procedures were staged, with a planned incompletely closed perforation at the first stage. Excluding these staged procedures, 41/45 (91.1%) continued to be closed at the site of repair during the follow up period.

Failure

Of the total 47 procedures, six perforations (12.8%) remained during the follow up period. Two of the perforations were in the patients scheduled to undergo staged procedures and will be discussed below. The remaining four perforations developed in patients who underwent primary procedures.

Of the total 45 planned complete closures, one patient developed a perforation at the site of closure after the immediate post-operative period (termed “Reperforation”). Three patients developed perforations at sites separate from the site of surgical repair (termed “Second Perforation”). Of note, one of these appeared to be at the site of a splint suture and remains stable at 2mm.

As mentioned above, two failures were in patients scheduled to undergo staged procedures with the expectation of incomplete closure in the immediate post-operative period (termed “Residual Perforation”). Only one of these patients had undergone secondary procedure at the time of writing. The other staged patient had her perforation significantly reduced (1.5 cm to 0.2cm) by the initial procedure, and has not pursued the second stage of operation given the relief of presenting symptoms.

The outcomes of the procedures are listed in Table 4.

Table 4. Outcomes	N	%	Description
Primary Procedures	45		Planned complete closure
Staged Procedures	2		Planned incomplete closure
Total	47		Total # PROCEDURES (not patients)
Closures	41	87.2%	Total # of HEALED perforations at site of repair, including staged
Failures	6	12.8%	Total # of perforations during the follow up period, including staged
Reperforation	1	2.1%	Perforation at repair site, initially closed
Second Perforation	3	6.4%	Perforation separate from repair site
Residual Perforation	2	4.3%	Intentional perforation in the immediate post-operative period

As the ultimate goal of this analysis is to identify risk factors that might allow proper selection of patients and individualized procedures, it is instructive to examine carefully the failures, which include patients who required staged procedures, developed re-perforation, or second perforations

Table 5 describes the patients in this study who had subtotal closure of their nasal septum. Two procedures were planned staged procedures. Both of these patients had septal perforation repair attempts prior to initial consultation, and 3 cm perforations.

One patient developed re-perforation. Patient 3 had a near-total perforation, approximately 4.7 cm x 3.4 cm with saddle nose deformity. She had concurrent rhinoplasty and repair of nasal vestibular stenosis. Unfortunately, she restarted intranasal cocaine use postoperatively. No closure was planned given the cocaine use and asymptomatic nature of this re-perforated septum.

Two patients, Patients 4 and 5, had residual perforations. Patient 4 represents the second stage of Patient 1. She underwent placement of tissue expanders in the nasal floor. Patient 5 is a patient with sarcoidosis, who required tissue expanders as well for adequate mucosal tissue for advancement. She achieved approximately 80% closure and did not proceed with a subsequent procedure given the relief of her symptoms. Of note, both procedures with tissue expander placement resulted in residual perforation. The senior author has discontinued use of tissue expanders in the setting of nasal septal perforation repair.

Three patients (Patients 6, 7, and 8) developed new perforations at a site separate from the original perforation. The second perforations arose at sites near the original perforation and may represent areas of denuded septum during the advancement flap rotation or devascularized tissue from elevation and rotation of the mucoperichondrial flaps. One of these clearly resulted from the splint suture in the anterior septum.

Table 5. Description of Patients with Incomplete Closure									
ID	Age	Sex	Etiology	Perforation Size (mm)		Repair	Outcome	Defect Size (mm)	Notes
				Largest Dimension	Other Dimension				
1*	53	F	infection - MRSA	30	13	Open/Surgisis/MP flap/Buccal flap	Staged	22	prior perforation repair
2	39	F	cocaine/surgery	30	15	Surgisis/MP flap	Staged	10	h/o prior perf repair, refused rhinoplasty, no floor mucosa
3	32	F	cocaine	47	34	Surgisis/MP flap	Reperforation	5	near total perf;cont'd cocaine; revision rhinoplasty
4*	57	F	infection - MRSA	22	NR	Surgisis/MP flap/T XP	Residual	3	had previous perforation repair x2, 2nd stage
5	44	F	sarcoid/surgery	32	22	Surgisis/MP flap/T XP	Residual	6	sarcoidosis
6	17	F	idiopathic	15	10	Surgisis/MP flap	2nd perforation	3	superior to repair, rheum w/u ongoing
7	35	M	surgery	20	18	Surgisis/MP flap	2nd perforation	2	posterior to repair
8	41	F	surgery	15	NR	Surgisis/MP flap	2nd perforation	2	anterior to repair, from splint suture

* - denotes that this is the same patient, who underwent 2 separate procedures

Symptoms

The results of the preoperative and postoperative profile for the three most commonly reported presenting symptoms are documented in **Table 6**. Each of the 3 symptoms is measured on a 4-point scale (0, 1, 2, 3) based on severity of the symptom. A clear shift toward improvement is seen postoperatively. We considered the difference in score (change score = post-op score – pre-op score) as a measure of the change in severity of the symptom. The number of pre-repair symptoms and post-repair symptoms differ, because one patient underwent two procedures. The patient who did not complete the 2 stage procedure is excluded from this table.

Table 6. Symptom Scores				
	Pre-Repair Symptoms		Post-Repair Symptoms	
	N	%	N	%
Crusting				
0 (Not a symptom)	17	37.8	38	82.6
1 (Mild)	12	26.7	7	15.2
2 (Moderate)	13	28.9	1	2.2
3 (Severe)	3	6.7	0	0
Epistaxis				
0 (Not a symptom)	24	53.3	41	89.1
1 (Mild)	13	28.9	5	10.9
2 (Moderate)	7	15.6	0	0
3 (Severe)	1	2.2	0	0
Obstruction				
0 (Not a symptom)	7	15.9	21	45.7
1 (Mild)	16	36.4	17	37
2 (Moderate)	18	40.9	6	13
3 (Severe)	3	6.8	2	4.4

We found that major symptoms improved after surgery (Table 7), as expected. Even the patients with subtotal closure of the nasal septal perforation routinely experienced a dramatic improvement of their symptoms, sometimes obviating the indications for further surgical repair. Table 7 displays the frequencies of each possible change score (-3 to +2, with negative values indicating improvement in severity of symptoms) and tests whether, on average, the change score is different from 0. We used the Wilcoxon signed rank test for this, since the data, being a difference of scores, is quite non-normal. We found that all the symptoms showed improvement on average after surgery. 47% showed improvement in epistaxis, 54.55% in obstruction and 55.56% in crusting.

We did note a persistent and paradoxical increase in obstructive symptoms in 5 patients (10.9%) postoperatively. Two of these patients were found to have exuberant granulation and regrowth at the repair site that necessitated surgical intervention. The remainder experienced primarily chronic sinus complaints.

Table 7. Change in Symptom Scores									
Change from Pre- Repair to Post-Repair	Epistaxis*			Obstruction**			Crusting*		
	n	Cumulative %	p	n	Cumulative %	p	n	Cumulative %	p
-3	1	2.27	<.0001	1	2.27	0.0002	2	4.44	<.0001
-2	4	11.36		9	22.73		13	33.33	
-1	16	47.73		14	54.55		10	55.56	
0	22	97.73		14	86.36		17	93.33	
+1	1	100		5	97.73		2	97.78	
+2	0	100		1	100		1	100	

*n=45, **n=44

p from Wilcoxon signed rank test

Taking into account all patients, including planned staged patients, statistical analysis does correlate repair outcome with perforation size. Table 8 compares, using a two-sample t-test, the mean perforation size between patients with closed perforation post-surgery (~1.5 cm) and patients with the perforation not closed post-surgery (2.6 cm). We find that this average difference of 1.1 cm is statistically significant (p-value=0.011), reinforcing the observation that larger perforations are more likely to have worse outcomes.

Table 8. Perforation Size and Repair Outcome	Largest OR Measurement*	
	mean	std
Perforation NOT Closed	26.22	10.02
Perforation Closed	15.21	5.63
Mean Difference	11.01	p = 0.011

*n=45

Other results

Biopsy results were available for 35 patients. Two of these (5.7%) supported a diagnosis for granulomatous disease, and the remainder demonstrated various degrees of inflammation without contributing significantly to the diagnostic evaluation. One of the biopsy positive patients was known to have sarcoidosis, and the other had no clinical evidence supporting a systemic disease process. Of two patients known to have sarcoidosis, one (50%) revealed granulomatous disease on biopsy. No nasal septal biopsies led to diagnosis of an unknown systemic process. This is consistent with the findings of Diamantopoulos et al. [11] that demonstrate the low yield of this convention.

Discussion

The septal perforation closure rates cited in this study correspond favorably with those reported by other authors. Reviews of the literature reveal that reconstruction of the nasal septum in three distinct layers using mucoperichondrial flaps with interpositional grafting achieves high rates of closure. However, no consensus on the material for interpositional grafting is apparent. Autologous grafts (temporalis fascia, septal cartilage and bone, pericranium, mastoid bone and perichondrium, tragal cartilage and perichondrium, ethmoid bone, iliac crest, conchal cartilage and skin graft) all require a donor site that can add to procedural morbidity, complications such as hematoma and wound infection, and increased operative time. Autografts can result in thin, awkward flaps (fascia), or bulky material that must be modified or thinned (bony and cartilaginous grafts). Allografts and xenografts that can reconstruct the cartilaginous layer with similar outcomes may offer a compelling alternative if their use is not associated with increased risk. Currently, published available alternatives include acellular human dermal [6, 8], bioglass [9], and porcine small intestinal submucosa [7]. All of these obviate the need for graft harvest, and eliminate donor site morbidity.

The senior author (EP) previously published a series of 10 patients with nasal septal perforations repaired using an external rhinoplasty approach, mucoperichondrial bipedicled advancement flaps with interpositional graft using PSIS xenograft. The results in this small case series with short follow up (3-12 months) were very promising, given the 100% closure rate. The present study includes longer follow-up data and a much larger number of patients. The overall closure rate of 87.2% is comparable to rates cited by authors employing a wide variety of surgical approaches, techniques, and interpositional grafts [1].

PSIS was chosen as a material for interpositional grafting given the multiple advantages over autografts previously listed as well as theorized physiologic factors. Advantages over autografts are listed above. Technical advantages of this graft include the ease with which the graft may be trimmed, shaped and modified, the uniformity of thickness, the ease of readiness (10 minute rehydration), and graft pliability. The physiologic basis for use includes the preservation of extracellular matrix components that enhance wound healing. The fibrillar collagens and glycoproteins provide a scaffold for epithelial and connective tissue migration. Glycosaminoglycans, proteoglycans, and growth factors are retained and help to regulate the response to injury. Thus, PSIS serves requisite functions as a bioactive interpositional graft similar to autografts.

PSIS is contraindicated in patients with allergy or sensitivity to porcine products. The porcine derivation of this product should certainly be disclosed to patients with potential religious or cultural objections to its use.

In our experience, PSIS successfully formed a neoseptum with sufficient integrity to remain stable during inspiratory and expiratory forces. In the one patient who underwent second stage septal perforation repair, this neoseptum could be separated into two flaps that could receive a second interpositional graft of PSIS between the leafs. In fact, the method of reconstructing the nasal septum in three layers with a bioactive interpositional graft could theoretically encourage neocartilage formation. Two patients returned to the operating room in this series for management of nasal obstruction secondary to robust neoseptum formation. Upon pathologic evaluation of specimen retrieved from the site of prior septal perforation repair with PSIS, one of the specimens

identified “fragments of fibrocartilage consistent with nasal septum”, while the other revealed “reactive fibrosis, scattered chronic inflammatory cells and focal multinucleated giant cell reaction.”

Conclusions

Surgical repair of nasal septal perforations using porcine small intestinal submucosa for interpositional grafting appears to be a viable alternative technique, with closure outcomes rivaling those generally accepted by otolaryngologists. The comparable biologic activity, coupled with ease of use and lack of donor site morbidity present a clear advantage over autograft materials.

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