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Porcine small intestinal submucosa (SIS) myringoplasty in children: A randomized controlled study

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ABSTRACT

Introduction: A novel bioactive material for tissue graft, derived from porcine small intestinal mucosa (SIS) has been marketed. This material promotes early vessel growth, provides scaffolding for the remodeling tissues, and is inexpensive and ready-to-use. We evaluated efficacy, safety, and surgery time of SIS myringoplasty, in comparison with autologous temporalis fascia (PTF) repair in children in a prospective, two-group (SIS and PTF) randomized, blinded study at a tertiary-care pediatric institution.
Materials and methods: 404 children with tympanic membrane (TM) repair were randomly assigned to receive SIS or PTF myringoplasty. Primary outcome was the healing of the TM at 6 months. Secondary outcomes were surgical time, and adverse events. Long-term follow-up ranging from 11 to 2 years was obtained in all enrolled children. Audiometric tests as pure-tone thresholds were applied in all patients. The Fisher's exact test and the Kriskal–Wallis test were applied for statistical analysis.
Results and discussions: Four-hundred-thirty-two TM perforations were treated, 217 in the SIS and 215 in the PTF groups. There were 209 stable TM closures in the SIS (96.3%) and 204 (94.8%) in the PTF arm. This difference was not statistically significant (odds ratio = 0.4, 95%; confidence interval = 0.12–1.41). SIS myringoplasty yielded reduced surgical time. No adverse reaction to SIS was encountered. Audiometric tests revealed no statistically significant difference in the two groups.
Conclusions: SIS myringoplasty is a safe and effective method for TM closure in children with reduced surgical time, as compared to PTF.

1. Introduction

Tympanic membrane (TM) perforation is encountered frequently in pediatric otolaryngology practice. Numerous techniques for closure of TM perforation are utilized, closure including either an overlay or an underlay approach [1], paper patch, fat plug procedure [2,3] or scar tissue graft in revisions [4]. Autogenous temporalis fascia (TF) is the most commonly used and most satisfactory grafting material applied, with reported success rates up to 94% [1–4]. Advantages of autograft materials for TM closure include ready availability and low cost as well as excellent biocompatibility and non-antigenicity, specifics that can outweigh donor site morbidity (i.e. retroauricular scar, hematoma, etc.). However, children with previous unsuccessful tympanoplasty, second-look cases, or when autogenous TF quality is poor, alternative donor sites and materials have to be considered, like perichondrium, veins, and pericranium [5–7].

Recently, a new bioactive material derived from porcine small intestinal submucosa (SIS) has been marketed. SurgiSIS (Cook Surgical, Bloomington, IN) is an acellular, freeze-dried soft tissue graft derived from porcine SIS [8]. This material maintains growth factors and glycosaminoglycans [9–11], and elicits no immune response in the recipient organism [12]. SIS is terminally sterilized to eliminate cell-borne pathogens, and promotes tissue-specific growth a differentiation of cells in vitro [13], thus providing a bioscaffold for the regeneration of contiguous host tissue. Pribitkin et al. [14] demonstrated cartilage regeneration with the use of SIS in an animal model, and SIS is currently and successfully utilized for different and delicate surgical procedures (i.e. nasal septum perforations, artery and vein, dura and urinary tract repair, etc.) in humans [15]. Spiegel and Kessler [16] confirmed SIS as a viable alternative to autologous grafts in tympanoplasty in chinchillas, and more recently, Ort et al. [17], verified fascia regeneration with the use of SIS in an animal model, suggesting applications for revision tympanoplasty. SIS is therefore a low-expensive and ready-to-use alternative to autologous grafts. We evaluated the

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efficacy, safety, and surgery time of SIS myringoplasty in children, and compared clinical outcomes with patients' autogenous TF (PTF) for TM perforation repair with an 11-year prospective study.

2. Materials and methods

This was a prospective randomized, single-blinded study, performed from February 17, 2001, to July 2, 2012, at a tertiary care pediatric institution. The study protocol followed the CONSORT [18,19] guidelines and was approved by the Ethics Committee (VCZ-EthCom) from the first author's institution. Written informed consent was obtained from each parent before admission of children to the study. Five hundred and fifty-seven pediatric patients were evaluated at our clinic for TM perforation over the past 11 years. Of these, 414 agreed to participate in this study and were scheduled for simple myringoplasty with no other procedure. Among these patients, 16 were lost from follow-up during the study, thus leaving 398 children (432 ears total) object of the present investigation (Fig. 1). Indication for the procedure was the presence of TM perforation, and cases were put on waiting list for surgery at time of initial consultation. Patients with post-traumatic perforation or perforation after acute otitis media were included in this study. The cause of the perforation was post-traumatic in 25 ears (5.8%), whereas perforation after acute otitis media was present in 407 ears (94.2%). Stable dry TM perforations (i.e., perforation present for more than 6 months, no ear discharge for 3 months prior surgery) were considered as amenable to surgical repair. Exclusion criteria were presence of cholesteatoma, previous history of middle ear surgery or ventilation tube insertion on the same ear, ossicular chain abnormalities, cleft palate or previous pharyngeal surgery, or psychiatric disorder. Parents and patients were blinded regarding the type of surgical procedure. All patients were examined with the operating microscope to confirm the presence of TM perforation. Tympanic otoscopy with 2.7-mm-diameter (0, 30, and 70 deg.) endoscopes (Karl Storz GmbH & Co., Tüttlingen, Germany) was performed to confirm absence of tympanic cholesteatoma and to assess ossicular chain status. Perforations were classified according to the TM quadrant involved (i.e., anterior, posterior, inferior, and superior). Involvement of only the central portion of the TM identified a perforation as central, whereas perforations were classified as subtotal if there was involvement of more than 3/4 of the surface of TM. All patients underwent pure tone audiometry before surgery and either bone conduction and air conduction thresholds were obtained among the 0.250 kHz through 8 kHz frequencies span.

All children were operated under general anesthesia by the same attending surgeon (RDE). The surgeon was blinded to grafting material to be used (i.e. SIS or PTF) until entering the OR. All surgeries were performed via the post-auricular approach, elevating a posterior tympanomeatal flap. TM grafts were obtained from the temporalis fascia of each PTF patient, and all grafts were placed in position using an underlay technique. Similarly, SIS grafts were placed via the same underlay technique. In the SIS arm, the grafting material was placed in sterile saline solution right after skin incision, to obtain optimal re-hydration prior utilization. The edges of the perforation were excised in all cases. In all approaches (i.e. permeatal or retroauricular a curvilinear incision was made over the posterior canal wall to elevate a tympanomeatal flap in a standard fashion, starting at the 6 o'clock and ending at the 12 o'clock positions. Chorda tympani was preserved in all cases. The condition of the middle ear ossicles and labyrinthine windows was reassessed. Children were randomly assigned to the SIS or the PTF arm. Randomization was obtained with a computer-generated random number table. The allocated procedures were placed in a numbered envelope, to be opened by the scrub nurse upon preparation of the OR table the day of surgery. The allocation sequence was therefore concealed until surgery took place and not altered in any circumstances. In all procedures the graft was placed as an underlay under the malleus and TM remnants, and supported in position by the insertion of Curaspon™ gelatin pledgets (Curaspon Healthcare, Zwanenburg, The Netherlands) within the tympanic cavity. Tympanomeatal flap was placed back, and the external auditory canal (EAC) was then filled with saline-soaked Curaspon™ pledgets. The postauricular incision was sutured with intradermal 4–0 chromic sutures, and standard ear dressing was applied in all patients. Parents were asked to report in a questionnaire any complication observed during the postoperative period of survey. All patients were treated in an inpatient basis and were discharged the day after the procedure. Patients were scheduled for postoperative evaluation including pure tone threshold measure at day 21, and then at month 2, 3, 6, 9, 12, and then 2 times per year. During the visit, the grafts were evaluated with the operating microscope and with powered assisted 2.7 mm (0° and 30°) otoendoscopy. The presence of recurrent perforation, blunting or retraction of the graft was recorded. Any other complication that might occur was recorded, and hearing thresholds were recorded as well. The ENT examiner (member of staff of the Institution) was blinded to surgical grafting technique.

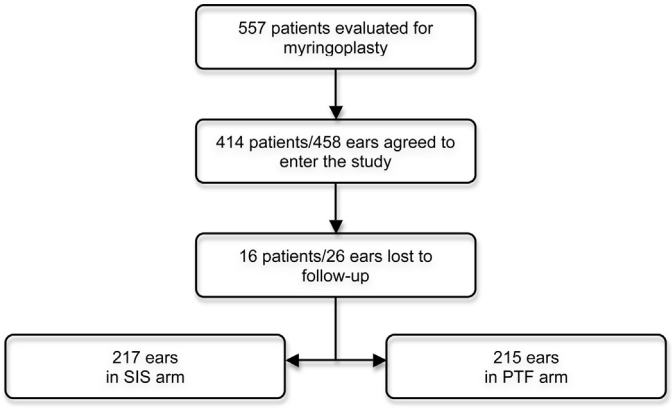

Fig. 1. Randomization diagram. SIS and PTF see text.

3. Analysis

Outcome data were dichotomized by age, with 8 years as the cutoff [3,13]. Results were dichotomized into young (<8) and older age groups to investigate effect of age on age on outcome.

The primary outcome was the healing of the TM; the secondary outcomes were anterior blunting of the graft and presence of retraction of the TM. Cases were defined as surgical failures if perforation recurred within 6 months after surgery and was confirmed throughout the following 6 months. Analysis was conducted by intention to treat. The differences of categoric variables among the two groups were analyzed with the Fisher's exact test (two tailed), whereas for continuous variables and discrete data with skewed distribution a nonparametric Kruskal–Wallis test was used. Because there were many possible comparisons, conservative values of $P < 0.05$ were considered significant. We calculated crude odds ratio and 95% confidence intervals. The data were analyzed using the statistical package SAS, version 9.1 (SAS Institute, Inc., Cary, NC).

4. Results

Four hundred and four pediatric patients were enrolled in the study. There were 210 males and 194 females. The median age was

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Table 1
Distribution of size of perforations and outcome in the SIS and the PTF myringoplasty arms.

Size of perforation	PTF arm (*N* = 215)				SIS arm (*N* = 217)			
	Preoperative		Postoperative		Preoperative		Postoperative	
	N	%	*N*	%	*N*	%	*N*	%
Subtotal (>3/4 of MT surface)	54	25.1	4	2.0	48	22.2	2	0.9
1/2 of MT surface	79	36.7	5	2.2	85	39.1	4	1.8
1/4 of MT surface	33	15.4	1	0.5	44	20.3	1	0.5
Punctiform (<1/2 of MT surface)	49	22.8	1	0.5	40	18.4	1	0.5
Ears total	215	100.0	11	5.2	217	100.0	8	3.7

9.3 years with a range from 3 to 15 years. Two-hundred and seventeen patients were assigned to SIS myringoplasty, while 215 patients were assigned to PTF myringoplasty. In the SIS myringoplasty arm there were 124 males (52.5%) and 113 females (47.5%). The median age was 9.1 years (range: 3 to 15 years). In the PTF myringoplasty arm there were 111 males (51.6%) and 104 females (48.4%). The median age was 9.6 years (range: 4 to 15 years). There were no statistically significant differences in the two groups comparing age, gender, sizes or site of initial perforation.

Surgical success was defined as an intact graft up to 6 months after surgery. Long-term success denoted children with an intact TM at the end of the study. Follow-up time frame ranged from 2 to 11 years, (median 7.7 years). Two years after the surgical procedure a stable TM closure was observed in 89.2% of the PTF arm, while in 91.2% of the SIS patients. A second procedure for TM repair was then performed using the same grafting material in the same patient. The distribution of TM's perforation site and TM's perforations' size is summarized as in Tables 1 and 2. At the end of follow-up healing rates in the SIS arm and PTF arm were 96.3% and 94.8% respectively (Tables 1 and 2). Although the healing rate was higher in the SIS arm than in the PTF arm, the results were not statistically significant (odds ratio = 0.4, 95%; confidence interval = 0.12–1.41).

Outcome data were dichotomized divided by age, (8 years as the cutoff—see analysis section). Eighty children (19.8%) were under 8. In the SIS arm 44 children (20.3%) were younger than 8. Overall surgical failure was observed in 27 children (12.4%) of 8 years or older, while only 9 children (4.1%) younger than 8 experienced a recurrent perforation.

SIS myringoplasty time was significantly shorter when compared to PTF ($p < 0.001$) with an overall time savings of 7.7 min on average for the SIS group.

4.1. Audiometric tests results

All patients underwent pure-tone thresholds measures. We observed no statistically significant difference ($p = 0.7$) of pure tone averages – from 0.5 to 3 kHz (PTA), mean air-bone gap 7.5 dB, mean air-to-air thresholds gap 8.3 dB – either for air and bone conduction between the two groups.

5. Discussion

TM perforation in children is frequently observed in pediatric otolaryngology practice, and may present a difficult therapeutic challenge for the pediatric otolaryngologist surgeon. Different factors may influence surgical success, from such anatomical issues as the narrowness of the EAC or site of perforation [20,21]. In addition, the skill and the experience of the otologic surgeon in performing this type of surgery can influence the success of surgical outcome [22–24]. PTF is the most commonly used grafting material for TM repair, and children are not an exception. It has a very high rate of success [4] and offers several advantages. As an autograft, it avoids risk of potential pathogen spread, and its excellent biocompatibility and non-antigenicity results in no immunogenic response with subsequent graft failure. The PTF fascia is usually harvested through the standard postauricular incision, obviating the need for a second surgical site. However, revision tympanoplasty and/or second-look procedures are common practice in pediatric otology [20–23]. Eustachian tube dysfunction may persist, resulting in re-retraction or re-perforation of TM, for example. Previous PTF harvest may not leave sufficient tissue for a second graft at revision surgery, in second-look cases, or when autogenous TF quality is poor. Alternative donor sites (i.e. grafts from a second surgical site such as the contralateral temporalis fascia) or different materials have to be considered, like perichondrium, veins, pericranium, and scar tissue [4–7].

In recent years, several reports [25–30] have examined acellular homograft and xenograft extracellular matrix (ECM) materials for TM reconstruction. The matrix materials are carefully sterilized and cleared of all cellular and antigenic materials, providing a dense scaffold of ECM proteins and glycosaminoglycans [17]. AlloDerm (LifeCell Corp., Branchburg, NJ) is composed of cadaveric human dermal tissue that has been cleared of cellular and antigenic materials to reduce both the host's immune response and the risk of viral transmission. AlloDerm has good success as a tissue graft in a number of surgical fields [17]. Direct TM grafting with AlloDerm has reported success in both animal and human studies [25–30]. TM perforation repair has been achieved with reported high success rates, but given its human source, a potential

Table 2
Distribution of site of perforations and outcome in the SIS and the PTF myringoplasty arms.

Site of perforation	PTF arm (*N* = 215)				SIS arm (*N* = 217)			
	Preoperative		Postoperative		Preoperative		Postoperative	
	N	%	*N*	%	*N*	%	*N*	%
Inferior	41	19.1	4	2.0	45	20.7	2	0.9
Anterior	118	54.9	5	2.2	121	55.7	4	1.8
Posterior	35	16.2	1	0.5	32	14.7	1	0.5
Central	21	9.8	1	0.5	19	8.9	1	0.5
Ears total	215	100.0	11	5.2	217	100.0	8	3.7

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drawback is its relative limited supply and expense. In addition, concerns may arise from use of human-derived graft materials, such as the risk of spread of latent viruses or Creutzfeld–Jakobs disease. Some of the concerns associated with human-derived graft materials can be reduced with the use of a xenograft. A pure connective tissue matrix material obtained from an animal source would be ultimately less expensive and more readily available. In addition, a statistical reduction in operative time as noted by use of an AlloDerm graft versus both fascia and cartilage tympanoplasty [31] may be also the case with use of a xenograft.

Recently, a new graft material derived from porcine acellular small intestine submucosa – nor SIS – (SurgiSIS, Cook Biotech, West Lafayette, IN) has been marketed. SIS is reported to have success and safety as a tissue reinforcement material in several surgical specialties, including general pediatric surgery, urology, and neurosurgery [32–34]. SIS is an ECM tissue graft composed of collagen primarily type I and fibronectin [10]. It includes glycosaminoglycans, chondroitin sulphate, hyaluronate, heparin, and dermatan sulfate [9,11]. In previous studies, SIS is rapidly infiltrated with host cells alone, followed by deposition of new tissue [8,12–14,17]. In addition, growth factors have been identified in SIS [11].

SIS grafts are often impossible to differentiate from the surrounding host issue at histological examination due the excellent remodelling and colonization of the recipient tissue [14,17]. Pribitkin et al. [14] demonstrated complete cartilage replacement of SIS grafting material three months postoperatively, in a rabbit ear cartilage model. Microscopic findings confirmed the early inflammatory infiltration containing eosinophils, multinucleated giant cells and lymphocytes in different studies [14,17]. ECM graft is gradually substituted by recipient tissue bioscaffold rather than exclusive ingrowth of native cellular material [14,35]. Successful TM perforation repair after SIS direct tympanoplasty has been demonstrated in an animal model with reported TM closure in all implanted ears [16]. No safety issue has arisen so far. SIS demonstrated avoidance of risk of human transmitted disease, as it has been used in several uneventful surgical procedures in humans [32–34], but hypothetical risk of inter species transmission is to bear in mind.

The overall healing rates in the present study compare quite favorably with those reports. Although the TM closure was higher in the SIS than in the PTF arm (96.3% and 94.8%, respectively) this difference was not statistically significant in our series. However, due the number of patients included in our trial, the difference in TM closure between the SIS patients versus PTF patients. We found that myringoplasty for posterior or central perforation repair had an overall better outcome compared with anterior perforation closure (Tables 1 and 2) in both arms. Repair of an anterior TM perforation is well known to be more difficult [36,37], and the overall results in our series are not an exception. Anterior perforations are more challenging as graft placement may be inaccurate [21], and the anterior aspect of the TM is more difficult to visualize especially in children where EAC dimensions are a constraint [21,36]. These factors probably influenced our overall results in both arms of the study as well.

Serial observation of SIS-repaired TMs revealed excellent integration of the SIS graft with the remnants of the surrounding TM over time. The transition point between the SIS graft and the recipient tissue was observed to become less noticeable during the years. In addition, examination with otoendoscopes revealed new vessel growth over the SIS graft, providing nutrient support to the implanted tissue. These findings are consistent with microscopic observation of Ort et al. [17], and the intrinsic characteristics of SIS [32–35] (i.e. growth factors may have played a role).

SIS re-hydrated graft is easy to manipulate, has predictable and extremely low swelling after hydration, thus improved surgical precision during positioning is straightforward. Reduced tissue manipulation, associated with no need to harvest PTF graft from the donor site are reflected in reduced overall surgical times. The "learning curves" involved with the use of the SIS and PTF graft and manipulation were similar, so the same level of comfort and proficiency with each of these two materials was analogous. However, only one surgeon was involved and this might have added limitations to this study, even if single a surgeon reduces confounding effect of surgical technique from various operators and learning curve. Further studies with multiple surgeons included might address these issues, in the future.

6. Conclusion

SIS myringoplasty appears to be safe and effective method for TM closure in children with reduced surgical time, as compared to PTF. SIS material provided high healing rates in perforation repair. However, in our group of 404 randomized children, the higher rate of closure versus PTF repair was not found to be statistically significant.

Advantages of SIS appear to be clear: is ready accessible when PTF is unavailable (e.g. revision cases, endoscopic and/or permeatal surgery – perichondrium can be too small especially in children); avoids external incision for harvest of graft – popular with patients and avoids keloids in those at risk; saves time and small amount of morbidity associated with harvest of autograft.

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