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What is This?
Preliminary Report of Vocal Fold Augmentation with Cross-Linked Porcine Collagen

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. To evaluate the short-term outcomes of using cross-linked porcine collagen for vocal fold augmentation.

Study Design. Case series with planned data collection.

Setting. Tertiary referral hospital.

Subjects and Methods. Twenty consecutive patients of unilateral vocal fold paralysis (UVFP) were recruited, including 10 males and 10 females. All the subjects received videolaryngostroboscopic (VLS) evaluation for the glottic closure pattern, perceptual grading using the GRB scale (grade, roughness, breathiness), acoustic analysis, maximal phonation time (MPT), and Voice Handicap Index (VHI) questionnaire. Purified telopeptide-free, glutaraldehyde cross-linked porcine collagen was injected under local anesthesia with fiberscopic guidance.

Results. Treatment outcomes were evaluated 3 months after the injection. Fifteen (75%) of 20 patients reported complete resolution of symptoms, whereas the other 5 (25%) patients had substantial improvements. The median score of perceptual analysis of voice quality showed significant improvements from G2/R2/B2 to G1/R1/B0 (P < .001). Glottic closure pattern under stroboscopy had improved from “predominantly open” before the procedure to a “half-open and half-close” pattern after the procedure (P < .001). Acoustic analysis demonstrated significant improvements of jitter and normalized noise energy (P < .05). Maximal phonation time revealed a significant improvement from 7.5 ± 3.2 seconds to 13.1 ± 3.9 seconds (P < .01). The VHI had also decreased from 53 ± 25 points to 27 ± 20 points (P < .01). No patients had serious adverse events during the follow-up period.

Conclusion. This case series demonstrated that porcine collagen may be a suitable material for temporary vocal fold augmentation.

Keywords

vocal fold, injection laryngoplasty, porcine collagen, vocal fold paralysis

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Materials and Methods

Patient Recruitment

Between April and December 2010, 20 consecutive patients (10 males and 10 females) with unilateral vocal fold paralysis (UVFP) were referred to a tertiary teaching hospital. All subjects received a thorough physical examination; the UVFP diagnosis was based on the finding of the videolaryngostroboscopic (VLS) evaluation. For UVFP subjects without an underlying cause, we performed contrast-enhanced computed tomographic (CT) scans from skull base to chest/mediastinum to rule out the occurrence of occult neoplasm along the route of the recurrent laryngeal nerve. No subject had a medical history of collagen vascular disease or previous allergic reactions to animal/collagen products. All the patients signed an informed consent, and this study was approved by the Far Eastern Memorial Hospital (FEMH) Research Ethics Review Committee.

Videolaryngostroboscopy

Each patient received VLS evaluation during the clinical visits before and after the procedure. This was performed by instructing the patient to phonate a sustained “ee” sound with habitual pitch and intensity, using a 70° rigid endoscope (Model 2706 CA; KARL STORZ, Tuttingen, Germany) and a 3-chip CCD camera (Model 20222120; KARL STORZ). Each session of the VLS test was digitally recorded onto a portable hard disk via computerized video processor (NHXB10; Grass Valley, Inc, Nevada City, California). Two otolaryngologists evaluated the closure pattern of vocal folds using a stroboscopy research instrument. They reached consensus on the rating value, which was further numerated on a 4-point scale for easier statistical computation (1 = predominantly closed; 2 = closed/open; 3 = predominantly open; 4 = always open).

Perceptual and Acoustic Analysis of Voice Quality

Two independent clinicians evaluated voice quality using a 4-point GRB scale (grade, roughness, breathiness). Voice recordings were obtained using a unidirectional microphone placed 10 cm in front of a subject’s mouth. A 3-second sample of a sustained “ee” sound was analyzed using Dr. Speech software, version 4 (Tiger DRS, Inc, Seattle, Washington). Analytical parameters included jitter (%), shimmer (%), and normalized noise energy (dB). Maximal phonation time (MPT) was measured by 3 consecutive trials.

Injection Material

Purified telopeptide-free, glutaraldehyde cross-linked porcine collagen was derived from specific pathogen-free porcine dermal tissue (Sunmax Collagen Implant I-Plus, Taipei, Taiwan). Each syringe contained 35 mg/mL purified cross-linked collagen, primarily composed of type I atelocollagen. Because significant allergic reactions to porcine collagen did not occur in the previous study, we did not perform a routine skin test in this series.

Vocal Fold Augmentation

Vocal fold augmentation was performed after adequate local anesthesia of the nose, pharynx, and larynx, including a local spray of 10% Xylocaine over the pharynx, tonsil, vallecula, and epiglottis, followed by “laryngeal gargling” using 2% Xylocaine solution. An experienced doctor operated on the transnasal digital fibroscope for glottic visualization (VNL-1590STi; Kaypentax, Lincoln Park, New Jersey). Then, a 25-gauge, 1.5-inch needle was passed just above the thyroid notch. The technique for the thyrohyoid approach of vocal fold augmentation was described elsewhere. Injection locations were (1) lateral to the vocal process and (2) mid-third of the vocal fold, at the level of deep lamina propria (between the vocal ligament and vocalis muscle). The required amount of augmentation was based on individual need, usually around 0.5 to 1.0 mL. To compensate for early absorption of the water component of injectables, approximately 25% overcorrection was performed. The vocal fold should be convex at the conclusion of the procedures. Subsequently, all the patients underwent voice rest for 3 days to prevent leakage or local hematoma.

Outcome Evaluation and Statistical Analysis

Outcome measurements were conducted at 3 months after the procedure, including (1) perceptual analysis of voice quality using the GRB scale; (2) patients’ subjective rating, categorized as complete resolution of symptoms, substantial improvement, or no improvement or worse; (3) acoustic analysis; (4) MPT; (5) stroboscopic evaluation of vocal fold closure pattern; and (6) Voice Handicap Index (VHI) questionnaire. Subsequently, MPT and VHI were measured again at 6 months after the injections. Paired t test was applied to compare continuous parameters (ie, MPT, VHI, and acoustic analysis). For ordinal data, such as perceptual and stroboscopic ratings, Wilcoxon signed-rank test was used to evaluate the differences before and after the procedure. A P value <.05 was considered statistically significant. All statistical analyses were conducted with SPSS software, version 18.0 (SPSS, Inc, an IBM Company, Chicago, Illinois).

Results

Age distribution of the 20 recruited patients was 32 to 89 years (median, 66 years). The left vocal fold was involved in 17 patients, whereas the other 3 had their right fold involved. The recognized etiologies of vocal fold paralysis were thyroid cancer in 4 patients, lung cancer in 3, esophageal surgery in 3, cerebral vascular event in 2, Parkinsonism in 1, and neck trauma in 1. For the remaining 6 subjects, a clear etiology could not be determined after subsequent CT scan and, hence, the cause was categorized as “idiopathic.” Subjective treatment outcomes measured at 3 months after the injection showed complete resolution of symptoms in 15 (75%) patients and substantial improvement in the other 5 (25%) patients. Figure 1 demonstrates serial pictures of VLS before and 3 months after the treatment in a case of left vocal fold paralysis after cardiovascular surgery.

Perceptual analysis of voice quality showed that the median preinjection scores were G2/R2/B2 in comparison
with postinjection scores of G1/R1/B0, demonstrating significant improvements ($P < .01$, Wilcoxon signed-rank test). Stroboscopic evaluation indicated that the pattern of glottic closure was “predominantly open” before the procedure (median: 3 points), which significantly improved to a “half-open and half-closed” pattern 3 months after the procedure (median: 2 points; $P < .001$, Wilcoxon signed-rank test). Furthermore, acoustic analysis of voice quality using computer software demonstrated significant improvements in both jitter and normalized noise energy (Table 1; $P ≤ .001$, paired $t$ test). Although the value of shimmer improved after the treatment, it did not achieve statistical significance ($P = .053$, paired $t$ test).

Results of MPT revealed a significant improvement from 7.5 ± 3.2 seconds (mean ± standard deviation) before the injection to 13.1 ± 3.9 seconds 3 months after the injection (Figure 2; $P < .01$, paired $t$ test). The improvement remained significant at 6 months (12.6 ± 3.2 seconds, $P < .01$, compared with baseline; Figure 2). On the other hand, subjective outcome evaluation using VHI demonstrated a significant decrease from 53 ± 25 points to 27 ± 20 points 3 months after the procedure (Figure 3; $P < .01$, paired $t$ test). The VHI scores were 25 ± 17 points at 6 months, which also revealed a sustained improvement ($P < .01$, compared with baseline; Figure 3).

Table 1. Acoustic Analysis before and 3 Months after the Treatment in 20 Patients with Unilateral Vocal Fold Paralysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before</th>
<th>3 Months</th>
<th>Change</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jitter, %</td>
<td>0.66 (0.57)</td>
<td>0.24 (0.18)</td>
<td>0.42 (0.33)</td>
<td>.001</td>
</tr>
<tr>
<td>Shimmer, %</td>
<td>4.32 (3.87)</td>
<td>2.88 (2.83)</td>
<td>1.44 (1.31)</td>
<td>.053</td>
</tr>
<tr>
<td>NNE, dB</td>
<td>–5.31 (–3.09)</td>
<td>–11.41 (–12.28)</td>
<td>6.10 (4.88)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean (median) value. NNE, normalized noise energy.

*Paired $t$ test.

During the follow-up period, no patient developed allergic reactions to porcine collagen. Eight patients reported increased laryngeal secretion, and 3 encountered mild vocal fold hematoma, both of which resolved spontaneously within 2 weeks. On the other hand, 1 patient had undercorrection of the glottic gap, whereas another patient had early absorption of implant material in the third month. We did not experience any case of superficial injection into Reinke space, vocal fold granuloma formation, or stiffened vocal folds in this series.

**Discussion**

Collagen-based injection materials have been widely used in vocal fold augmentation since the 1980s, and the proposed indications include unilateral vocal fold paralysis, glottic insufficiency, and vocal fold scarring. Injectable collagen primarily acts as a soft tissue filler but may also stimulate fibroblasts of the recipient site, resulting in some degree of host collagen deposition. Although the cross-linked form of bovine collagen (Zyplast; Allergan, Irvine, California) has decreased the hypersensitivity rate and lengthened the duration of clinical effectiveness, preinjection skin tests are still required. Although the use of micronized homologous dermis (Cymetra; LifeCell, Branchburg, New Jersey) in vocal fold augmentation has been proposed with documented efficacy and safety, this dry-powered material requires additional time for rehydrating process before usage. Some patients may also have psychological concerns regarding the cadaveric origin of skin tissue.

In addition to these collagen-based products, porcine collagen has been widely used as a safe and effective tissue filler. Histopathological studies have demonstrated a well-tolerated host-implant interaction without evidence of local inflammation or other adverse events. According to the previous literature, none of the 519 subjects developed significant allergic reactions after the intradermal injection of porcine collagen, and hence a preinjection skin test appears unnecessary. Except for the material used in this study, there are several other commercially available products of porcine collagen, such as Evolence (ColBar Life-Science, Ltd, Herzliya, Israel), Permacol (Tissue Science Laboratories, Swillington, UK), and Dermicol (Evolence Breeze; Ortho Dermatologics, Skillman, New Jersey). All these materials are readily injectable, which saves preparation time before the procedure. Although we cannot be certain that pigs are absolutely free of the transmission risk of viral or prion disease, to our best knowledge, no such adverse event has been reported in the literature. Therefore, this study
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intends to examine whether porcine collagen can be a potential candidate material for vocal fold augmentation.

We demonstrated that vocal fold augmentation with porcine collagen is a practical treatment option for UVFP patients. Because these patients may have a severe underlying disease or be recovering from a major operation, other treatment modalities requiring general anesthesia such as autologous fat injection may not be suitable. Alternatively, all patients tolerated the procedure well under local anesthesia without developing any postinjection airway compromise or allergic reaction.

This study applied a multidimensional protocol to evaluate the functional results of vocal fold augmentation. First, subjective ratings of treatment outcomes showed that 75% (n = 15) of the patients reported complete resolution of clinical symptoms, whereas 25% (n = 5) of the patients stated substantial remission. Second, the VHI decreased from $53 \pm 25$ points to $27 \pm 20$ and $25 \pm 17$ points at 3 and 6 months, respectively (Figure 3; $P < .01$). Third, the phonatory efficiency test using MPT showed a marked improvement from $7.5 \pm 3.2$ seconds to $13.1 \pm 3.9$ and $12.6 \pm 3.2$ seconds at 3 and 6 months, respectively (Figure 2; $P < .01$). Thus, both MPT and VHI evaluations demonstrated a significant and sustained change up to 6 months after the procedure. Fourth, perceptual analysis of voice quality using the GRB scale revealed significant improvements from G2/R2/B2 to G1/R1/B0 ($P < .001$). Fifth, stroboscopic assessment also demonstrated a much improved closure pattern of vocal folds after the procedure ($P < .001$). Finally, acoustic analysis using various measurement parameters revealed significant improvements in voice quality (Table 1; $P \leq .001$). In sum, this pilot series documented beneficial clinical outcomes of porcine collagen in treating UVFP.

In this series, none of the patients developed allergic reactions to porcine collagen, nor did they show clinical signs of foreign body reactions. These results indicated a good biocompatibility of this material, which may be comparable with modern synthetic injection materials. Minor adverse effects occurring after the procedure could be managed conservatively. Vocal fold hematoma was most likely due to needle injury during the procedure or strenuous coughing afterward, which usually resolved spontaneously within 2 weeks and did not lead to focal scar formation. Furthermore, none of the patients encountered material misinjection into the superficial lamina propria, nor did they develop focal stiffening of vocal folds due to uneven augmentation. These preferable outcomes could be attributed to the better visibility of the needle tip and the lower extrusion force of porcine collagen, which helped the surgeon to maintain a smooth and steady injection process. However, because the material was injected transluminally, the case of undercorrection might have resulted from extrusion of injection material through the needle hole.

In conclusion, this case series demonstrated that porcine collagen may be a suitable material for temporary vocal fold augmentation. A subsequent long-term follow-up study is warranted to document the sustained duration of this material, as well as to delineate the likelihood of long-term complications. Meanwhile, larger sample sizes are required before confident safety profiles can be stated. On the basis of our preliminary results, further studies may proceed to compare the therapeutic effectiveness between porcine collagen and other injection materials.

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Author Contributions
Chi-Te Wang, conception and design, analysis and interpretation of data; Li-Jen Liao, acquisition of data; Tsung-Wei Huang, acquisition of data; Po-Wen Cheng, conception and design, analysis and interpretation of data.
Disclosures
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