Assessment of Canine Vocal Fold Function After Injection of a New Biomaterial Designed to Treat Phonatory Mucosal Scarring

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Objectives: Most cases of irresolvable hoarseness are due to deficiencies in the pliability and volume of the superficial lamina propria of the phonatory mucosa. By using a US Food and Drug Administration–approved polymer, polyethylene glycol (PEG), we created a novel hydrogel (PEG30) and investigated its effects on multiple vocal fold structural and functional parameters.

Methods: We injected PEG30 unilaterally into 16 normal canine vocal folds with survival times of 1 to 4 months. High-speed videos of vocal fold vibration, induced by intratracheal airflow, and phonation threshold pressures were recorded at 4 time points per subject. Three-dimensional reconstruction analysis of 11.7 T magnetic resonance images and histologic analysis identified 3 cases wherein PEG30 injections were the most superficial, so as to maximally impact vibratory function. These cases were subjected to in-depth analyses.

Results: High-speed video analysis of the 3 selected cases showed minimal to no reduction in the maximum vibratory amplitudes of vocal folds injected with PEG30 compared to the non-injected, contralateral vocal fold. All PEG30-injected vocal folds displayed mucosal wave activity with low average phonation threshold pressures. No significant inflammation was observed on microlaryngoscopic examination. Magnetic resonance imaging and histologic analyses revealed time-dependent resorption of the PEG30 hydrogel by phagocytosis with minimal tissue reaction or fibrosis.

Conclusions: The PEG30 hydrogel is a promising biocompatible candidate biomaterial to restore form and function to deficient phonatory mucosa, while not mechanically impeding residual endogenous superficial lamina propria.

Key Words: hoarseness, hydrogel, polyethylene glycol, scar.

INTRODUCTION

Optimal vocal function requires an aerodynamically competent glottal valve and pliable phonatory mucosa. During the past century, surgeons became adept at repairing aerodynamic incompetence by restoring glottal closure. This was achieved by augmenting the paraglottic space1-4 and/or repositioning the arytenoids5,6 to close the rima glottidis. However, there has not been a reliable method to restore normal suppleness to stiff vocal folds.7,8 This capability would be highly desirable, given the large numbers of patients with benign and malignant processes who sustain diminished pliability of phonatory mucosa from phonotrauma, disease, or instrumentation. About 6.6% of the American working-age population is affected by voice-related disorders, and most of these patients present with diminished phonatory
mucosal pliability of their vocal folds.9

The need for methods to restore vocal fold pliability has generated an increasing number of efforts to develop biological and/or synthetic remedies. A recent series of review articles provides an excellent overview of the wide range of treatment strategies that are under development.10-17 These proposed therapies include the use of synthetic biomaterials (some based on natural extracellular matrix components such as hyaluronic acid [HA] and collagen), cells (stem cells or fibroblasts), autologous tissue (fat or fascia), scaffolds (synthetic or tissue-based), and growth factors and other chemical agents, such as steroids and phytochemicals. All of these approaches have demonstrated some positive results in animal studies, and small-scale human trials have studied several types of treatment.

Biomaterials have several potential advantages over other approaches, including availability, limited biological side-effects, control over viscoelastic material properties, immediate benefit, and procedural simplicity (eg, delivery via injection). Recently, some human subject experiments suggested that biomaterial therapy may be effective for vocal fold scar. In a 2-year study, 40 patients with vocal fold scar, vocal fold atrophy, or sulcus vocalis were injected with auto–cross-linked polysaccharide HA gel (Fidia Advanced Biopolymers, Abano Terme, Padova, Italy).18 The material was placed into the lamina propria for treating the scar and sulcus or into the thyroarytenoid muscle for closing the glottal gap. This study had a pretreatment-posttreatment design, with multivariate statistical analysis of voice and endoscopic parameters. Glottal closure, vibratory pattern, and mucosal waves were significantly improved at the first follow-up (1 to 3 months) and at 12 months after injection. In two other studies using esterified HA (MeroGel; Medtronic Xomed, Jacksonville, Florida), the placement of HA-based fibers beneath phonosurgical microflaps appeared to have a positive effect on the long-term measures of voice production.19,20

The positive vocal outcomes reported in these initial human experiments are somewhat tempered by the heterogeneity of the vocal conditions treated and by inadequate controls. However, this work, as well as a host of animal studies,13,21-23 does suggest that biomaterials may provide short- and long-term benefits for treatment of vocal fold scar, and that materials with established biocompatibility in other parts of the body can be relatively safe for use in the vocal folds.

Hylan-B, auto-crosslinked polysaccharide HA gel, and MeroGel were initially designed for application in other tissues (eg, skin or dermis), and it would be serendipitous if they happened to be optimal for vocal fold applications. Ideally, substances would be designed specifically for the vocal fold on the basis of the rheological and functional properties of the normal vocal fold mucosa, as well as for their use in scar-stiffened tissue. Since the primary component of the vocal fold’s layered microstructure responsible for vibration is the superficial lamina propria (SLP), we created a novel hydrogel, PEG30 (patent pending), with rheological properties that lie near the lower limits of normal vocal fold stiffness. In choosing materials, an additional consideration becomes the potential regulatory hurdles for approval of novel chemical formulations. We therefore based PEG30 on polyethylene glycol (PEG) because PEG is an established biocompatible polymer widely used in numerous products approved by the US Food and Drug Administration. We investigated its effects on multiple vocal fold structural and functional parameters.

MATERIALS AND METHODS

Preparation of PEG30 Hydrogel. PEG30 hydrogels were prepared by photopolymerization of PEG diacrylate (PEG-DA; SunBio Inc, Orinda, California) in the presence of PEG (Aldrich, St Louis, Missouri; both with molecular weight of 10 kd). Briefly, aqueous solutions of PEG and PEG-DA (both 100 mg/mL) were made in sterile phosphate-buffered saline solution (PBS) and mixed in the volumetric ratio 3:1 of PEG-DA to PEG. This solution (1 mL) was gelled for 200 seconds with 0.05% (wt/vol) of Irgacure 2959 (Ciba, Tarrytown, New York) as the photoinitiator. An EXFO Lite lamp (Lumen Dynamix Group, Mississauga, Canada) that generated ultraviolet light of intensity 10 mW/cm2 (measured at 365 nm) was used for the gelation. The entire process was carried out in a sterile laminar flow hood. The gel disks thus formed were rinsed with 70% ethanol (3× at 1 minute per wash), rinsed in sterile PBS (3× at 5 minutes per wash), and then incubated in sterile PBS for 24 hours at 37°C. The swollen gels were progressively sheared through needles of decreasing bore size to make them injectable through a 25-gauge needle. The gels were stored at 4°C sealed in a capped syringe until further use.

Mechanical Testing of Hydrogels. The viscoelastic shear properties of the hydrogels were measured at low frequencies with an AR-2000 rheometer (TA Instruments, Inc, New Castle, Delaware). A cone-and-plate geometry was used to apply oscillatory shear to hydrogel samples with an acrylic cone (60-mm diameter, 2° angle) and a flat metallic Peltier plate heated to 37°C. Sheared gels were placed be-
between the heated plate and the cone so that a manufacturer-specified gap of 61 μm was maintained between the cone and the plate. The gel was subjected to an oscillatory shear at 1 Hz for 2 minutes to equilibrate the entire gel to a uniform temperature of 37°C. Strain sweep tests were done to ensure that the shear property measurements were done in the linear region of the stress-strain curve. The viscoelastic shear properties are independent of the percentage strain in the linear region. A target shear strain value was therefore identified by measuring the viscoelastic shear properties as a function of the percentage strain applied. A 0.6% strain was typically used to measure the shear properties by means of a frequency sweep. Measurements of the shear properties were then made by systematically varying the frequency from 1 to 10 Hz. The elastic shear modulus (G') at 10 Hz was used as a measure of the frequency from 1 to 10 Hz. The elastic shear modulus (G') at 10 Hz was used as a measure of the mechanical properties of the PEG30 hydrogel used in this study. The elastic shear modulus of PEG30 fell within or below the ranges reported in the literature for normal phonatory mucosa, thereby demonstrating adequate softness and/or pliability at low frequencies to justify in vivo testing.

Animal Care. This study was performed in accordance with the PHS Policy on Human Care and Use of Laboratory Animals, the NIH Guide for the Care and Use of Laboratory Animals, and the Animal Welfare Act (7 U.S.C. et seq.). All experimentation followed an animal use protocol that was approved by the Committee on Animal Care and the Institutional Animal Care and Use Committee of the Massachusetts General Hospital. All surgical procedures and housing of animals took place at the Massachusetts General Hospital.

Sixteen research-bred dogs (young adult male hounds, 8 months to 1 year in age) were obtained from Covance Research Products (Cumberland, Virginia). Through an arrangement with the supplier, we were able to obtain animals that had been endoscopically pre-screened for laryngeal disorders, which are not uncommon due to excessive barking. Before every procedure, the dogs were premedicated with acepromazine maleate (0.05 mg/kg), glycopyrrolate (0.01 mg/kg), and butorphanol tartrate (0.2 mg/kg). Anesthesia was maintained throughout the surgical procedures with intravenous propofol (10 mL for induction, followed by 0.5 mg/kg per minute or more given intravenously as needed). Spontaneous respiration was maintained, medical-grade oxygen was supplied continuously through the mouth, and a heating pad was used to maintain body temperature throughout the surgery. Heart and respiratory rates were monitored continuously by a monitoring device and visual observation. At the conclusion of each phonatory testing session (see below), the dogs were watched until they regained consciousness and were given the nonsteroidal anti-inflammatory drug meloxicam (0.2 mg/kg), buprenorphine hydrochloride (0.01 mg/kg), and the antibiotic Baytril (enrofloxacin; 5 mg/kg).

Surgical Procedures. The dogs were placed in a supine posture on a surgical table with the head and neck supported. The vocal folds were exposed by standard endoscopic techniques and visualized with a Leica F40 surgical microscope. PEG30 was injected unilaterally in 16 normal canine vocal folds with postinjection survival periods of 1, 2, 3, and 4 months (n = 4 per time point). The contralateral fold served as a control. An average of 60 μL of PEG30 was injected in the vocal fold with a 25-gauge Zeits Vocal-Fold Infusion Needle (Endocraft, Providence, Rhode Island) and a specially modified industrial viscous fluid dispenser (model HP7x by Nordson EFD, Westlake, Ohio) that was pneumatically driven and provided improved injection control compared with conventional handheld syringes or injection guns. The HP7x handpiece was modified to use a high-precision linear transducer and digital meter so that dispenser output could be measured in real time. The injection volumes for dogs 1 to 3 reported in this study were 69, 52, and 53 μL, respectively.

We made periodic examinations of in vivo vocal fold appearance using standard microlaryngoscopy. Specifically, examinations were made at the following time points after injection for dogs with 1-, 2-, 3-, and 4-month survival times, respectively: 1, 2, and 4 weeks; 2, 5, and 8 weeks; 4, 8, and 12 weeks; and 4, 8, 12, and 16 weeks. High-speed videos (4,000 frames per second) of the vocal fold vibration were also recorded during these examinations by using a 16-gauge needle inserted in the trachea to create subglottic air pressure for phonation. Air delivered for phonation was warmed (37°C to 39°C) and humidified by a Conchatherm unit (high-flow model; Hudson RCI, Temecula, California). A pressure sensor (MPX2010GP; Motorola, Schaumburg, Illinois) was mounted on the air supply tube near its connection to the needle inserted into the trachea, and a condenser microphone (ECM50PSW; Sony, New York, New York) was positioned approximately 15 cm from the mouth opening. Simultaneous acoustic and pressure signals were filtered and recorded digitally (20,000-Hz sampling rate) with Axon Instruments hardware (Cyberamp 380, Digidata 1440a) and software. Phonation threshold pressures were monitored in real time during data collection in or-
order to monitor and control phonation driving pressures, and were also measured from recorded signals during subsequent analyses. Our method for testing vocal function uses a tracheal needle to supply air with instrument-manipulated adduction of the vocal folds to initiate phonation. These recordings allow us to assess the pliability of the vocal folds under physiological conditions. Furthermore, this in vivo procedure allows us to test vocal function at multiple time points, which is ideal for following the progress of the effect of PEG30 injection over time and minimizes the number of animals needed.

High-Speed Video Data Collection and Analysis. Imaging of canine vocal fold vibration during induced phonation was accomplished by attaching a Phantom v7.3 high-speed video camera (Vision Research, Inc, Wayne, New Jersey) to the optical adapter of the operating microscope. This enabled magnified high-quality color imaging at 12-bit quantization with a complementary metal–oxide–semiconductor image sensor. High-speed video data were recorded at 4,000 images per second with maximum integration time and a spatial resolution of 448 horizontal × 424 vertical pixels to capture an approximately 2-cm² target area. Illumination was provided by a Leica F40 surgical microscope with an integrated 300-W xenon arc light source. Each high-speed video data segment consisted of 1,000 images (250 ms).

A previous report describes the digital image processing methods that were used to estimate lateral displacements of the left and right vocal folds from the recorded high-speed video segments.27 Briefly, the processing steps included correction of motion artifact; user selection of a glottal midline; rotation and cropping of images to vertically orient the midline; conversion from color to monochromatic images; user selection of an intensity threshold that optimized glottal edge detection; generation of a digital kymogram at the mid-musculomembranous glottis; and extraction of waveforms representing the amplitude of left and right vocal fold motion from the kymograms (Fig 1). To assess the impact of the injected biomaterial on the pliability of the vocal fold, we defined a measure of left-right amplitude asymmetry as the ratio between the maximum amplitude of the injected vocal fold and the maximum amplitude of the noninjected vocal fold.

Magnetic Resonance Microscopy and/or Microimaging. Immediately after euthanasia, the larynges were removed, rinsed with 0.9% saline solution, and fixed in cold PBS-buffered 4% paraformaldehyde. Magnetic resonance microimaging of the excised larynges was done as described elsewhere.28 Briefly, the larynges were suspended in Fomblin and imaged with a Bruker Avance-500 nuclear magnetic resonance spectrometer (11.7 T; 500 MHz for proton). A 30-mm “birdcage” transmitter and/or receiver coil was used for imaging. Transverse and/or coronal scans were obtained throughout the length of the segment with multi-slice multi-echo sequences. Transverse and/or coronal and axial images were then obtained through regions of interest. Gradient recalled echo images were acquired according to the following parameters: slice thickness, 0.3 mm; field of view, 20 mm; MTX, 512 (pixel size, 39 μm); and the following pulse parameters: repetition time, 1,000 ms; echo time (effective), 8.3 ms; flip angle, 10°; and NEX, 32. Sixty-four transverse or coronal slices and 32 axial slices were obtained per dog larynx for all 16 dogs injected. Fat was suppressed.

Fig 1. Example endoscopic view of vocal folds and derivation of amplitude asymmetry measure. A) High-speed video image taken during maximum abduction during phonation. B) Derivation of lateral displacement waveforms for right and left vocal folds. Images are rotated to orient glottis vertically and are cropped to optimize image processing. Digital kymogram is generated from position halfway between anterior and posterior commissures. Lateral displacement waveforms are then obtained by tracing edges of vocal folds in digital kymogram. Relative vocal fold pliability is estimated by calculating ratio between maximum amplitude of vocal fold injected with biomaterial and that of noninjected vocal fold.

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with a fat-presaturation pulse during imaging. Data were processed with Paravision software provided by the vendor.

**Histologic Analysis.** Each excised larynx was bisected in the sagittal plane, and each half was then trimmed and cut in two pieces in the coronal plane near the middle of the vocal folds. The pieces were oriented appropriately and embedded in paraffin. Coronal sections, 5 μm thick, were cut and saved at fixed intervals along the anterior-posterior extent of the vocal fold. For each specimen, we used the magnetic resonance images to guide the cutting of the paraffin sections such that the injection sites were fully encompassed. Alternate slides were stained with hematoxylin and eosin and Masson’s trichrome stains and examined with brightfield microscopy. Digital photomicrographs were obtained with a Zeiss Axioskop2 microscope system. When necessary, differential interference contrast microscopy was used to improve image quality.

**Identification of Cases With Superficial Injections.** In order to correctly attribute potential postinjection changes in the in vivo vibration of the vocal folds to the injected biomaterial, we reasoned that it would be important that the injected biomaterial and the reaction that it caused be extremely superficial so as to maximally affect vocal fold vibration. In order to visualize and quantify the 3-dimensional (3-D) location of the residual biomaterial and the accompanying biological reaction, we used calibrated magnetic resonance images in combination with histologic imaging. Masson’s trichrome–stained histologic sections were matched with coronal magnetic resonance microimaging slices in order to delineate residual biomaterial and cellular infiltrate from the surrounding vocal fold tissue in the magnetic resonance microimages as described in detail elsewhere. An example of magnetic resonance imaging–histology image matching is shown in Fig 2 (top panels). Three-dimensional reconstruction of consecutive calibrated magnetic resonance microimaging slices was then done with Amira software (Visage Imaging, Inc, San Diego, California) to visualize the location and quantify the volume of the residual biomaterial and cellular infiltrate (Fig 2,
Data from all 16 cases were screened to identify subjects that had residual biomaterial and/or cellular infiltrate in the key “vibratory zone” of the vocal folds. The vibratory zone of the vocal fold was identified as the area in the SLP defined by points 1 mm on the superior surface and 2.5 mm on the medial surface from the free edge of the vocal fold (Fig 3). As part of the screening process, subjects that had less than 5 μL of residual biomaterial and cellular infiltrate were eliminated. For each of the remaining subjects, 3 to 4 consecutive magnetic resonance microimaging slices with the highest percentage of residual biomaterial and cellular infiltrate were identified. For each of these magnetic resonance microimaging slices, we computed the “vibratory fraction,” ie, the percentage of the vibratory zone occupied by the residual biomaterial and cellular infiltrate, and averaged it across the measured slices. The 3 animals that had the highest average vibratory fractions were identified and subjected to in-depth analyses. Representative magnetic resonance microimages and the 3-D reconstructions of vocal folds for the 3 selected cases are shown in Fig 4. One subject each with survival time points of 1 month, 2 months, and 3 months constituted the 3 subjects selected by this screening process.

RESULTS

Vocal Fold Function Before and After PEG30 Injection. We evaluated vocal fold function for the 3 selected animals (those with the most superficial PEG30 injections; see Methods) during in vivo phonation, whereby delivery of subglottic air pressure and manual adduction of the arytenoid cartilages caused the vocal folds to valve the airstream in a manner resembling natural phonation. All vocal folds at all time points displayed clear evidence of mucosal wave activity. The average phonation threshold pressures were low (4 to 8.5 cm H2O). Analysis of symmetry in vocal fold amplitude failed to show a consistent difference in lateral tissue excursion for the injected versus noninjected (control) vocal folds (Fig 5). Statistical comparison of the relative vocal fold amplitude (injected divided by noninjected) prior to injection versus the last recording time for each animal failed to find a difference (2-tailed paired t-test, p = 0.26). Likewise, phonation threshold pressures did not differ between pre-injection measures and the last recording session for each animal (2-tailed t-test, p = 0.40; Fig 6). Taken together, these two findings suggest that the injected gel and/or tissue response did not appreciably alter the pliability of the superficialmost portion of the SLP during manually elicited phonation.

Biocompatibility of PEG30. Multiple in vivo examinations of the canine vocal folds with an operating microscope and gentle blunt-instrument palpation revealed no clinical evidence of inflammation such as erythema or edema. In all 3 cases, the injected vocal fold surface looked identical to the noninjected vocal fold under high magnification. Histologic analysis of the vocal fold for canine 1 (survival time of 1 month after injection) revealed the presence of PEG30 in the vocal fold, accompanied by significant macrophage infiltration at the implantation site, including and surrounding the PEG30 (Fig 7A,B). To a lesser extent, lymphocytes and plasma cells were also present. No giant cells or neutrophils were observed. Slight to mild fibrosis was seen, but no fibrotic capsule formation was observed around the PEG30. The macrophages adjacent to the implant had a foamy cytoplasm suggesting active phagocytosis of the PEG30 by the macrophages. These observations suggest that PEG30 is biodegradable by macrophage-mediated phagocytosis. Similar histopathologic findings were observed for canine 2 (survival time of 2 months after injection) and canine 3 (survival time of 3 months after injection), although with amounts of residual PEG30 and macrophages that decreased with each successive month (Fig 7C,D). No fibrosis in the vocal fold was seen for either canine 2 or canine 3. The foreign body response to PEG30 seemed to resolve over time, with no apparent damage to the surrounding vocal fold tissue and with replacement of the lost material by loose connective tissue.
In all 3 animals, no signs of any long-lasting fibrosis or other tissue damage were seen. Overall, the absence of a neutrophil response, the lack of a fibrotic capsule, and the macrophage-mediated clearance of PEG30 with minimal to no fibrosis suggest that PEG30 is biocompatible and biodegradable in the vocal folds.

DISCUSSION

Normal vocal fold vibration is manifested primarily as a wave of displaced mucosal tissue on the sur-
face of the vocal folds, i.e., the mucosal wave. The phonatory or vibratory mucosa is mostly composed of a soft and pliable layer of SLP with a thin covering of epithelium that essentially mimics the biomechanical properties of the SLP substrate. The main cause of chronic dysphonia or voice loss is permanent damage and/or scarring of the normal SLP. No proven methods currently exist for restoring normal function to vocal folds that have lost the pliability of this key vibratory layer.

This report describes the results from initial testing of a new synthetic PEG30 hydrogel being developed to restore vibratory function to vocal folds that have lost some pliability of the phonatory mucosa. Polyethylene glycol was chosen as the basis for this new material because numerous PEG-based materials are already approved by the US Food and Drug Administration for implants in other parts of the body, and therefore our modification had good potential to be biocompatible. In addition, during initial low-frequency rheometric screening, the PEG30 formulation seemed soft and pliable enough to potentially mimic the biomechanical function of normal SLP, and it could be injected through the different types of 25-gauge needles currently used for vocal fold infusion during phonosurgery.26 It was deemed necessary to first determine if the impact of PEG30 on healthy vocal fold tissue and function was acceptable prior to investigating its use in vocal fold pathology, particularly since most patients who have lost some pliability of the phonatory mucosa still retain some normal regions of SLP.

The biocompatibility and impact on vocal function of PEG30 were tested longitudinally in an in vivo canine model with survival times ranging from 1 to 4 months. This report focuses on results from 3 dogs (1 each at 1, 2, and 3 months) for whom 3-dimensional reconstruction analysis of 11.7-T magnetic resonance imaging and serial-section histologic analysis of excised larynges showed that the PEG30 injections were superficial, so as to ensure maximal impact on vocal fold vibratory function. The presence of PEG30 did not negatively affect normal phonatory vibration: the injected canine vocal folds displayed clear mucosal waves at all 3 postinjection time points, vibratory amplitudes that did not differ significantly from those of the contralateral noninjected vocal folds, and no significant change in phonation threshold pressure relative to preinjection phonation.

The PEG30 also appeared to elicit a minimal biological response when implanted in the SLP of ca-
nine vocal folds, with no evidence of an overt inflammatory response either in terms of the vocal fold surface or with respect to histologic findings. The biological response to PEG30 in the vocal folds of the remaining 13 dogs was similar to that seen in the 3 selected cases. In all dogs, the residual PEG30 was actively phagocytosed by macrophages, and the amount of residual PEG30 and macrophages progressively decreased with an increase in survival period. The PEG30 and the foreign body reaction were resorbed with no apparent damage to the surrounding vocal fold tissue, and the lost PEG30 was replaced by nonfibrotic loose connective tissue. An in-depth examination of the biological response to PEG30 in all 16 animals, however, is out of the scope of this report that focuses primarily on the functional evaluation of PEG30 injected in the phonatory mucosa. A future report will utilize histologic data from the entire cohort of 16 animals to evaluate the biological response to PEG30 in detail.

Overall, comparative analysis of histologic results across 1- to 3-month survival end points indicates that after PEG30 is injected into the SLP of vocal folds it biodegrades within 3 to 4 months without creating damage (fibrosis) or mechanical changes (stiffness) in healthy tissue. If it is assumed that there are no residual beneficial effects after PEG30 has been resorbed (eg, stimulation of tissue remodeling), then the current formulation of PEG30 would probably have to be reinjected at approximately 3-month intervals to maintain its positive impact on vocal function. Reinjections could probably be accomplished as an outpatient procedure. This 3-month outpatient treatment interval for chronic vocal fold scarring is generally in line with the timing of the repeated Botox injections that are currently used to manage chronic laryngeal dystonias. Devising strategies to increase the residence time of PEG30 by using chemical engineering and other approaches, however, is also an important goal.

In summary, the results of this initial assessment provide support for the continued development and testing of PEG30 as a potential treatment for hoarseness resulting from deficiencies in pliability and contour of the phonatory mucosa.

CONCLUSIONS

The PEG30 hydrogel is a promising candidate biomaterial to restore vibration to scarred or deficient phonatory mucosa, since PEG30 exhibits in vivo biocompatibility and pliability without impeding normal SLP function. These characteristics support a potential treatment paradigm for a majority of cases of irresolvable hoarseness, including vocal fold scar, since most patients have some residual pliable mucosa impeded by focal zones of stiffness.

REFERENCES


