Vocal fold augmentation with calcium hydroxylapatite

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OBJECTIVES: **Voice disorders affect more than 3% of the general population. Vocal fold atrophy is a part of the normal aging process, with up to 60% of 60-year-old individuals displaying evidence of glottal insufficiency. A safe, effective, and durable substance for injection augmentation of the vocal folds is not currently available. The purpose of this investigation was to describe our preliminary experience with calcium hydroxylapatite (CaHA) for vocal fold augmentation.**

METHODOLOGY: **All patients undergoing injection augmentation of the vocal folds with CaHA between January 1, 2002 and June 1, 2003 were prospectively evaluated. Data concerning indications, technique, functional outcome, and complications were collected. In addition, the larynx donated from a woman who underwent vocal fold augmentation with CaHA and subsequently died from terminal cancer was histologically examined.**

RESULTS: **A total of 39 vocal folds in 23 individuals were injected with CaHA. The mean age of the cohort was 62. Fifty-two percent were male. The indications for augmentation were unilateral vocal fold paralysis (9/23), unilateral vocal fold paresis (5/23), presbylarynx (3/23), Parkinson's (3/23), bilateral vocal fold paresis (2/23), and abductor spasmodic dysphonia (1/20). There were no adverse reactions. All individuals reported improvement on a self-administered disease-specific outcome measure ($P < 0.001$). The pathology from the donated larynx 3 months after injection revealed intact CaHA spherules in good position with a minimal, monocellular inflammatory reaction to the gel carrier and no evidence of implant rejection.**

CONCLUSIONS: **Initial experience with vocal fold augmentation using CaHA is promising. Long-term safety and efficacy needs to be established.** (Otolaryngol Head Neck Surg 2004;131:351-4.)

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Glottal insufficiency can be caused by a variety of disorders including vocal fold paresis and paralysis, abductor spasmodic dysphonia, Parkinson's disease, vocal fold scar, and presbylarynx. Bowing of the vocal folds is part of the normal aging process, with more than 60% of individuals over 60 years of age displaying endoscopic evidence of vocal fold atrophy.[1,2] Endoscopic injection augmentation of the vocal folds was first described by Brunings in 1911.[3] Since his experience with paraffin, nearly a dozen substances have been utilized for this purpose. Some of these materials include Teflon, silicone, fat, fascia, gelfoam, and collagen.[4-10] None of these substances has been ideal and all have experienced limitations with safety, durability, and/or efficacy.[11-17]

Synthetic calcium hydroxylapatite (BioForm Inc., Franksville, WI, USA) was approved for vocal fold augmentation by the United States Food and Drug Administration Center for Devices and Radiological Health on January 9, 2002. Calcium hydroxylapatite (CaHA) is the primary mineral constituent of bone and teeth. As a class, hydroxyapatite implants have been shown to be highly biocompatible. Hydroxyapatite implants have shown little inflammatory response and studies evaluating their safety have shown no evidence of toxicity.[18-23] The implant is created by suspending CaHA in a gel carrier consisting primarily of water and glycerin. The gel is reabsorbed and eventually replaced with soft tissue ingrowth. The CaHA remains at the site of injection and has the potential for long-term augmentation. Although CaHA is approved for vocal fold augmentation, there have been no studies evaluating its safety and efficacy for this purpose.

METHODOLOGY

All persons undergoing vocal fold augmentation with CaHA between January 1, 2002 and June 1, 2003 were prospectively evaluated. All individuals underwent strobovideolaryngoscopy and were administered a disease-specific outcome instrument for glottal insufficiency (glottal closure index or GCI; Table 1) before and after vocal fold augmentation. Information regarding patient demographics, indications, technique, amount of injected implant, length of follow-up, and complications were recorded into a clinical database. The preaugmentation and most recent postaugmentation GCI were compared using the paired-sample *t* test.

The larynx of a woman who expired 3 months after injection was sectioned and histologically examined.

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Table 1. Glottal Closure Index (GCI)

Within the last MONTH how did the following problems affect you?	0 = No Problem, 5 = Severe Problem					
1. Speaking took extra effort	0	1	2	3	4	5
2. Throat discomfort or pain after using your voice	0	1	2	3	4	5
3. Vocal fatigue (voice weakened as you talked)	0	1	2	3	4	5
4. Voice cracks or sounds different	0	1	2	3	4	5
				Total		

The laryngeal specimen was fixed in 10% formalin and decalcified in 10% disodium ethylenediamine tetra acetate (EDTA) at a pH of 7.3 at 37°C. After the specimen was decalcified it was rinsed and processed using a paraffin infiltrator. The infiltrated tissue was then embedded in a paraffin block for sectioning. The block was cut on a rotary microtome and a hematoxylin and eosin (H & E) stain was performed.

RESULTS

A total of 39 vocal folds in 23 individuals were injected with CaHA. All individuals were injected peroral with microscopic guidance through a rigid laryngoscope under general anesthesia with intermittent venturi jet ventilation. The mean age of the cohort was 62 ± 18 years. Fifty-two percent (12/23) were male. The indications for augmentation were unilateral vocal fold paralysis (9/23), unilateral vocal fold paresis (5/23), presbylarynx (3/23), Parkinson's (3/23), bilateral vocal fold paresis (2/23), and abductor spasmodic dysphonia (1/20) (Table 2). The mean presurgical GCI was 15 (± 5). This improved to a mean postoperative GCI of 5 (± 5). The mean paired difference between preoperative and postoperative scores was 9 (± 6, $P < 0.001$). All persons except for the individual with abductor spasmodic dysphonia reported at least some symptomatic improvement. The mean amount of CaHA injected was 0.4 cc per vocal fold. The mean time of follow-up was 20 ± 23 weeks. Two individuals experienced partial implant absorption at 12 weeks and underwent a second injection. There were no adverse reactions. Postoperative strobovideolaryngoscopy revealed healthy-appearing vocal folds with normal mucosal waves in all individuals. There was no evidence of vocal fold stiffness or inflammation (Fig 1).

Examination of the glottis of a woman who died from metastatic small cell carcinoma 3 months after a unilateral injection with CaHA revealed no gross morphologic changes (Fig 2). Histologic examination (H & E, 40× magnification) displayed multiple clear round spaces representing decalcified embedded calcium hydroxylapatite spherules. There was no significant inflammatory response. A minimal macrophage reaction to the carboxymethyl-cellulose vehicle with a monolayer of macrophages surrounding each CaHA spherule was observed (Fig 3).

Table 2. Indication for vocal fold augmentation with CaHA

Indication	n	Percent
Left vocal fold paralysis	6	26%
Left vocal fold paresis	3	13%
Right vocal fold paralysis	3	13%
Presbylarynx	3	13%
Parkinson's disease	3	13%
Right vocal fold paresis	2	9%
Bilateral vocal fold paresis	2	9%
Abductor spasmodic dysphonia	1	4%

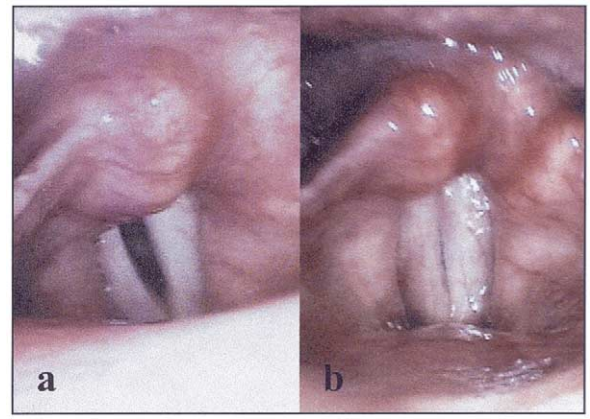

Fig 1. (a):Videoendoscopic image of a right vocal fold paralyzed in the paramedian position. **(b)**: Videoendoscopic image 3 months after injection of 0.5 cc of CaHA lateral to the right thyroarytenoid muscle.

DISCUSSION

Our initial experience with CaHA indicates that it may be a safe and effective alternative for vocal fold augmentation. Several caveats to this statement must be emphasized. Although some individuals in this cohort were followed for over a year, these data are still preliminary and long-term safety and efficacy must be established. All of the individuals in this cohort were injected by fellowship-trained laryngologists (PCB/

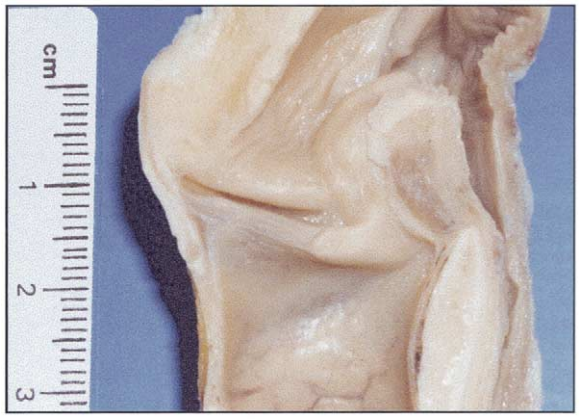

Fig 2. Right hemilarynx 3 months after CaHA injection. No gross morphologic changes are appreciated.

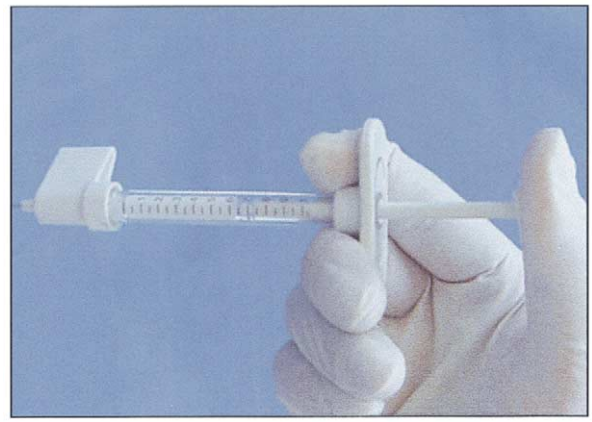

Fig 4. Each package of Radiance (BioForm Inc., Franksville, WI) includes 1 cc of CaHA in a luer lock syringe.

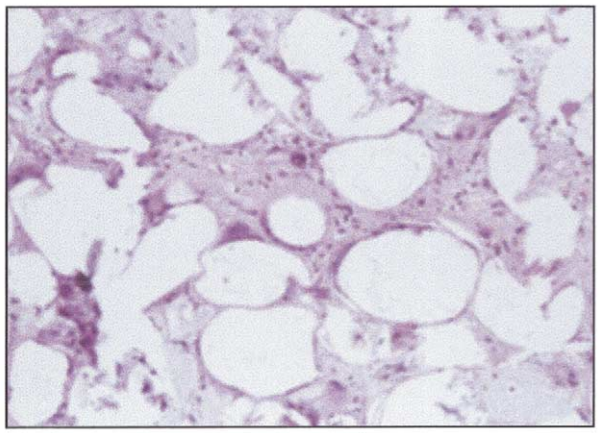

Fig 3. H & E stain at 40× magnification of human vocal fold 3 months after CaHA injection. The clear round spaces represent decalcified calcium hydroxylapatite spherules. Note the minimal inflammatory reaction with a monolayer of macrophages surrounding each CaHA spherule.

GNP) with microscopic guidance in the operating room under general anesthesia. This provided highly accurate injections deep into the lateral portion of the thyroarytenoid muscle. We are uncertain how the implant would perform if injected into a more superficial layer of the vocal fold, or if the vocal fold was overinjected. Great care was taken to avoid inadvertent implant delivery to the tracheobronchial tree. We are uncertain as to the danger of aspirated CaHA. The substance can also be injected percutaneously or per-orally in the office with indirect laryngoscopy and topical anesthesia. Because of the uncertainty regarding inaccurate injections, we chose to perform all procedures in the operating room under the microscope. Our data must not be compared to results obtained from percutaneous or per-oral injections performed under flexible laryngoscopic guidance in the office.

In addition to these warnings, our experience has allowed us to make several recommendations regarding the technique of CaHA injection. The first author does not use the injection system packaged with the CaHA (Fig 4). The first author (PCB) uses a Bruning's-style injector that allows for precise implant delivery (Storz viscous fluid injector, Karl Storz, Tuttlingen, Germany). Each click of the Storz injector delivers 0.04 cc of implant. This helps prevent overinjection that may occur when pressure due to "log-jamming" of the CaHA spherules in the needle is overcome with excessive plunger pressure. The senior author (GNP) prefers the injection system packaged with the CaHA and has not reported problems with "log-jamming."

After implant injection we recommend removing the needle very slowly from the vocal fold. This helps seal the puncture site and limit implant extrusion. We recommend 3 days of strict voice rest to help limit implant extrusion through the puncture site. The CO_2 laser on a low setting (2 watts) with a defocused beam has also been effective in "spot welding" the injection site. Since 2 of the individuals in our cohort experienced some implant absorption at 3 months, we inform all of our patients that a repeat injection may be necessary. Due to the fear of vocal fold overinjection with a potentially permanent implant, we have avoided overcorrection. For this reason, some of our patients have been undercorrected.

CaHA for vocal fold augmentation is available in 2 particle sizes. Standard Radiance has a particle size of 75 to 125 microns. It may be injected through a needle up to 21G. Radiance FN has a particle size of 25 to 45 microns. It may be injected through a needle up to 27G. Although Radiance FN is finer and will fit through a

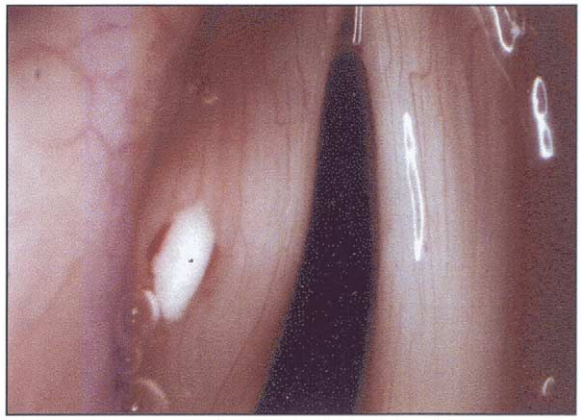

Fig 5. Extruding Radiance FN. This amount of extrusion is not seen with the standard Radiance.

smaller needle, in the first author's experience it is more likely to extrude out of the needle site (Fig 5). The development of smaller needles (25G) for laryngeal injection may prevent this extrusion.

CONCLUSIONS

Initial experience with vocal fold augmentation using CaHA is promising. Long-term safety and efficacy needs to be established.

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