Vocal Fold Augmentation with Injectable Calcium Hydroxylapatite: Short-Term Results

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Summary: Symptoms of unilateral vocal fold paralysis are improved significantly by augmenting the paralyzed vocal fold via vocal fold injection. In this trial, augmentation with a new calcium hydroxylapatite implant was evaluated. In addition, two different phonosurgical injection techniques were used, and these procedures were compared for accuracy and reliability. A total of 11 terminal patients with unilateral vocal fold paralysis underwent vocal fold injection with calcium hydroxylapatite. Efficacy of the implant was evaluated by comparing results from the Voice Handicap Index (VHI) and mean airflow measurements before and 6 months after injection. Surgeon evaluations determined the comparative benefits of either endoscopic direct vocal fold injection or percutaneous vocal fold injection. Six-month data were obtained for a cohort of five patients. VHI scores improved for all five patients available for full evaluation and four of the five achieved improvements in mean airflow rates. Of the remaining patients, one later had a medialization laryngoplasty, two died from their terminal diseases before the 6-month follow-up, and two of the remaining three reported satisfaction with the results via telephone follow-up. Vocal fold injection via endoscopic, direct laryngoscopy was found to be a more reliable procedure for vocal fold injection than percutaneous injection. Slight overinjection (10% to 15%) was found to provide optimum results. Vocal fold injection of calcium hydroxylapatite for unilateral vocal fold paralysis improved voice quality and reduced mean airflow rates in this patient group with short-term results. Long-term studies are needed to confirm the durability of these findings.

Key Words: Vocal cord paralysis—Vocal cord injection—Calcium Hydroxylapatite.

INTRODUCTION

Patients with unilateral vocal fold paralysis (UVFP) often suffer reduced quality of life because of voice and swallowing difficulties. Typical symptoms include a hoarse, breathy voice that is weak and difficult to sustain. Occasionally, there is difficulty
swallowing and aspiration can be a significant problem.\textsuperscript{1} Unless there is severe swallowing impairment, treatment focuses on improving voice quality, thereby improving quality of life. Voice therapy may provide adequate improvement and should be considered as either sole or adjunctive therapy. If voice therapy is inadequate to correct voice quality, phonosurgery to augment the paralyzed vocal fold may be indicated. The first modern surgical treatment for UVFP was vocal fold injection of Teflon (Teflon Mentor Company, Santa Barbara, California).\textsuperscript{2,3} Another treatment method for UVFP was developed in 1974, when Ishihiki et al\textsuperscript{4} introduced thyroplasty (medialization laryngoplasty). Several implantation procedures and a variety of implant products have since been investigated. Generally these phonosurgical techniques have proven successful.\textsuperscript{2,4–8} Often the particular technique preferred by physicians and patients is phonosurgical vocal fold injection. Injection is less invasive than medialization laryngoplasty and may provide results that are equally durable and effective.\textsuperscript{9}

With any of these procedures, a key obstacle has been the use of a satisfactory implant/injection material. The ideal injection material would be inert, biologically stable, and deliverable through a fine-gauge needle. Initially, polytetrafluoroethylene was thought to be a satisfactory material; however, long-term results have demonstrated an unacceptably high rate of granuloma formation.\textsuperscript{10} Another commonly used material has been either bovine or human collagen. Repeated injections of bovine collagen have demonstrated mild-to-moderate efficacy in patients with glottal incompetence caused by vocal fold scarring, but eventual resorption of the material has proven frustrating.\textsuperscript{11} Vocal fold injection with absorbable gelatin sponge foam (Gelfoam Pharmacia and Upjohn, Kalamazoo, Michigan) has also been an option. This material has been used successfully; however, the implant material is absorbed within 1 to 2 months. Thus, Gelfoam is appropriate only when the possibility exists for near-term recovery of vocal fold function.\textsuperscript{12} Fat and fascia vocal fold injection have also been used for vocal fold paralysis. The former has a variable success rate, and the latter has not been used by many surgeons.

None of these implant materials are completely satisfactory. Consequently, the introduction of a calcium hydroxylapatite injection material (Radiance; BioForm Inc., San Mateo, California) has been met with great interest. Calcium hydroxylapatite (CaHA) is a bioceramic compound of phosphate and calcium; it is inert and biologically stable. In the BioForm formulation, small particles of CaHA (25 to 125 microns) are suspended in an aqueous-based gel carrier. This design allows injection through needles as fine as 26-gauge. The stability and biocompatibility of CaHA have allowed it to be used successfully as an implant material in other applications.\textsuperscript{13,14}

Biocompatibility studies have demonstrated that CaHA creates no antigenic or inflammatory responses. These findings would be expected as it is formed from calcium and phosphate ions, which are natural to the human body (teeth, bone). This composition creates a highly dense bioceramic compound that supports the implant’s long-term durability. As a result, for several decades, it has been used as an implant material in procedures from plastic and reconstructive surgery to orthopedics and dentistry.\textsuperscript{13,14} While the gel carrier is absorbed, the small particles of calcium hydroxylapatite remain fixed in place. Surrounding tissue grows into the matrix of the implant as the gel is absorbed. Studies of the calcium hydroxylapatite implant formulation have found the implant to remain intact at the injection site with no evidence of migration or calcification of the CaHA for up to 5 years after injection.\textsuperscript{13,14}

\section*{METHODS}

\section*{Patients}

Between August 2002 and December 2002, 11 men and women with unilateral vocal fold paralysis underwent vocal fold injection to treat their voice symptoms. All patients were elderly (\textgtrsim65 years of age) and their conditions were diagnosed with terminal cancer. In most cases, their cancer was the cause of their vocal fold paralysis; in one patient, the UVFP had resulted from thyroid surgery for benign thyroid disease and another patient had an idiopathic etiology.
Design

Patients underwent either endoscopic vocal fold injection (EVFI) or percutaneous vocal fold injection of the CaHA implant. PVFI was performed in the office setting using local anesthesia. EVFI has been described previously and was done in the operating room under local anesthesia with minimal sedation. The amount of implant injected ranged from 0.20 cc to 1.10 cc. All patients were placed on voice rest for 6 days after the injection procedure, although there are no data to support the value of this practice. Six months after the procedure, patients were contacted for follow-up evaluation.

In the EVFI procedure, a slotted, anterior commissure laryngoscope (Pilling Co., Fort Washington, Pennsylvania) was positioned over the vocal fold to be injected so that the distal tip of the laryngoscope retracted the false vocal fold. This position was maintained throughout the procedure to ensure good exposure and to avoid distorting the true vocal fold. The injection needle (18 gauge) attached to a 1-cc syringe of CaHA was passed through the laryngoscope under direct endoscopic guidance using a 30-cc long, zero degree, 5-mm diameter telescope (Karl Storz Inc., Culver City, California). After injection, the needle was retracted into the laryngoscope, and glottic closure during phonation was observed using the endoscopic image.9

Percutaneous vocal fold injections were administered through the thyroid cartilage or through the cricothyroid membrane directly into the vocal fold using a 25-gauge needle. A flexible, fiberoptic laryngoscope was used to visualize the vocal folds during the procedure.15

Outcome measures

To assess the patients’ perception of their voice handicap and glottal closure efficiency, two evaluation tools were instituted before and 6 months after vocal fold injection. Spirometry assessments at each visit measured the mean flow rate of expelled air during phonation (AeroPhone; Kay Elemetrics, Englewood, New Jersey). The mean flow rate assessment method has been previously described.16 Patients completed the Voice Handicap Index (VHI) before and after the procedure. The VHI is a patient-based survey comprising 30 statements that allow quantification of the patient’s perception of his or her vocal handicap. A two-tailed t-test was used to evaluate the VHI results.

The two injection procedures were evaluated and compared by the surgeon in terms of accuracy and reliability in placing the implant. None of the patient’s received postinjection voice therapy or antibiotics.

RESULTS

Patient characteristics

A total of 11 patients underwent CaHA vocal fold injection. Eight patients received injection via an endoscopic approach, and three patients received a percutaneous vocal fold injection. Preinjection and postinjection VHI assessments and mean airflow evaluations were completed on a cohort of five patients at 6 months after injection, four of the patients had an EVFI, and one was treated with a percutaneous vocal fold injection.

VHI and spirometry results

In the cohort of five patients with complete evaluation data, all the VHI scores (5/5) and most of the aerodynamic measurements (4/5) demonstrated marked improvement after the procedure. At the 6-month follow-up, all patients reported a positive change in their perception of voice handicap (Table 1). Improved vocal efficiency was demonstrated with reduced mean airflow for four of the five subjects (Table 2). Overall, the mean volume of air expelled while speaking was cut nearly in half after vocal fold injection.

Incomplete data were available for the remaining six patients. One patient was treated successfully with a medialization laryngoplasty 6 weeks after injection because of incomplete voice improvement after CaHA injection. Through telephone follow-up, it was determined that two patients had died from their cancer. Of the remaining three patients, two reported that they were satisfied with the results of the procedure by telephone follow-up but were unable to return for formal evaluation. The last patient was lost to follow-up.

Evaluation of injection procedures

Endoscopic vocal fold injection was the preferred injection procedure for accuracy and reliability, according to the surgeon (CAR). Placing the implant
TABLE 1. Voice Handicap Index Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre-Injection Score*</th>
<th>Post-Injection Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>104</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>101</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>54</td>
</tr>
<tr>
<td>Mean</td>
<td>73</td>
<td>42**</td>
</tr>
</tbody>
</table>

*Higher scores indicate greater disability.

**P = 0.054.

in the correct location was more difficult using the percutaneous method, and precise placement could not be achieved consistently with the percutaneous method. In contrast, the EVFI technique facilitated an easy vocal fold injection and allowed an accurate placement of the implant in all cases.

Stroboscopy examination on all 6-month follow-up patients after CaHA injection demonstrated neither evidence of material migration nor diminution of the mucosal wave activity of the injected vocal fold. In fact, the vocal fold vibratory activity was improved in all five patients because of the improved vocal fold closure pattern.

The one patient treated with a medialization laryngoplasty 6 weeks after CaHA injection experienced significant and immediate postoperative nausea and vomiting after the injection. This may have contributed to the poor injection result. In this same patient, some CaHA implant was found in the paraglottic space during the medialization laryngoplasty and was removed through the medialization laryngoplasty window without difficulty.

DISCUSSION

Enhancing quality of life by creating a more effective and understandable voice is the primary purpose of phonosurgical vocal fold injection. Thus, a patient’s subjective experience of improvement is the most important measure of a procedure’s efficacy. In this short-term trial, injection with the calcium hydroxylapatite produced successful results, with all fully evaluated patients reporting an improvement in voice quality. Supporting these self-evaluations were the aerodynamic results comparing mean airflow rates before and after injection. Unilateral vocal fold paralysis usually causes a breathy voice with a considerable amount of air escaping during phonation. Thus, a reduction of the preinjection mean airflow rate during phonation is strong evidence of the successful vocal fold augmentation with the CaHA injection material at 6 months. The one patient with an improved VHI but not a positive change in the mean airflow most likely was using an altered speaking technique after injection, which relied on increased airflow. This patient (no.1) did have a relatively high VHI at 6 months and thus may not have been completely medialized with the CaHA injection.

A second objective of this investigation was to compare two injection techniques for vocal injection: EVFI and percutaneous vocal fold injection. It was immediately apparent to the surgeon that EVFI was the more accurate and reliable method. Consistent and reliable vocal fold injection accuracy could not be achieved in his hands with the percutaneous injection method. In contrast, EVFI facilitated precise placement of the CaHA.

An incidental but important finding in this regard was the benefit of slight overinjection with either procedure. Part of the design of the CaHA implant is the absorption of its gel carrier and consequent infiltration of surrounding tissue. In the 6-month window of this trial, because of carrier absorption, a 10% to 15% overinjection was found to provide optimal results.

CONCLUSION

Based on the preliminary results of this trial, the CaHA formulation is a promising addition to the
treatment options available for patients with unilateral vocal fold paralysis. The implant has the desired characteristics of being inert, biologically stable, and injectable through a fine-gauge needle. In addition to its reliable use with endoscopic direct laryngoscopy or with suspension microlaryngoscopy, it can be injected transorally, under local anesthesia, thus allowing the injection to be an in-office procedure. It also can be removed easily at 6 weeks, if necessary. To confirm its long-term utility in improving patients’ vocal capabilities and consequent quality of life, a larger long-term study using CaHA is underway.

REFERENCES