Objective: To determine the long-term clinical efficacy and safety of injections of Artecoll, a soft-tissue filler consisting of a suspension of polymethyl methacrylate microspheres in a 3.5% solution of bovine collagen, into a vocal fold for managing glottal insufficiency secondary to unilateral vocal fold motion impairment.

Design: Single-institution retrospective study.

Setting: A single tertiary care teaching hospital of Sungkyunkwan University School of Medicine.

Patients: Ninety-six patients with unilateral vocal fold motion impairment.

Interventions: Percutaneous Artecoll injection laryngoplasty under local anesthesia.

Main Outcome Measures: Acoustic, aerodynamic, and stroboscopic analyses were performed before injection and 1 week and 3, 6, and 12 months after injection. Two speech-language pathologists performed the perceptual assessment, and we used the subjective rating of hoarseness by the patients.

Results: The maximal phonation time, shimmer (amplitude variation), jitter (frequency variation), and ratio of noise to harmonic showed significant improvement 3 months after injection; these improvements were maintained 12 months after injection (P < .05). The GRBAS scale (overall grade of hoarseness, roughness, breathiness, asthenicity, and strain) grades and subjective patient-rated scores of hoarseness improved from 1 week after injection, and the improvements were maintained 12 months after injection (P < .05). We observed no significant early or delayed adverse events.

Conclusion: Injection laryngoplasty with Artecoll is a safe, useful, and durable treatment option for the management of glottal insufficiency secondary to unilateral vocal fold motion impairment.
solution of partly denatured bovine collagen (80% by volume), which serves as a vehicle for deep dermal implantation. After injection, the collagen carrier is rapidly degraded by the body within 1 to 3 months and is completely replaced by the body’s own collagen at a similar rate, ensuring a steady augmentation result. The PMMA microspheres in Artecoll have exceptional surface smoothness, they are large enough not to be phagocytosed by macrophages, and they have no electrostatic charge, so they become encapsulated by the patient’s own collagen fibers. Therefore, they do not easily migrate in body tissues, and they have little foreign body reaction or granuloma formation. Since its introduction in 1994, an estimated 400,000 patients have been treated with Artecoll for soft-tissue augmentation, with a reported complication rate of only 0.01%. On October 27, 2006, the US Food and Drug Administration approved ArteFill (Artes Medical, Inc, San Diego, California) for the augmentation of wrinkles and soft-tissue contour deficiencies; ArteFill has the same composition as Artecoll but the microspheres are of a more uniform size.

In this study, we injected Artecoll into the paralyzed vocal folds of 96 patients who presented with dysphonia secondary to unilateral VFMI. The objective and subjective acoustic measurements, which were obtained until 12 months after injection, were compared to evaluate the long-term clinical efficacy of injection laryngoplasty with Artecoll. Any adverse effects were also noted. To our knowledge, this is the first report of injection laryngoplasty with Artecoll for treating patients with dysphonia secondary to unilateral VFMI.

METHODS

SUBJECTS

This study included 96 adult patients with dysphonia secondary to unilateral VFMI who underwent injection laryngoplasty with Artecoll between December 17, 2003, and November 30, 2005, at Samsung Medical Center. Informed consent was obtained from all of the patients. The patients or their guardians decided whether the patient would receive injection laryngoplasty depending on the degree of the patient's dysphonia and the social desire for a better voice. We excluded those patients who had a history of voice surgery, including injection laryngoplasty with other materials or laryngeal framework surgery. The study patients included 57 men and 39 women, with a mean age of 55 (range, 19-93) years. Nerve injury after thoracic surgery (46 patients [48%]) and thyroid surgery (20 [21%]) were common causes of unilateral VFMI (Table 1).

INJECTION TECHNIQUE

All of the injections were performed with the patient under local anesthesia and by the same surgeon (Y.-I.S.) at the day surgery center of our institution. Preinjection medication consisting of atropine sulfate, 0.5 mg, and meperidine hydrochloride, 50 mg, was administered intramuscularly, and 5 mL of lidocaine hydrochloride, 4%, was nebulized into the pharyngolarynx by the patient as he or she performed deep breathing for 10 minutes. To lessen the discomfort of the laryngoscope, 3 mL of lidocaine hydrochloride, 2%, was sprayed into the wider nasal cavity with the use of an atomizer. With the patient in the supine position and the neck extended, the skin was sterilized with povidone solution, and 0.5 to 1.0 mL of lidocaine hydrochloride local anesthetic in a 2% solution was subcutaneously injected into the area of the cricothyroid membrane. A flexible fiberoptic laryngoscope (ENF P3; Olympus, Tokyo, Japan) was introduced through the nasal cavity. Thereafter, a 26-gauge, 3.8-cm needle was advanced in a posterolateral direction 2 mm lateral from the midline of the cricothyroid membrane. After we confirmed that the tip of the needle was correctly positioned at the area of tissue lateral to the vocal process tip or at the midpoint of the membranous vocal fold, Artecoll was slowly injected. We tried to inject it just lateral to the vocal ligament in the horizontal plane and at the same level or at a level inferior to the free edge of the vocal fold in the vertical plane (Figure 1B). Given the volume of the needle and the small amount of lidocaine mixed in the Artecoll, we aimed for a slight overcorrection beyond the midline. The average amount of injected Artecoll was 0.49 (range, 0.25-1.00) mL.

OBJECTIVE EVALUATION

Objective and subjective voice evaluations were performed before injection and 1 week and 3, 6, and 12 months after injection. For the objective evaluations, we obtained the maximal phonation time (MPT), measurement of shimmer (amplitude variation) and jitter (frequency variation), ratio of noise to harmonics (NHR), and results of stroboscopic analyses. We used a commercially available computer program (Multi-Dimensional Voice Program; Kay Elemetrics Corp, Lincoln Park, New Jersey) for the acoustic analyses. With the patient in a quiet room, a microphone worn over the head was placed 3 cm from the patient’s mouth; the patient, in a sitting position, produced a continuous vowel sound /a/ at an easy, comfortable pitch and loudness. The voice spectrum was analyzed with exclusion of the portions of the spectrum within 0.2 second from the beginning and the end of phonation, to eliminate their effects on the analysis. In the designated range, we calculated the fundamental frequency, the percentages of jitter and shimmer, and the NHR.

Aerodynamic analysis was performed using a spectrum analyzer (Aerophone II Voice Function Analyzer; Kay Elemetrics Corp). A vowel /a/ was produced more than 3 times at maximum length and at constant pitch and loudness, and the MPT.
was measured. Stroboscopic analysis was performed using a rhinolaryngeal stroboscope (model 9100; Kay Elemetrics Corp). The mucosal waves, the patterns of glottal closure, and the amplitude and phase symmetry of the vocal fold vibrations were analyzed while the phoneme /i/ was being produced.

SUBJECTIVE EVALUATION

For the subjective evaluations, we performed perceptual grading using the GRBAS scale (overall grade of hoarseness, roughness, breathiness, asthenicity, and strain), and the patients rated their own hoarseness. For the GRBAS scale, 2 experienced speech-language pathologists listened to the recorded sentence and classified it into the rough, breathy, asthenic, and strained components. Overall grading of hoarseness was rated on a scale of 0 to 3, where 0 indicated a normal voice and 1, mild, 2, moderate, and 3, severe hoarseness. The subjective ratings of hoarseness by the patients were obtained by using a visual analog scale with a scale of 0 to 100.

STATISTICAL ANALYSIS

Data including the MPT, shimmer, jitter, NHR, GRBAS grades, and visual analog scale scores of hoarseness obtained before and after the injection were analyzed using the paired t test and the Mann-Whitney test. Significance levels for all the analyses were set at \( P < 0.05 \). Unless otherwise indicated, data are expressed as mean (SD).

RESULTS

Of the 96 patients who underwent Artecoll injection laryngoplasty, 46 (48%) had satisfactory outcomes with a single injection, 38 (40%) required a second injection, and 10 (10%) showed spontaneous recovery of their vocal fold motion during the follow-up period. Of the 96 patients who underwent Artecoll injection laryngoplasty, 46 (48%) had satisfactory outcomes with a single injection, 38 (40%) required a second injection, and 10 (10%) showed spontaneous recovery of their vocal fold motion during the follow-up period (Figure 2). Pre-injection and postinjection stroboscopic findings of a representative case are presented in Figure 3. For 1 patient, Artecoll was inadvertently injected into the superficial space medial to the vocal ligament, and the material was easily removed by laryngomicroscopic surgery. Medialization thyroplasty and/or arytenoid adduction were performed in 4 patients, in 1 patient after a single injection and in 3 after the second injection.
OBJECTIVE VOICE EVALUATION AFTER A SINGLE INJECTION

The results of the objective assessment after a single injection are summarized in Table 2, in which the data of 46 patients who received a single injection and those who received the second injection more than 12 months after the first injection were analyzed together. The MPT, shimmer, jitter, and NHR values began to show significant improvement by 3 months after injection. The mean MPT was 4.17 (3.13) seconds before injection, 5.78 (4.84) seconds at 1 week, 8.20 (4.12) seconds at 3 months, 9.72 (5.46) seconds at 6 months, and 8.09 (4.57) seconds at 12 months after injection. The MPTs at postinjection months 3, 6, and 12 were significantly better than those measured before and 1 week after injection ($P < .001$).

Shimmer values improved from 10.14% (6.37%) before injection to 5.67% (3.18%) 3 months after injection; this improvement was maintained 12 months after injection ($P < .001$). Jitter values improved from 4.61% (3.45%) before injection to 2.26% (2.52%) 12 months after injection, and the NHR improved from 0.24 (0.14) before injection to 0.18 (0.15) 12 months after injection, improvements that were also statistically significant ($P = .002$ and $P = .02$, respectively).

The mucosal wave and phase symmetry were intact in most of the patients when satisfactory glottal closure was obtained. The vibratory amplitude seemed to be slightly decreased, but the decrease was not clinically significant (data not shown).

SUBJECTIVE VOICE EVALUATION AFTER A SINGLE INJECTION

After a single injection, the perceptual overall grading of hoarseness by the speech-language pathologists was 2.71 (0.50) before injection and 1.74 (0.82) at 1 week, 1.24 (0.77) at 3 months, 1.08 (1.00) at 6 months, and 0.83 (0.92) at 12 months after injection. The patients’ ratings of their own hoarseness (using a visual analog scale of 0-100) were 72.00 (28.00) before injection and 57.32 (22.80) at 1 week, 37.70 (22.04) at 3 months, 34.38 (22.27) at 6 months, and 26.00 (17.91) at 12 months after injection (Table 2). The perceptual grade and subjective rating of hoarseness were significantly improved at 1 week after injection and again at 3 months compared with those values of 1 week; these values were maintained as improved during the 12 months of follow-up.

SECOND INJECTIONS

Of 96 patients, 38 (40%) underwent a second injection, mostly because of insufficient improvement after the first injection or worsening of their voice quality over time. The average interval between the first and second injections was 4 months, with a range of 1 to 12 months. Ten (26%) of the 38 patients received the second injection within 1 month after the first one; 9 patients (24%), 1 to 3 months after the first one; 4 patients (11%), 3 to 6 months after the first one; and 15 patients (40%), 12 months after the first one. Although the perceptual values and MPT improved after the second injection compared with the preinjection values, the values after the second injection were not significantly different from those obtained just before the second injection (Table 2).
Subjective Measurements

Ten of the 96 patients receiving Artecoll injection showed partial or complete recovery of their vocal fold motion. Spontaneous recovery was noted 2 to 12 (mean, 5.5) months after injection. After recovery, the MPT was 9.68 (5.63) seconds, shimmer was 5.35 (3.13) seconds, jitter was 1.91 (1.77) seconds, and NHR was 0.14 (0.04) seconds. The perceptual GRBAS grading was 0.88 (0.83), and the patients’ own rating of hoarseness was 26.67 (16.19) after recovery.

ADVERSE EFFECTS

The vital signs, including heart rate, blood pressure, and oxygen saturation, were monitored, and they remained stable before, during, and after the procedure. Most of the patients reported no pain or discomfort around the injection site. There was minor bleeding when the needle punctured the tracheal mucosa, but the incidence of puncture and the resultant bleeding decreased as the surgeon gained more experience. All of the bleeding was negligible and stopped spontaneously within 1 minute. There were no observations of laryngeal edema, swelling, or dyspnea immediately after injection. There was no identifiable erythema, swelling, granuloma formation, or other local inflammatory signs in the skin and vocal fold when the patients underwent reevaluation 1 week and 3, 6, and 12 months after injection.

Artecoll was injected into the submucosal plane in 1 patient, which resulted in a marked reduction of the mucosal wave and unsatisfactory acoustic and perceptual voice measurements even 12 months after injection. While under general anesthesia, this patient underwent a procedure in which a longitudinal mucosal incision was made on the superior surface of the vocal fold and as much Artecoll as possible in the submucosal layer was carefully removed with cup forceps. Ultimately, improvement in the patient’s voice quality and recovery of the mucosal wave, vibration amplitude, and phase symmetry were obtained after the removal of the Artecoll. The objective and subjective voice measurements improved compared with those measured before the injection (data not shown).

Table 2. Results of Voice Assessment After Injections

<table>
<thead>
<tr>
<th></th>
<th>Objective Measurements</th>
<th>Subjective Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MPT, s</td>
<td>Shimmer, %</td>
</tr>
<tr>
<td>Before injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time after injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 wk</td>
<td>4.17 (3.13)</td>
<td>10.14 (6.37)</td>
</tr>
<tr>
<td>3 mo</td>
<td>5.78 (4.84)</td>
<td>10.22 (9.27)</td>
</tr>
<tr>
<td>6 mo</td>
<td>8.20 (4.12)</td>
<td>5.67 (3.18)</td>
</tr>
<tr>
<td>12 mo</td>
<td>9.72 (5.46)</td>
<td>6.40 (3.74)</td>
</tr>
<tr>
<td></td>
<td>8.09 (4.57)</td>
<td>6.41 (6.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MPT, maximal phonation time; NHR, noise to harmonic ratio.

The P values were obtained by comparing the values of “before injection” with those of different time points after injection.

The many advances in novel materials have allowed injection laryngoplasty to regain its popularity. Autologous fat and hyaluronic acid are major topics of recent publications because these materials are known to have excellent biocompatibility without the risk of allergic reactions. However, autologous fat must be obtained from some inevitable morbidity, and its resorption rate is unpredictable. Although some reports have claimed that hyaluronan gel has an efficacy of more than 2 years, our experience with cross-linked hyaluronic acid has shown that most of the patients failed to maintain the effects after approximately 3 to 6 months, and additional injection laryngoplasty was ultimately required. Therefore, we searched for and focused on the
more stable material, Artecoll, which has proved to be a reliable and predictable soft-tissue filler during more than 10 years of clinical use. Artecoll is an alloplastic material composed of PMMA microspheres suspended in a mixture of bovine collagen, 3.5% (atelocollagen); lidocaine, 0.3%; and sodium chloride, 0.3%, in a phosphate buffer set at a pH of 7.3. The PMMA microspheres, which have a defined diameter of 32 to 40 µm, act as a scaffold and a stimulus for continuous production of the tissue. The microspheres become encapsulated with the collagen fibers secreted by the body’s own fibroblasts.2,12

Of the 96 patients who received Artecoll injections, 46 (48%) achieved satisfactory outcomes with just a single injection. Among the 38 patients (40%) who required second injections, half of them (19 patients) received the reinjection within 3 months. Ten of these 19 patients stated that the positive effects lasted for only a few days. One possible reason for this failure is an improper injection technique. If we punctured the mucosa while advancing the needle, there would be a certain amount of inevitable leakage of the injected Artecoll. Inadequate case selection may be another reason for the failure. If a wide posterior gap is present or there are significant vertical level differences between the 2 vocal folds, then theoretically injection laryngoplasty cannot be an appropriate procedure. The fact that additional injection for those patients failed to show further improvement may support this assumption.

There is a much lower rate of allergic reaction to the atelocollagen of Artecoll than to another collagen filler (Zyderm; Inamed Aesthetics, Santa Barbara, California) (0.1% vs 3%).2,12 Although Artecoll is approved for use without a skin test in some European countries and also in Canada,13,14 the possibility of allergic and hypersensitivity reactions to bovine collagen must be kept in mind and properly explained to the patients before obtaining their consent. We performed skin tests for the earlier trials but not for every patient. Although we have experienced no anaphylactic reactions so far, we believe that at least 1 intradermal collagen skin test should be mandatory.

A recent animal study of Artecoll injected into the paralyzed vocal fold of beagles demonstrated that the mucosal waves of the Artecoll-treated vocal fold were not different from those of the normal contralateral one.15 In addition, there were no significant foreign body reactions when the sites were histologically evaluated 6 months after injection.12 Artecoll may produce granulomas in a small number of patients receiving the injections; however, the incidence of true granuloma formation is likely to be very low and has been described as a rare event, occurring in less than 0.01% of patients.3

In our study, we saw no significant early or delayed inflammatory reactions such as swelling, redness, or granuloma formation.

The materials for performing injection laryngoplasty in the patients with unilateral VFMI should be selected according to the purpose of the surgery. For permanent correction, calcium hydroxyapatite17 and polydimethylsiloxane gel18 have been introduced recently, but these should not be used in cases with a possibility of spontaneous recovery because of their permanent and irreversible nature. Given the fact that PMMA microspheres will be in the injected site as a permanent scaffold that constitutes about 20% of the injected volume, there may be arguments against using Artecoll in patients who have the potential for spontaneous recovery from VFMI.

Ten patients in this study achieved spontaneous recovery during the follow-up period. Five of them showed a complete or almost complete return of vocal cord mobility. After spontaneous recovery of vocal cord motion, these patients reported no dissatisfaction with their voice quality, although none of the 5 patients was a professional speaker or singer. The objective data helped us conclude that there would be no harmful effect of injected Artecoll even in cases of spontaneous recovery, but only if the material is not superficially injected into the lamina propria.

In this study, iatrogenic nerve injury was the most common cause of VFMI, whether the injury was inevitable or inadvertent. The rapport between the physician and the patient may break down if a patient experiences abrupt and unexpected dysphonia after an otherwise successful thoracic or thyroid surgery. Because improvements in voice quality are usually observed immediately after injection, and because there was no evident harmful effect of injected Artecoll, even in the patients with spontaneous recovery from VFMI, injecting Artecoll in patients who experience an unexpected VFMI would probably help to maintain a good physician-patient relationship and to minimize the patient’s distress.

In summary, of the 96 patients who underwent Artecoll injection laryngoplasty, 46 (48%) had satisfactory outcomes with a single injection. The MPT, shimmer, jitter, and NHR values began to show significant improvement from 3 months after injection, and this improvement was maintained 12 months after injection. No significant early or delayed adverse events were observed. It was technically easy to remove Artecoll that was inadvertently placed in the lamina propria. Therefore, we conclude that injection laryngoplasty with Artecoll is a convenient, safe, useful, and durable option for managing glottal insufficiency secondary to unilateral VFMI.
REFERENCES