Injection Laryngoplasty Using Micronized Acellular Dermis for Vocal Fold Paralysis: Long-term Voice Outcomes

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Abstract

Objectives. Micronized acellular dermis has been used for nearly 15 years to correct glottic insufficiency. With previous demonstration of safety and efficacy, this study aims to evaluate intermediate and long-term voice outcomes in those who underwent injection laryngoplasty for unilateral vocal fold paralysis. Technique and timing of injection were also reviewed to assess their impact on outcomes.

Study Design. Case series with chart review.

Setting. Tertiary care center.

Subjects and Methods. Patients undergoing injection laryngoplasty from May 2007 to September 2012 were reviewed for possible inclusion. Pre- and postoperative Voice Handicap Index (VHI) scores, as well as senior speech-language pathologists’ blinded assessment of voice, were collected for analysis. The final sample included patients who underwent injection laryngoplasty for unilateral vocal fold paralysis, 33 of whom had VHI results and 37 of whom had voice recordings. Additional data were obtained, including technique and timing of injection.

Results. Analysis was performed on those patients above with VHI and perceptual voice grades before and at least 6 months following injection. Mean VHI improved by 28.7 points at 6 to 12 months and 22.8 points at 12 months (P = .001). Mean perceptual voice grades improved by 17.6 points at 6 to 12 months and 16.3 points at 12 months (P < .001). No statistically significant difference was found with technique or time to injection.

Conclusion. Micronized acellular dermis is a safe injectable that improved both patient-completed voice ratings and blinded reviewer voice gradings at intermediate and long-term follow-up. Further investigation may be warranted regarding technique and timing of injection.

Keywords
vocal fold paralysis, glottal incompetence, vocal cord injection, injection laryngoplasty, micronized acellular dermis

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Unilateral vocal fold paralysis (UVFP) with associated glottal incompetence is frequently encountered in general otolaryngology practices today. Patients often present with dysphonia, dysphagia, and recurrent aspiration. Procedures have been developed to minimize these symptoms by promoting glottic closure, including medialization thyroplasty, laryngeal reinnervation, and injection laryngoplasty. Brunings first introduced the concept of injection laryngoplasty in 1911,¹ and multiple substances have since been developed for augmentation of the vocal fold. These include calcium hydroxylapatite, carboxymethylcellulose, hyaluronic acid derivatives, and many others.²

Acellular dermis (AlloDerm; LifeCell Corporation, Somerville, New Jersey) is developed from processed cadaveric dermis after selective removal of dermal and epidermal components.³ What remains is an acellular matrix of collagen and elastin that is immunologically nonreactive and may allow for tissue in-growth and incorporation of the implant into the native tissue. Micronized acellular dermis

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(Cymetra; LifeCell Corporation) was developed as an injectable form that preserves its collagen and elastin matrix and has been studied now for nearly 15 years. Pearl and colleagues first demonstrated short-term improvement in glottal incompetence by reviewing voice outcomes, acoustic analysis, and videostroboscopic findings at 3 months in a series of 14 patients. Tan and Woo’s large retrospective review demonstrated long-term efficacy of micronized acellular dermis in the treatment of glottal incompetence secondary to an array of pathologies; however, voice outcomes were not tabulated in this study. While it has been shown to be a safe and efficacious injectable material in the treatment of glottal incompetence, demonstration of long-term voice outcomes has been studied in only a limited fashion.

The primary objective of this study is to evaluate the intermediate and long-term voice outcomes after vocal fold injection augmentation with micronized acellular dermis by measurement of Voice Handicap Index (VHI) scores and blinded reviewer assessment of voice in the setting of vocal fold paralysis. Secondary objectives include evaluation of injection technique and timing of injection to determine their effect on overall outcomes.

Methods

A case series with chart review was performed for all patients undergoing injection laryngoplasty with micronized acellular dermis from March 2007 to September 2012. Indications for injection were unilateral true vocal fold paralysis due to a variety of etiologies (Figure 1), and all injections were performed by the senior author (A.J.M.). Approval for this study was obtained from the Institutional Review Board of the Louisiana State University Health Sciences Center in New Orleans, Louisiana, and Our Lady of the Lake Regional Medical Center.

Patients were asked to complete a standard VHI at the preprocedure clinical encounter and at each subsequent postprocedure visit. The VHI is a standard 30-item questionnaire that is used for assessment of voice disorders and their potential effect on patients’ daily activities. A scale from 0 to 4 is used for each part of the questionnaire for a maximum score of 120 and a minimum score of 0. In addition, patients were asked to read the “rainbow passage” at their pre- and postprocedure visits, and their voices were recorded for analysis. The recordings were de-identified and reviewed by 2 blinded senior speech-language pathologists with >10 years of experience. Voice was graded on a scale from 0 to 100, with 0 being aphonia and 100 being the optimal voice. This scoring system was used in lieu of the GRBAS (grade, roughness, breathiness, asthenia, and strain) for the representation of scores along a visual analog scale, analogous to what is seen in Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) perceptual analysis. In this manner, a vertical tick mark is placed along a 100-mm linear scale, which is then measured and a score recorded from a possible total of 100. Developers of CAPE-V have noted that visual analog scales are easier for raters to use and inhibit end effects, which may be seen in the use of ordinal scales such as the GRBAS. Given the fact that the rainbow passage was used for voice recordings, CAPE-V analysis could not be directly utilized. However, the rainbow passage is an established phonetically balanced statement, and the 0-100 visual analog scale of the CAPE-V has demonstrated reliability and validity. The mean scores of the 2 raters were used for final analysis. VHI scores and perceptual voice grades were recorded at different time intervals, including preoperatively, 6 to 12 months following injection, and >12 months following injection. “Intermediate” voice outcomes are defined as those scores from the 6- to 12-month follow-up interval, and “long-term” voice outcomes are defined as results from the >12-month follow-up interval. Patients who had spontaneous return of motion or in whom a different injectable material was used were excluded. Patients who did not have a complete reading of the rainbow passage were excluded from the perceptual analysis.

Additional data were collected, including age, etiology and laterality of paralysis, technique of injection, and timing to injection from the onset of paralysis. Statistical analysis was performed with SPSS (version 13.0; IBM, Chicago, Illinois). Wilcoxon’s signed-rank test was utilized for comparison of mean VHI scores, as the VHI data were not normally distributed, and a paired-sample t test was used for comparison of perceptual voice grades, as these data were normally distributed. The Mann-Whitney U test and independent-sample t test were used when technique and time to injection were analyzed.

Results

A total of 140 patients were identified who underwent injection laryngoplasty with micronized acellular dermis for UVFP between March 2007 and September 2012. Of those 140 patients, 66 had preoperative and postoperative VHI scores available for review and comparison. Thirty-three patients did not have a completed VHI score 6 months after injection and were thus excluded. The other 33 patients met inclusion criteria and were encompassed in the final analysis. In this group of patients, 13 (39%) were male and 20 (61%) were female, with an average age of 66.3 years (range, 20-86). Thirteen (39%) underwent transoral injection in the operating room, while the other 20 (61%) underwent transcervical injection under local anesthesia in the clinic.
Fifteen patients (45%) underwent injection ≤6 months from the onset of paralysis, while 17 others (52%) underwent injection >6 months following the onset of paralysis. One patient did not have time to injection adequately documented.

Upon review of the voice recordings, a total of 37 patients were identified who completed voice recordings prior to the procedure and at least 6 months postinjection. Patients without a full recording both before and at least 6 months after the injection were excluded. In this group, 16 (43%) were male and 21 (57%) were female, with an average age of 65.4 years (range, 20-86). Eleven patients (30%) underwent injection in the operating room, and the remaining 26 (70%) underwent transcervical injection in the office. Fifteen patients (41%) were injected ≤6 months from the onset of paralysis, while 18 others (49%) were injected >6 months from the onset of paralysis. Four patients did not have time to injection adequately documented.

Of patients with both VHI data and perceptual voice grades included in the analysis, 3 ultimately required repeat injection laryngoplasty, all of whom were initially injected >6 months from the onset of paralysis. There were no complications related to injection, and none of the above patients required laryngeal framework surgery during this study period.

VHI Data

As described, 33 patients were ultimately identified with long-term follow-up data for analysis. Mean follow-up from the time of injection for this group was 16.9 months. Twenty-three patients (69.7%) had follow-up at 6 to 12 months following injection augmentation, and mean VHI scores improved from 66.6 to 37.9 postoperatively (P < .001). Twenty-two patients (66.7%) had VHI scores preoperatively and >12 months after injection, again showing improvement from 65.2 to 42.4 (P = .001; Table 1).

Perceptual Voice Grades

Thirty-seven patients had voice recordings both preoperatively and at long-term postoperative visits. The mean follow-up time for this group following injection was 14.3 months. Twenty-five patients (67.6%) had recordings at 6 to 12 months following injection augmentation, and their mean perceptual voice grades improved from 51.7 preoperatively to 69.3 postoperatively (P < .001). Another 19 patients (51.4%) had recordings >12 months following injection, and they also demonstrated significant improvement in mean perceptual voice grades from 48.9 preoperatively to 65.2 postoperatively (P < .001; Table 1).

Timing to Injection and Technique

We also looked at time from onset of paralysis to injection to assess its impact on voice outcomes, defining early injection as ≤6 months after onset and late injection as >6 months from onset. The early and late groups experienced similar improvement in the change in VHI scores at the 6- to 12-month and >12-month follow-up intervals, with no statistically significant difference between them (Table 2). Analysis of the perceptual voice scores yielded similar results. Both groups demonstrated improvement in the change in perceptual voice grade at each follow-up interval, with no significant difference in the amount of change between the early and late injection groups.

No statistically significant difference was noted in the change in mean VHI or perceptual voice grades when patients were subdivided by in-office transcervical injection versus injection under general anesthesia in the operating room (Table 3).

Discussion

Unilateral vocal fold paralysis causing glottic insufficiency continues to be a routinely encountered problem in otolaryngology clinics. Treatments have developed to improve glottal incompetence, including laryngeal framework surgery, reinervation procedures, and injection laryngoplasty. Much attention has been paid to injection laryngoplasty for unilateral vocal fold paralysis in recent years due to its less invasive nature, improved bioavailability of modern injectables, and potential for long-term benefit. Arnold described the criteria for the “ideal” injectable material as follows: It should produce a minimal inflammatory host response, maintain its volume with time, and be easily injected into the vocal fold.9

Micronized acellular dermis has been shown to be a safe, biocompatible, and easily injectable material. Pearl and
colleagues prospectively evaluated 14 patients who underwent injection laryngoplasty with micronized acellular dermis with follow-up intervals at 1 week, 1 month, and 3 months. They noted improvement in videostroboscopic findings, including glottal closure, acoustic analysis, and VHI scores at each follow-up interval, confirming efficacy of the material in the short term. \(^4\)

While effective in immediate improvement in symptoms of glottic insufficiency, there has been some question regarding the long-term effects of micronized acellular dermis. Milstein et al retrospectively reviewed a subset of 20 patients who underwent injection laryngoplasty with micronized acellular dermis. \(^1\) Outcome measures included voice-related quality-of-life scores and glottal closure as demonstrated on videostroboscopy. Eight patients had maintained improvement in scores at follow-up \(>12\) months. Tan and Woo reviewed 381 micronized acellular dermis injections in 344 patients with glottic insufficiency secondary to multiple etiologies. \(^5\) Findings suggested long-term efficacy due to the low rate of open procedures (20%); however, voice outcomes were not tabulated.

In this retrospective review, patients demonstrated statistically significant improvement in both VHI scores and perceptual voice grades at intermediate and long-term follow-up intervals. These findings are consistent with previous reports of improvement in glottal incompetence following injection laryngoplasty with micronized acellular dermis while also demonstrating a sustained improvement in voice outcomes. \(^10,11\)

In the recent literature, there has been an increased focus on the evaluation of timing to injection from the onset of paralysis. Historical management favored a “watch and wait” approach, as reinnervation might occur over a period of several months and the materials available for injection historically were more high risk than those available today. It is now theorized that early medialization of the paralyzed vocal fold allows for more appropriate positioning during the time where synkinesis may occur, improving long-term voice outcomes and decreasing the need for laryngeal framework surgery. \(^12\) Young and colleagues noted improved long-term voice outcomes as measured by VHI-10 in patients who underwent early injection versus those who were observed, regardless of regaining vocal fold mobility \((P = .0009)\). \(^13\) Likewise, in a review of 38 patients comparing 14 who underwent injection within 6 months of injury with 24 patients who were observed, P tendon and colleagues noted significant improvement in 11 of 18 laryngoscopic criteria, 7 of 12 CAPE-V criteria, as well as a significant reduction in the need for a permanent procedure \((P = .008)\). \(^14\) Finally, Alghonaim et al reviewed a series of 66 patients undergoing transcervical injection laryngoplasty at different intervals from the onset of paralysis. \(^15\) They noted that patients who underwent injection within 6 months from onset of paralysis were significantly less likely to require medialization thyroplasty \((P < .001)\). In our study, we subcategorized patients into 2 categories: (1) an early group, which underwent injection \(\leq 6\) months from the onset of paralysis, and (2) a late group, which underwent injection \(>6\) months from the onset of paralysis. Both groups demonstrated long-term improvement in VHI scores and perceptual voice grades, but no statistically significant difference could be seen between the early and late injection groups. Perhaps this can be attributed to a low volume of patients for comparison. Incidentally, 3 patients in this review required repeat injection augmentation, and all of those patients were found in the late injection group.

Indeed, one of the appealing characteristics of injection laryngoplasty is its ability to be performed under local anesthesia in the office. While the ultimate location of the injectable remains ostensibly the same, these approaches are very different, and we wanted to evaluate any potential for changes in voice outcomes. Some studies compared different techniques noting no significant difference in voice outcomes or acoustic parameters. \(^16,17\) The transcervical techniques in this review included the transthyrohyoid, transcricothyroid, and transthyroid cartilage approaches. When mean VHI scores and mean perceptual voice grades were examined, no statistically significant difference was noted between transoral or transcervical techniques (Table 3).

This study is limited in that it is a retrospective analysis. After the chart review was completed, 33 patients with VHI data and 37 patients with voice recordings met inclusion

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### Table 2. Scores and Grades Comparing Early and Late Injection.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Follow-up</th>
<th>Injection Early (≤6 mo)</th>
<th>Injection Late (&gt;6 mo)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔVHI</td>
<td>6-12 mo (n = 22)</td>
<td>26.2</td>
<td>32.2</td>
<td>.198</td>
</tr>
<tr>
<td></td>
<td>&gt;12 mo (n = 21)</td>
<td>24.4</td>
<td>24.3</td>
<td>.696</td>
</tr>
<tr>
<td>ΔPVG</td>
<td>6-12 mo (n = 22)</td>
<td>18.7</td>
<td>17.2</td>
<td>.828</td>
</tr>
<tr>
<td></td>
<td>&gt;12 mo (n = 17)</td>
<td>16.6</td>
<td>16.1</td>
<td>.959</td>
</tr>
</tbody>
</table>

**Abbreviations:** PVG, perceptual voice grade; VHI, Voice Handicap Index. 
*Postoperative minus preoperative score/grade.

### Table 3. VHI Scores and PVGs Comparing Transcervical and Transoral Techniques.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Follow-up</th>
<th>Transcervical (Clinic)</th>
<th>Transoral (OR)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔVHI</td>
<td>6-12 mo (n = 23)</td>
<td>32.8</td>
<td>22.3</td>
<td>.412</td>
</tr>
<tr>
<td></td>
<td>&gt;12 mo (n = 22)</td>
<td>22.4</td>
<td>23.7</td>
<td>.724</td>
</tr>
<tr>
<td>ΔPVG</td>
<td>6-12 mo (n = 24)</td>
<td>16.6</td>
<td>20.0</td>
<td>.642</td>
</tr>
<tr>
<td></td>
<td>&gt;12 mo (n = 18)</td>
<td>18.4</td>
<td>11.9</td>
<td>.391</td>
</tr>
</tbody>
</table>

**Abbreviations:** OR, operating room; PVG, perceptual voice grade; VHI, Voice Handicap Index. 
*Postoperative minus preoperative score/grade.
criteria for this analysis. In addition, those who spontaneously regained vocal fold motion were excluded to truly assess only that patient population with UVFP. As discussed, only 37 patients were identified with adequate completion of both preoperative and postoperative voice recordings for analysis. This obviously limits the sample size to a large degree. Post hoc power analysis was calculated with the paired t test, revealing retrospective power of 98% and 99% for VHI and perceptual analysis, respectively. Further data in this study did not achieve statistical significance. Synkinetic reinnervation is also expected to occur in a great number of patients; however, no electromyographic studies or other data are accounted for here to control for this effect. This may significantly affect the interpretation of these intermediate and long-term results. While the data statistically show improvement in both VHI scores and perceptual voice grades, it is difficult to assert an absolute long-term effect given the confounding nature of synkinetic reinnervation, which could not be studied here. In addition, while the 0-100 visual analog scale has been validated for CAPE-V perceptual analysis, it is important to note that CAPE-V itself was not directly used. The 0-100 visual analog scale was used in conjunction with the “rainbow passage,” and this specific system has not been validated statistically. This must be kept in mind when interpreting this outcome measure. We elected not to review videostroboscopic findings or acoustic analysis in the evaluation, as this has been performed in previous studies and the primary end point here was voice assessment by both the patients and the blinded expert reviewers. This does limit the amount of objective data regarding voice outcomes.

Conclusion

Micronized acellular dermis has proven to be a useful injectable material for improvement of symptoms related to glottal incompetence. In terms of Arnold’s criteria for the ideal injectable, it has proven to be safe, biocompatible, and easily injected into the vocal fold. The data in this review also seem to suggest a potential for long-term benefit that could sometimes obviate the need for laryngeal framework surgery. No statistically significant conclusions can be made regarding time to injection or technique of injection and how they affect overall outcomes, but this may warrant further investigation with prospective data.

Author Contributions

Stephen C. Hernandez, data acquisition and analysis, manuscript drafting and revisions, content accountability, final approval; Haley Sibley, data acquisition, manuscript drafting, content accountability, final approval; Daniel S. Fink, data acquisition and analysis, manuscript drafting and revisions, content accountability, final approval; Melda Kunduk, data acquisition and analysis, manuscript drafting and revisions, content accountability, final approval; Mell Schexnaildre, data acquisition and analysis, manuscript drafting and revisions, content accountability, final approval; Anagha Kakade, data analysis, manuscript revisions, content accountability, final approval; Andrew J. McWhorter, data acquisition and analysis, manuscript drafting and revisions, content accountability, final approval.

Disclosures

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