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WILEY
Patient-Defined Duration of Benefit from Juvederm (Hyaluronic Acid) Used in Injection Laryngoplasty

J. Tyler Bertroche, MD; Megan Radder, MM, MA; Dorina Kallogjeri, MD, MPH; Randal C. Paniello, MD, PhD; Joseph P. Bradley, MD

Objectives/Hypothesis: Injection laryngoplasty has become valuable in treating laryngologic disorders including vocal cord atrophy, paralysis, and paresis. Although materials such as carboxymethylcellulose and calcium hydroxyapatite are Food and Drug Administration (FDA) approved, they are not without limitations. Juvederm (hyaluronic acid) is an alternative treatment that is not FDA approved. Although studies have examined Juvederm’s longevity in cutaneous injections, there are limited data examining durability of Juvederm used in laryngoplasty. We aimed to determine the longevity and effectiveness of Juvederm used in injection laryngoplasty.

Study Design: Retrospective cohort study.

Methods: Subjects who underwent injection laryngoplasty using Juvederm were reviewed. Longevity was defined as the time between injection and the date that a patient first noted subjective deterioration of their voice. All subjects were subsequently followed using videostroboscopy to evaluate for Juvederm resorption. Longevity was analyzed using a Kaplan-Meier survival model, and effectiveness of laryngoplasty was determined using the Voice-Related Quality of Life index scores and analyzed using a Wilcoxon signed ranks test.

Results: Fifty-nine subjects met inclusion criteria and underwent Juvederm injection laryngoplasty. Kaplan-Meier survival analysis revealed a mean longevity of 10.6 months (95% confidence interval: 9.1-12.0 months). Wilcoxon signed ranks analysis of the pre- and postinjection Voice Related Quality of Life (VRQOL) scores revealed improvement, with a mean preinjection VRQOL of 49.2 (standard deviation [SD] = 25.8) and mean postinjection VRQOL of 68.2 (SD = 27.5) (P < .001).

Conclusions: Injection laryngoplasty using Juvederm is an effective treatment for vocal cord atrophy, paralysis, and paresis. Knowledge of the patient-defined duration of benefit following laryngoplasty using Juvederm plays an important role in counseling patients as well as in the planning of future interventions.

Key Words: Injection laryngoplasty, Juvederm, hyaluronic acid, dysphonia, vocal cord paralysis, vocal cord paresis, vocal cord atrophy, glottic insufficiency.

Level of Evidence: 4

INTRODUCTION

Injection laryngoplasty with temporary injectable materials is a well-established procedure for managing glottic insufficiency from various laryngeal pathologies including vocal fold atrophy, vocal fold paralysis, and paresis. Untreated or undertreated glottic insufficiency can have profound medical and social implications. Since it was first reported in 1911 by Bruening, injection laryngoplasty has become a mainstay in the treatment of glottic insufficiency.1 Over the past several decades, various autologous, as well as commercially available, substances have been used in injection laryngoplasty procedures including carboxymethylcellulose, calcium hydroxyapatite, and polytetrafluoroethylene (Teflon).2 Although several of these substances have been Food and Drug Administration (FDA) approved for injection laryngoplasty, they are not without their limitations. First introduced into the literature by Ward et al. in 1985, Teflon (polytetrafluoroethylene) was soon found to cause severe inflammatory reactions and granuloma formation, which resulted in notable vocal fold injury.3-5 Although temporarily useful, carboxymethylcellulose is greatly limited by its quite short duration of effect, which necessitates subsequent procedures.6 Calcium hydroxyapatite has been FDA approved for several years; however, its use is limited by diffuse inflammatory reactions following injection and overall difficulty in uniform material delivery due to its rigid viscoelastic properties.7,8 Hyaluronic acid exists under different brand names (e.g., Juvederm, Restylane), but is an alternative treatment that is not currently FDA approved. Although several studies have examined Restylane’s longevity as a cutaneous injection material, there are few studies that have examined its off-label use as a laryngeal injectable.9,10 To our knowledge, there has been only one study that has specifically examined Juvederm’s longevity or efficacy over a period greater than several months.11 Thus, the durability of the material in the larynx remains

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unclear. In this study, our primary outcome was to determine the expected patient-defined longevity of Juvederm when used in injection laryngoplasty in patients diagnosed with vocal fold atrophy, paralysis, or paresis. Secondary outcomes were to determine improvement in vocal quality of life and safety.

MATERIALS AND METHODS

The research proposal and study design were approved by the Washington University in St. Louis Human Research Protection Office.

Patient Selection

Subjects evaluated at the Washington University Voice and Airway Center who underwent injection laryngoplasty using Juvederm between July 2015 and January 2017 were included for study. Patients were initially identified using procedural billing codes for laryngologic injection procedures using codes 31570, 31571, and 31599, and were included whether the injection was performed under local or general anesthesia. Patients were included in the study if they were diagnosed with vocal cord atrophy, vocal cord paralysis, or vocal cord paresis and underwent injection laryngoplasty using Juvederm. Patients were excluded from the study if they underwent other concurrent procedures along with vocal fold injection (e.g., removal of vocal fold polypoma, steroid injection), or if they were lost to follow-up immediately after the initial injection procedure.

Assessment and Recordings

All patients included in our study underwent recorded videostroboscopic and perceptual voice analysis performed by a fellowship-trained laryngologist or an experienced speech and language pathologist at initial and all follow-up appointments. Video and images were saved using KayPentax software (PENTAX Medical Co., Montvale, NJ). The stroboscopic exams were reviewed by both the laryngologist and speech and language pathologist and evaluated for signs of Juvederm resorption including incomplete glottic closure and reduction in vocal fold volume. Recorded perceptual voice analysis were obtained at every patient visit and serially assessed for changes indicative of glottic insufficiency such as increased breathiness and decreased volume. The findings obtained from stroboscopic exam and perceptual voice analysis were used to direct further interventions. Patient-reported Voice-Related Quality of Life (VRQOL) scores were obtained during pre- and postoperative patient visits and documented in the electronic medical record. Demographic information, including patient age, gender, etiology of glottic insufficiency, and route of injection procedure were recorded for each patient for analysis. The longevity of injection was defined as the time in days between the date of injection procedure and the reported date at which patients first noted signs of glottic insufficiency. For instance, if the patient reported worsening of their voice starting 1 month prior to their follow-up appointment, this date was used as the time of implant failure. Patients who demonstrated findings of Juvederm resorption on videostroboscopic evaluation and perceptual voice analysis were offered subsequent injection procedures or medialization thyroplasty.

Procedure

Patients underwent either awake transcutaneous injections or suspension microlaryngoscopy with injection under general anesthesia. All procedures were performed by laryngologists. Awake injections were performed using either a transcricothyroid or transthyrohyoid membrane approach as previously described. Juvederm was injected until satisfactory medialization of the vocal fold was accomplished based on visualization and/or auditory perception by the performing surgeon. Patients were routinely seen within 2 weeks after the procedure and then approximately every 3 months.

Data Analysis

The longevity of the Juvederm injection was determined using a Kaplan-Meier survival model using SPSS Statistics (IBM, Armonk, NY). VRQOL measured out of 100 were obtained both before and after injection procedures. Given the nonnormal distribution of the data, differences in pre- and first visit postinjection VRQOL scores were analyzed using a Wilcoxon signed ranks test.

RESULTS

One hundred four subjects underwent injection laryngoplasty using Juvederm during the study period. Fifty-nine of these patients were ultimately included in our study for analysis, whereas 45 patients were excluded from the study as they were lost to follow-up immediately after the initial injection procedure. Patients were instructed to follow up 2 weeks after injection, and 55 of the 59 included patients (93%) followed up accordingly. Patients were then instructed to follow-up within 4 months after their second visit, and 49 of 59 patients (83%) followed up according to this regimen. Follow-up after 4 months varied from patient to patient. The median age of injected subjects was 66 years (range, 19–85 years), with 30 females (51%) and 29 males (49%). Table I demonstrates the distribution of pathology among subjects injected. Of the 59 subjects included, 19 (32%) experienced implant failure during our study period requiring further intervention. The subjects experiencing resorption during the study period were offered repeat injection laryngoplasty or type I medialization thyroplasty for lasting correction of glottic insufficiency.

Kaplan-Meier survival analysis revealed a mean implant longevity of 10.6 months (95% confidence interval: 9.1–12.0 months) (Fig. 1). No statistically significant differences in time from injection to implant failure were seen by etiology for subjects undergoing injection for vocal cord atrophy, paralysis, or paresis, although this was limited by the small numbers of subjects within each subgroup. Ultimately, eight patients underwent type I medialization thyroplasty, whereas 11 underwent a second injection laryngoplasty during the study period. Medialization procedures were

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**TABLE I.**

Etiology of Glottic Insufficiency.

<table>
<thead>
<tr>
<th>Etiology of Glottic Insufficiency</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocal fold atrophy</td>
<td>17</td>
<td>29%</td>
</tr>
<tr>
<td>Vocal fold paralysis</td>
<td>26</td>
<td>44%</td>
</tr>
<tr>
<td>Vocal fold paresis</td>
<td>16</td>
<td>27%</td>
</tr>
</tbody>
</table>
typically performed 6 months following the time of implant failure to allow for complete resorption of any remaining Juvederm. Five patients with vocal fold paralysis demonstrated partial recovery vocal fold mobility on follow-up videostroboscopy and were not offered subsequent interventions during the study period.

No patients experienced any significant medical or surgical complications during or following their injection procedure. None of the 59 postinjection videostroboscopic examinations revealed granuloma formation, local inflammation, signs of subepithelial injection, or foreign body reactions at the site of injections. The earliest implant failure occurred at 85 days postinjection and was first noted by the patient several weeks after beginning systemic chemotherapy.

Pre- and postinjection VRQOL scores were available for 52 subjects (88%). Wilcoxon signed ranks analysis revealed statistically significant voice improvement, with a mean preinjection VRQOL of 49.2 (SD = 25.8) and mean postinjection VRQOL of 68.2 (SD = 27.5) (P < .001) (Fig. 2).

DISCUSSION

To our knowledge, this study represents the largest and longest investigation into the durability of Juvederm as a laryngeal injectable. The only published study to have previously investigated the duration or efficacy of Juvederm used in injection laryngoplasty demonstrated both its safety and efficacy; however, it was limited by a sample size of 30 patients and follow-up period of 4 months.14 Other commercially available injection materials such as carboxymethylcellulose, calcium hydroxylapatite, and other hyaluronic acid derivatives are not without their limitations.2 Previous studies investigating the longevity of carboxymethylcellulose have revealed a very brief duration of benefits.6 Investigation into the longevity of calcium hydroxylapatite has revealed presence of the material up to 12 months postinjection; however, despite this notable longevity, it is limited by its side-effect profile, including vocal cord stiffening and potential for inadvertent subepithelial application due to its unforgiving viscoelastic properties.7,8 Restylane, another commercially available hyaluronic acid material, has been used in injection laryngoplasty for over a decade with a very safe side-effect profile. Retrospective studies investigating the duration of benefit of Restylane, however, have demonstrated an overall limited longevity, with a mean benefit of just 3 months.15 Juvederm is unique in its microarchitecture with its high concentration of crosslinked hyaluronic acid molecules. It is this high degree of crosslinking between adjacent molecules that is hypothesized to reduce implant hydrolysis and give Juvederm greater longevity.16 As with the other injectables, patients have significant improvement in voice outcomes as measured with the VRQOL. Additionally, safety is of utmost importance, and in our experience, injection laryngoplasty using Juvederm is a safe and effective treatment for patients diagnosed with glottic insufficiency. The knowledge of longevity of Juvederm following injection laryngoplasty plays a critical role in properly counseling regarding the expected duration of benefit. Additionally, this information aids in the timing of patient follow-up and planning future procedures as necessary.

As with any retrospective study, there are clear limitations to the conclusions that can be drawn from this analysis. Although this is the largest study of patients injected with Juvederm, the sample size is still small and makes subgroup analysis difficult. Of the 104 patients who underwent injection laryngoplasty during the study period, 40 were lost to follow-up immediately following their injection procedure, which may introduce selection bias in our results. The time to failure measure was determined by the patients’ self-reported subjective assessment of their voice, and is therefore subject to bias. Additionally, the determination of material resorption was made by the senior surgeons by a subjective analysis of the stroboscopy in addition to

Fig. 1. Kaplan-Meier survival curve with analysis of time in months until noted implant failure. Mean implant longevity was 10.6 months (95% confidence interval: 9.1-12.0 months). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Fig. 2. Mean pre- and postinjection VRQOL scores with 95% confidence interval. Wilcoxon signed ranks analysis revealed statistically significant voice improvement with a mean preinjection VRQOL of 49.2 (SD = 25.8) and mean postinjection VRQOL of 68.2 (SD = 27.5) (P < .001). SD = standard deviation; VRQOL = Voice Related Quality of Life.
auditory perception and was not necessarily identified exactly at the time of resorption. As a result, time lag may confound the results. Although the results of all of the videostroboscopic evaluations were reviewed by both the treating surgeon and a speech and language pathologist at each patient visit, they were not reviewed retrospectively in a blinded manner by a second laryngologist. This may have introduced observer bias. This study cannot easily account for the impact of laryngeal nerve recovery, although by focusing the analysis on patients who required further interventions, this partially eliminates this confounding role. Despite these limitations, this work clearly demonstrates significant efficacy, safety, and durability of Juvederm as an injectable product for the larynx.

CONCLUSION
Injection laryngoplasty using Juvederm is an effective treatment for various etiologies of glottic insufficiency. Knowledge of the expected duration of benefit following injection procedures using Juvederm plays an important role in counseling patients and their families, as well as in the planning of future interventions.

BIBLIOGRAPHY