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Systematic Review

Early-Injection Laryngoplasty May Lower Risk of Thyroplasty: A Systematic Review and Meta-Analysis

Peter M. Vila, MD, MSPH; Neel K. Bhatt, MD; Randal C. Paniello, MD, PhD

**Objective:** To determine whether injection laryngoplasty within 6 months following the onset of unilateral vocal fold paralysis (UVFP) decreases the rate of permanent thyroplasty in adults.

**Data Sources:** Search strategies created by a medical librarian were implemented in multiple online research databases.

**Review Methods:** Inclusion and exclusion criteria were designed to capture randomized clinical trials and cohort studies examining adults with UVFP who received injection laryngoplasty early in the course of treatment, within 6 months of onset, or who were observed. The primary outcome was the rate of thyroplasty. The Newcastle-Ottawa scale was used to assess quality of included cohort studies. Random effects meta-analysis was used to calculate an overall relative risk (RR). Heterogeneity was evaluated with the I² statistic.

**Results:** The search strategy resulted in 1,177 studies, of which four cohort studies remained for meta-analysis after applying inclusion and exclusion criteria. All studies were rated as 9 of 9 on the Newcastle-Ottawa scale. Meta-analysis of 275 patients with UVFP revealed that the overall pooled RR of undergoing thyroplasty in those receiving an early injection was 0.25 (95% confidence interval 0.14–0.45) compared to conservative management (late or no injection). The I² overall was 62.4%.

**Conclusion:** Otolaryngologists should offer injection laryngoplasty to patients with a diagnosis of UVFP within 6 months of diagnosis (recommendation based on grade C evidence with a preponderance of benefit over harm).

**Key Words:** Paralysis, vocal cord, vocal fold, unilateral, adult, laryngoplasty, treatment outcome, meta-analysis.

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INTRODUCTION

Unilateral vocal fold paralysis (UVFP) can occur following injury to the recurrent laryngeal nerve (RLN), potentially leading to considerable morbidity including dysphonia, dysphagia, and aspiration. Following the onset of UVFP, a variable degree of RLN recovery often occurs over the next several months. If sufficient symptomatic recovery is achieved during this time, interventions such as permanent vocal fold medialization (thyroplasty) may not be needed. Thus, many otolaryngologists defer early thyroplasty to allow for spontaneous recovery in order to avoid performing an invasive surgical procedure on patients who otherwise would have improved without any intervention.

During this waiting period, the two management options are observation or temporary-injection laryngoplasty. Injection laryngoplasty can be performed in the office or in the operating room at very low risk to the patient. Recent studies suggest that injection laryngoplasty improves symptoms compared to observation alone during this waiting period, and there is compelling evidence that injections may decrease the need for permanent thyroplasty. In a retrospective cohort study reported by Yung et al., patients with UVFP who received injection laryngoplasty were compared to those who were managed expectantly. The authors found that a significantly higher proportion of patients underwent thyroplasty (23 of 32, 72%) in the observation group compared to the temporary-injection laryngoplasty group (5 of 19, 26%) more than 2 years from the time of diagnosis. Prendes et al. confirmed this finding in a subsequent retrospective cohort study, showing that patients in the observation group (18 of 24, 75%) were much more likely to require thyroplasty than patients who had received an early injection (4 of 14, 29%).

Additional supporting information may be found in the online version of this article.

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We decided to more rigorously explore whether administering early vocal-fold injection laryngoplasty could help patients avoid undergoing more invasive surgery. Thyroplasty requires exposure to anesthesia, a neck incision, and soft tissue dissection. It is associated with potential complications including wound infection, the need for repeat surgery, and unfavorable scarring. Thus, we performed a systematic review and meta-analysis of randomized controlled trials and cohort studies assessing outcomes following early-injection laryngoplasty versus observation in adults with UVFP. Our objective was to determine whether injection laryngoplasty during the first 6 months following the onset of UVFP decreases the rate of subsequent thyroplasty.

MATERIALS AND METHODS

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. This study was exempt from the Washington University Institutional Review Board because it used data from published literature.

Search Strategy and Study Selection

No review protocol was published for this study. Using the Population, Intervention, Comparator, Outcome, Study Design framework for this systematic review, the population of interest was adults aged greater than 18 years with a diagnosis of unilateral vocal fold paralysis or paresis; the intervention of interest was injection laryngoplasty early in the course of treatment, or within 6 months from diagnosis; the comparator was late injection, any time after the early-injection group, or no-injection laryngoplasty; the outcome was the rate of thyroplasty; and the study design was randomized clinical trials and cohort studies. The published literature was searched using strategies created by a medical librarian. The search strategies were established using a combination of standardized terms and key words, and implemented in Ovid Medline 1946-, Embase 1947-, Scopus 1823-, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, and Clinicaltrials.gov. Study-type filters for randomized controlled trial, prospective cohort study, and retrospective cohort study were used; they were adapted from the University of Texas School of Public Health’s filters. All searches were completed in February 2016. Full search strategies are provided in the Appendix (available online).

Two authors (P.M.V., N.K.B.) reviewed abstracts in duplicate. At the abstract review stage, we excluded studies if they were 1) not randomized controlled trials or cohort studies, 2) not focused on vocal cord function, 3) animal or cadaver studies, 4) studies on vocal cord pathology unrelated to immobility, 5) not studies of any intervention, 6) studies that only included children, 7) studies of bilateral dysfunction, 8) studies of patients with malignancy causing the paralysis, 9) not in English, and 10) not available in full text form. At the full text review stage, we subsequently excluded studies if they 1) did not include an injection arm for comparison; 2) did not use early-injection laryngoplasty, defined as earlier than 6 months; 3) were not randomized controlled trials or cohort studies; 4) were not in English; and 5) studied patients with dysphonia due to causes other than unilateral vocal fold paralysis (Fig. 1).

Data Extraction and Quality Assessment

Two authors (P.M.V., N.K.B.) independently reviewed the included studies to extract data. The primary outcome of interest was the rate of thyroplasty. This rate was determined by the number of patients with UVFP who underwent either early-injection laryngoplasty or conservative management, and how many from each group underwent thyroplasty within 2 years of onset. Study design, location, length of follow-up, time to injection, and type of injection material also were extracted. The Newcastle-Ottawa scale was selected to assess the quality of included cohort studies, and the Cochrane Collaboration Risk of Bias tool was selected to assess the risk of bias in randomized, controlled trials.

Analysis

Means were used to summarize follow-up time and time from diagnosis to injection. The means and medians did not differ by a meaningful amount. Mean time to injection for the early-injection group was calculated using study sample sizes as weights to account for differences in sample size between studies. No mean time was calculated for the late-injection group because some subjects never received any injection. The I² statistic was used to evaluate heterogeneity. Random effects meta-analysis was used to summarize the relative risk from each study and calculate an overall relative risk of the effect of early-injection laryngoplasty on the primary outcome variable. Sensitivity analyses were performed by serially excluding each study to examine the impact of removing potential outliers. A funnel plot was constructed to evaluate for publication bias. All analyses were performed in Stata 14.2 (StataCorp LP, College Station, TX) and Microsoft Excel 15.2 (Microsoft Corporation, Redmond, WA).

RESULTS

The search strategy resulted in 579 studies after excluding duplicates. Screening these abstracts resulted in 497 being excluded, yielding 81 studies for full text analysis. After excluding studies that did not fit our criteria for inclusion, four studies remained for analysis (Fig. 1).

Table I describes the characteristics of the included studies. Three were retrospective cohort studies, and one was a prospective cohort study. The studies were performed in various locations, including Canada, Taiwan, and the United States. In total, the overall sample size was 275 patients (range 35–132), with 205 receiving early injection and 70 in the conservative management.
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Design</th>
<th>Sample Size</th>
<th>Mean Follow-up (months)</th>
<th>Mean Time to Injection, Early (months)</th>
<th>Mean Time to Injection, Late (months)</th>
<th>Type of Injectable</th>
<th>Newcastle-Ottawa Score (of 9 possible points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedman et al. (2010)</td>
<td>Boston, Massachusetts, U.S.A.</td>
<td>Retrospective cohort</td>
<td>35 total (32 early injection, 3 late injection)</td>
<td>22.3</td>
<td>1.8</td>
<td>7.3</td>
<td>Hyaluronic acid</td>
<td>9</td>
</tr>
<tr>
<td>Alghonaim et al. (2013)</td>
<td>Montreal, Québec, Canada</td>
<td>Retrospective cohort</td>
<td>66 total (21 immediate injection, 17 early injection, 28 late injection)</td>
<td>18 (immediate), 19 (early), 32.7 (late)</td>
<td>2.8</td>
<td>&gt;12.0*</td>
<td>Hyaluronic acid, Gelfoam, Collagen</td>
<td>9</td>
</tr>
<tr>
<td>Fang et al. (2014)</td>
<td>Taoyuan, Taiwan</td>
<td>Prospective cohort</td>
<td>42 total (20 early injection, 22 conservative management)</td>
<td>12–24*</td>
<td>3.9</td>
<td>–</td>
<td>Hyaluronic acid</td>
<td>9</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>275 total (205 early injection, 70 conservative management)</td>
<td>18.2 (early), 22.2 (late)</td>
<td>4.5†</td>
<td>–</td>
<td>–</td>
<td>9</td>
</tr>
</tbody>
</table>

*Mean not reported.  
†Weighted mean.
The mean follow-up time was 18.2 months for the early group and 22.2 months for the conservative management group. The conservative management group ranged from receiving an injection several months after the early group to strict observation with no injection at all prior to thyroplasty. Because some studies did not report the number of patients who did not receive an injection in the conservative management group, we could not report this number; however, in the two studies that did report this, all patients in the conservative management group had at least one injection. The injection material used varied from study to study and included hyaluronic acid (3 of 4 studies), Gelfoam (Pfizer, New York, New York, U.S.A.) (1 study), Cymetra (Allergan, Parsippany, New Jersey, U.S.A.) (1 study), and collagen (1 study). All four studies scored a 9 out of 9 possible points on the Newcastle-Ottawa scale, indicating that all were high-quality cohort studies.

On average, patients in the early-injection group received an injection at 4.5 months from the time of diagnosis. A mean time to injection in the conservative management group could not be calculated due to some patients not receiving an injection. In all included studies, patients in the early-injection group received an injection laryngoplasty before patients in the conservative management group, if they received an injection at all.

Meta-analysis of 275 patients with UVFP revealed that the overall pooled relative risk of undergoing thyroplasty in those who received an early-injection laryngoplasty was 0.25 (95% confidence interval 0.14–0.45) compared to those who were managed conservatively. The overall heterogeneity was moderate, with an I² of 62.4%. The Forest plot is shown in Figure 2. No evidence of publication bias was observed in our analysis because the funnel plot showed the four studies centered around the pooled effect size (Fig. 3). As part of a sensitivity analysis, serially removing each study from the meta-analysis did not change the direction of the effect (not shown).

DISCUSSION

This systematic review and meta-analysis of treatment for adults with UVFP shows that patients who did not receive early-injection laryngoplasty were four times more likely (relative risk = 0.25; 1 of 0.25 = 4.0) to subsequently undergo thyroplasty. We found no evidence of publication bias in the included studies.

Our findings are consistent with prior studies that have shown a benefit to early-injection laryngoplasty in patients with UVFP, including improvements in short-term quality of life, voice quality, and acoustic parameters. Furthermore, others also have theorized that early-injection laryngoplasty would lead to a decrease in the rate of future thyroplasty based on their own retrospective studies. Our results, compiled from multiple high-quality observational studies with moderate heterogeneity, provide grade C evidence that patients diagnosed with acute UVFP should receive early-injection laryngoplasty, merit ing a recommendation for otolaryngologists to adopt this practice, with a preponderance of benefit over harm.

Timing the Intervention

Although waiting approximately 6 to 12 months prior to intervention generally is accepted as a time period for
conservative management of UVFP to allow for nerve regeneration to occur,\textsuperscript{27,28} the time period for early intervention is variable. As seen in our study, others have considered early intervention to range anywhere from within 1 month of diagnosis to within 6 months of diagnosis. The definition of early injection varied among included studies, but we nonetheless found consistent results in our meta-analysis showing a benefit to early intervention. However, because our study was not designed to evaluate the optimal time to early injection, we cannot comment on the optimal time required to maximize benefit. This is despite the fact that overall mean time to injection in our study was 4.5 months, which suggests most otolaryngologists would consider an early injection to be performed within 6 months of diagnosis. Future prospective studies could examine whether immediate (1–3 months) versus early (3–6 months) lead to a difference in overall outcomes, including quality of life, voice quality, and rate of thyroplasty.

**Limitations**

One limitation of this meta-analysis is that the included studies were observational in design. Thus, we cannot definitively conclude there is a causal link between early injection and decreased risk of permanent surgery based solely on the fact that the association was observed. Another limitation of using observational studies for the meta-analysis is that these studies are subject to selection bias because patients were not randomized into treatment groups. Thus, it is possible that patients in the early versus the late-injection group had a varying baseline rate of recovery, which may have led to different rates of symptoms and thus thyroplasty. This issue has been raised previously,\textsuperscript{27,29} and is inherent to an observational study design. Bypassing this selection bias would require randomizing patients into treatment groups. In addition, it likely would be helpful to consider standardized reporting of vocal fold paralysis patients, including the rate of return of voice,\textsuperscript{27} the specific mechanism of injury, and whether nerve repair was attempted. The use of a quantitative measure of nerve function such as the compound motor action potential also may help better risk-stratify patients in the future, although it currently still is limited to animal studies.

We found moderate statistical heterogeneity between the included studies. One potential reason for this heterogeneity is that the sample sizes were small in the included studies. Another potential reason is that the number of injections was not reported in the included studies. Although a range of injection materials was used in the included studies, it would be interesting to know how many injections each patient received. Because this number was not reported in all studies in this meta-analysis, it is possible that patients may have received more than one injection over a 2-year period, and Friedman et al. reported that up to three injections were required in some patients.\textsuperscript{29} Another possible reason for the heterogeneity is that injectable materials were not consistent between studies because some patients received short-acting injectable materials such as gelfoam, and others received intermediate-acting materials such as hyaluronic acid.

Furthermore, the method and location of injection was not reported in all studies and thus could not be included in the meta-analysis, which also may explain some of the heterogeneity.

Finally, the included studies did not report voice outcomes at follow-up. Although there was no loss to follow-up, we must assume that patients who underwent thyroplasty did not recover, but patients who opted not to have a thyroplasty may have chosen to live with an inferior voice outcome, undergo voice therapy only, or may not have been medically fit to undergo anesthesia for a thyroplasty. Because this information is not available in the published studies, the number of thyroplasties was used as a primary outcome in this meta-analysis.

**Recommendations**

Despite the small differences between the included studies, all four were consistent in the direction of the effect. Furthermore, existing literature also suggests that early-injection laryngoplasty may prevent the need for subsequent thyroplasty.\textsuperscript{6,8,29} Thus, given the low risk of injection laryngoplasty and the gains in quality of life from an injection, weighed against the risks of undergoing thyroplasty and the elapsed time with decreased quality of life due to vocal cord insufficiency, the authors feel that the presented evidence is sufficient to justify early-injection laryngoplasty. However, a randomized, controlled trial is needed to definitively answer the question of whether early-injection laryngoplasty decreases the risk of subsequent thyroplasty.

Future studies also could explore the mechanism for how early-injection laryngoplasty improves symptomatic recovery. One hypothesis is that synkinesis reinnervation during axon regeneration stabilizes the final position of the paralyzed vocal fold.\textsuperscript{29,30} Thus, temporary medialization during synkinesis reinnervation may promote a more favorable vocal fold position. Another speculated explanation is that injection laryngoplasty increases the degree of vibratory tactile feedback from the opposing, nonparalyzed vocal fold, and this sensory feedback promotes nerve regeneration.\textsuperscript{29} Alternatively, the injection material may induce local inflammation and subsequent fibrosis within the paralyzed vocal fold, providing a robust surface for vocal fold articulation.\textsuperscript{14} A better understanding of the phenomenon of enhanced symptomatic recovery with early-injection laryngoplasty may lead to novel therapeutic interventions and greater clarity about the optimal timing for early-injection laryngoplasty.

**CONCLUSION**

This systematic review and meta-analysis of high-quality cohort studies provides grade C evidence, justifying a recommendation for otolaryngologists to offer injection laryngoplasty within 6 months of diagnosis to adults with UVFP.

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BIBLIOGRAPHY


