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Safety of Office-Based Percutaneous Injection Laryngoplasty With Calcium Hydroxylapatite

Minhyung Lee, MD; Doh Young Lee, MD, PhD; Tack-Kyun Kwon, MD, PhD

Objective: To evaluate the safety of office-based calcium hydroxylapatite (CaHA) injection laryngoplasty via the cricothyroid approach through an analysis of all procedures performed over a period of 10 years at a single institution.

Methods: In total, 962 office-based CaHA injection laryngoplasty via the cricothyroid approach procedures were performed by a single physician at our institution between 2007 and 2016. From these, 955 procedures performed in 617 patients were included in our analysis. The medical records of all 617 patients were retrospectively reviewed. We classified all procedure-related complications according to the time of onset. Complications that occurred during the procedure were considered intraprocedural complications, whereas complications that developed within 1 week after injection and those that developed after 1 week and were recorded more than twice in the medical records were considered acute and delayed complications, respectively. Failed cases were categorized separately as failure.

Results: Five cases were failed (0.5%). Intraprocedural complications included superficial injection in eight cases (0.8%). Acute and delayed onset of dyspnea was observed in three (0.3%) and two (0.2%) cases, respectively. The incidence of failures and major complications requiring active intervention was 1.6%.

Conclusion: Our findings suggest that office-based CaHA injection laryngoplasty via the cricothyroid approach is as safe as conventional transoral injection laryngoplasty.

Key Words: Complication, injection laryngoplasty, calcium hydroxylapatite, dyspnea, vocal fold paralysis.

Level of Evidence: 4

INTRODUCTION

Injection laryngoplasty plays an important role in the treatment of various causes of vocal fold insufficiency. Various materials have been introduced, and calcium hydroxylapatite (CaHA) is the only long-lasting material that is currently approved as a vocal fold injection material by the Food and Drug Administration and has been used in various institutions and countries.\(^1\)\(^2\) CaHA is designed for injection through thin needles and is manufactured by mixing 25- to 45-μm calcium microspheres with carboxymethylcellulose gel-type carriers. It shows longer augmentation effects than do injected materials that do not contain microspheres because it maintains the volume of the vocal folds during calcium particle absorption in the soft tissue of the vocal folds or for a longer time.\(^3\)\(^4\) Consequently, such long-lasting materials can result in prolonged unwanted side effects if they are erroneously injected at undesired locations. This is why several practitioners preferred a transoral or transthyroid approach for visualization of the needle location.\(^5\) The cricothyroid and transthyroid approach offers the advantages of a shorter delivery route and good patient tolerance.\(^6\) However, the needle cannot be directly visualized, and it becomes difficult to estimate the position of the injection material.\(^7\) Nevertheless, office-based percutaneous injection laryngoplasty is preferred due to the cost effectiveness of injection laryngoplasty under local anesthesia\(^8\) and voice outcome similar to those of injection under general anesthesia.\(^9\) Considering the necessity of a long-term, large-scale study for determining the safety of office-based CaHA injection laryngoplasty via the cricothyroid approach in the actual clinical setting, we retrospectively analyzed the adverse event data for 955 procedures performed over a period of 10 years (2007–2016) at a single institution.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of patients who underwent CaHA (Radiesse, Merz Pharmaceuticals GmbH, Frankfurt, Germany) injection laryngoplasty at an outpatient clinic at a single institution from 2007 through 2016. All procedures were performed by a single physician (T.-K.K.). There was no data for 2013 because the physician was on sabbatical leave during that year. In total, 962 percutaneous CaHA injection laryngoplasties were performed during the study period. From these, seven procedures with medical record errors or duplicate recording were excluded, and 955 procedures performed in 617 patients were eventually included in our analysis. All patients presented with symptoms such as dysphonia and aspiration due to vocal fold insufficiency. The following data were retrospectively retrieved from the medical records of these patients:
age; sex; diagnosis; number of injections; and the side, amount of injected material, complications, and follow-up duration for each injection. The study complied with the Declaration of Helsinki. The study protocol was approved by the institutional review board (IRB) of Seoul National University Hospital (IRB number 1806-160-953).

**Procedure Details**

A transcricothyroid approach was used for 947 procedures, whereas a transcricotympanic approach was used for the remaining eight procedures in patients with fibrosis due to previous neck surgery or a soft thyroid cartilage. Injections were percutaneously administered through the cricothyroid membrane under local anesthesia in an office-based setting. Local anesthesia was achieved by the application of 2% lidocaine on the skin above the cricothyroid membrane and spraying of 4% lidocaine over the posterior nasal cavity. The patient was placed in a semirecumbent position with neck flexion and head extension, and transnasal flexible chip-tipped videolaryngoscopy was initiated by the assistant. Under satisfactory visualization of the vocal folds, the operator injected CaHA using a 25-gauge, 1.5-inch needle into the vocal fold. The amount of injected material was determined according to the diagnosis and stroboscopic findings. Patients were sent home after 1 hour of observation at the outpatient clinic; they were instructed to avoid talking until the next day and prescribed oral analgesics that could be taken when required. Antibiotics were not prescribed on a routine basis.10

**RESULTS**

The mean age of the patients was 58.5 years (range: 15–102 years). In total, 625 (65.4%) and 330 (34.6%) injections were administered to men and women, respectively. Stroboscopy-based diagnoses included vocal fold paralysis (683 injections; 71.5%), presbylaryngis (158 injections; 16.5%), vocal fold atrophy (57 injections; 6.0%), vocal fold scarring (51 injections; 5.3%), and vocal fold paresis (six injections; 0.63%). Patients over 55 years of age who presented bilateral vocal fold atrophy, but without any vocal pathology capable of affecting voice quality, were diagnosed to have presbylaryngis.9 Vocal fold atrophy is defined as any glottal insufficiency without mucosal pathology that is not explained by the aging process. With regard to the side, 269, 674, and 12 injections were administered on the right, left, and both sides, respectively.

There was a history of thyroplasty type I or arytenoid adduction prior to injection laryngoplasty in 24 cases and fat injection or fascia lata injection prior to injection laryngoplasty in 11 cases. Until 2012, touchup injections for tuning after the framework surgery were performed for the patients who had undergone thyroplasty type I or arytenoid adduction.

The mean value of overall injection amount was 0.52 cc; 0.58 cc was injected in patients with vocal fold paralysis, 0.35 cc in those with presbylaryngis, 0.37 cc in those with vocal fold atrophy, 0.34 cc in those with vocal fold scarring, and 0.54 cc in those with vocal fold paresis. With regard to the side, 0.47 and 0.54 cc were injected on the right and left sides, respectively. When the mean value of injection amount was analyzed by year, a statistically significant increase was observed in a chronologi
cal pattern (Fig. 1).

We defined failure as an injection amount of 0 cc. Complications were classified according to the time of onset. Complications that occurred during the procedure were considered intraprocedural complications, whereas complications that developed within 1 week after injection and those that developed after 1 week and were recorded more than twice in the medical charts were considered acute and delayed complications, respectively. Failure occurred in five cases (Table I). Intraprocedural complications occurred in 37 cases. Superficial injection was observed in eight patients (Table II). When superficial injection was detected during the procedure and the patient tolerated well, we placed the needle into the superficial layer of lamina propria and made an incision through the epithelium over the superficially injected material to let the material drain out in the airway through the incision. In total, 26 cases exhibited hemorrhage: one with superficial injection, five with underinjection, two with subcutaneous hemorrhage that resolved after compression, and 18 with minimal endolaryngeal bleeding. Four cases complained of pain; one complained of headache on the ipsilateral side; two complained of otalgia on the ipsilateral side; and one complained of pain around the injection site. All of these symptoms were alleviated with rest and were not reported thereafter.

Twelve cases developed acute complications, including dyspnea in three cases with unilateral vocal fold paralysis. These patients went home after injection and visited our emergency center or outpatient clinic with dyspnea symptoms within 1 week. Two cases were hospitalized and discharged after conservative care, with no complaints after that. One case with mild symptoms was followed up and showed spontaneous resolution. There were three cases with globus, one with headache, two with subepithelial hematomas in the stroboscopic exam, and one with
vocal fold swelling. All these conditions were monitored on an outpatient basis, with no further records. Delayed complications occurred in 59 cases and included globus, cough, neck pain, and mild dyspnea. All complications were treated by conservative methods or close observation.

After a review of articles related to complications of CaHA injection laryngoplasty,5,11–13 we classified complications that required active treatment, such as superficial injection, dyspnea requiring hospitalization, and granuloma formation, as major complications; the remaining were classified as minor complications (Table III). Accordingly, the total number of patients with failure and major complications was 15.

DISCUSSION

In the present study, we found that the complication rate for office-based CaHA injection laryngoplasty via the cricothyroid approach is similar to that for conventional transoral injection laryngoplasty.

Most of our patients had unilateral vocal fold paralysis in the regeneration period and were injected for symptom alleviation before permanent treatment. At the beginning of the learning curve, a smaller amount of CaHA was injected due to concerns regarding complications (Fig. 1). During the initial study period, 24 cases where prior framework surgery was performed showed satisfactory results with touch-up injections14; however, the effect of CaHA was not permanent, and this protocol was discontinued after

TABLE I.
Failed Cases of Office-Based Calcium Hydroxylapate Injection Laryngoplasty

<table>
<thead>
<tr>
<th>Serial no.</th>
<th>Year</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Etiology</th>
<th>Side</th>
<th>Cause</th>
<th>Plan</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2008</td>
<td>F</td>
<td>72</td>
<td>VF paralysis</td>
<td>Thyroid surgery</td>
<td>Left</td>
<td>Severe gag reflex</td>
<td>Short-term f/u injection</td>
<td>Success with f/u injection</td>
</tr>
<tr>
<td>2</td>
<td>2009</td>
<td>F</td>
<td>15</td>
<td>VF paralysis</td>
<td>Cardiovascular surgery</td>
<td>Left</td>
<td>Poor tolerance, Young age</td>
<td>Wait until suitable age</td>
<td>Lost to f/u</td>
</tr>
<tr>
<td>3</td>
<td>2009</td>
<td>F</td>
<td>71</td>
<td>VF paralysis</td>
<td>Idiopathic</td>
<td>Left</td>
<td>Severe gag reflex</td>
<td>Short-term f/u injection</td>
<td>Success with f/u injection</td>
</tr>
<tr>
<td>4</td>
<td>2010</td>
<td>M</td>
<td>67</td>
<td>VF paralysis</td>
<td>Brain infarction</td>
<td>Unknown</td>
<td>Acute submucosal hemorrhage</td>
<td>Short-term f/u injection</td>
<td>Lost to f/u</td>
</tr>
<tr>
<td>5</td>
<td>2011</td>
<td>M</td>
<td>62</td>
<td>VF paralysis</td>
<td>Trauma</td>
<td>Right</td>
<td>Poor exposure, Overhanging arytenoid</td>
<td>Open surgery</td>
<td>Thyroplasty type I</td>
</tr>
</tbody>
</table>

A total of 955 procedures were performed in 617 patients between 2007 and 2016. Subject 4 exhibited vocal fold bulging due to submucosal hemorrhage. Subject 5 occurred because of poor exposure associated with an abnormal laryngeal anatomy and arytenoid overhanging caused by trauma. This patient underwent thyroplasty type I after 9 months.

F = female; f/u = follow-up; M = male; VF = vocal fold.

TABLE II.
Characteristics of Patients Who Received Superficial Injection of Calcium Hydroxylapate During Office-Based Injection Laryngoplasty.

<table>
<thead>
<tr>
<th>Serial no.</th>
<th>Year</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Etiology</th>
<th>Side</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2008</td>
<td>F</td>
<td>28</td>
<td>VF paralysis</td>
<td>Thyroid surgery</td>
<td>Left</td>
<td>Removal and IL under GA</td>
<td>F/u IL under GA</td>
</tr>
<tr>
<td>2</td>
<td>2008</td>
<td>M</td>
<td>19</td>
<td>VF paralysis</td>
<td>Idiopathic</td>
<td>Right</td>
<td>Puncture and drainage</td>
<td>Short-term f/u IL</td>
</tr>
<tr>
<td>3</td>
<td>2008</td>
<td>F</td>
<td>61</td>
<td>VF paralysis</td>
<td>Neck surgery</td>
<td>Right</td>
<td>Removal under GA</td>
<td>Lost to f/u after removal</td>
</tr>
<tr>
<td>4</td>
<td>2009</td>
<td>F</td>
<td>52</td>
<td>VF paralysis</td>
<td>Idiopathic</td>
<td>Left</td>
<td>Puncture and drainage</td>
<td>Wait and watch</td>
</tr>
<tr>
<td>5</td>
<td>2009</td>
<td>F</td>
<td>16</td>
<td>VF paralysis</td>
<td>Neck surgery</td>
<td>Left</td>
<td>Puncture and drainage</td>
<td>Short-term f/u IL</td>
</tr>
<tr>
<td>6</td>
<td>2010</td>
<td>M</td>
<td>54</td>
<td>VF paralysis</td>
<td>RFA for thyroid nodule</td>
<td>Left</td>
<td>Puncture and drainage</td>
<td>Short-term f/u IL</td>
</tr>
<tr>
<td>7</td>
<td>2010</td>
<td>M</td>
<td>56</td>
<td>VF paralysis</td>
<td>Idiopathic</td>
<td>Right</td>
<td>Removal and IL under GA</td>
<td>Thyroplasty type I</td>
</tr>
<tr>
<td>8</td>
<td>2011</td>
<td>F</td>
<td>59</td>
<td>VF paralysis</td>
<td>Thoracic surgery</td>
<td>Right</td>
<td>Wait and watch</td>
<td>Thyroplasty type I, arytenoid adduction</td>
</tr>
</tbody>
</table>

A total of 955 procedures were performed in 617 patients between 2007 and 2016. Subjects 2, 5, and 6 received follow-up IL after 2 weeks, 8 weeks, and 1 week, from the time of puncture and drainage, respectively. Subject 8 showed minimal superficial injection and was simply monitored for 5 months, following which thyroplasty type I and arytenoid adduction were performed.

F = female; f/u = follow-up; GA = general anesthesia; IL = injection laryngoplasty; M = male; RFA = radiofrequency ablation; VF = vocal fold.

TABLE III.
Number of Failures and Major Complications of Office-Based Calcium Hydroxylapate Injection Laryngoplasty.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Complication</th>
<th>Number</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure</td>
<td></td>
<td>5</td>
<td>0.52</td>
</tr>
<tr>
<td>Intraprocedural</td>
<td>Superficial injection</td>
<td>8</td>
<td>0.84</td>
</tr>
<tr>
<td>Acute</td>
<td>Dyspnea, hospitalized</td>
<td>2</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Delayed</td>
<td>Dyspnea, hospitalized</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Granuloma formation</td>
<td>0</td>
<td>0.00</td>
</tr>
</tbody>
</table>

A total of 955 procedures were performed in 617 patients between 2007 and 2016.
2012. We also performed CaHA injection laryngoplasty via the cricothyroid approach for conditions characterized by glottal insufficiency with mobile vocal folds, such as presbylaryngis, vocal fold atrophy, and vocal fold paresis, and CaHA or fat injection was selectively repeated according to the patient’s requirements.

Most complications recorded in the present study were intraprocedural complications. As reported in previous studies, complications of CaHA injection laryngoplasty are related to technical problems rather than the CaHA itself. Failure is also an intraprocedural technical problem. In our study, failure and superficial injection were not recorded since 2012, once the learning curve had passed (Fig. 2). Failure and intraprocedural complications were primarily caused by poor patient tolerance and poor exposure. Sufficient correction of vocal fold insufficiency appears to be possible even in cases in which injection under local anesthesia is difficult after improvement of surgical skills. In cases of superficial injection, additional sequelae can be prevented if appropriate management strategies are used. If superficial injection is detected during the procedure, the physician should immediately stop the procedure, aspirate through a placed syringe if possible, and make a small incision for drainage on the vocal fold epithelium using a needle; this will eliminate the need for material removal under general anesthesia. If loculated superficial material that inhibits the mucosal wave is detected during follow-up, the physician should incise the overlying vocal fold under general anesthesia and suck out as much material as possible. Minimal leakage of material superficially, which does not affect the mucosal wave, is spontaneously distributed without any surgical treatment. Ipsilateral ear pain and headache, which can occur intraprocedurally or within 1 week after the procedure, are considered a consequence of referred pain through the auricular branch of the vagus nerve, which innervates the vocal fold. In all our cases, the pain was resolved by conservative care.

In patients with vocal fold paralysis, acute dyspnea may develop within 1 week after injection laryngoplasty. Although we could not determine the risk factors for this patient group, we observed symptom amelioration after conservative care in all cases. Although life-threatening airway obstruction did not occur in any patient, dyspnea with stridor was recorded. Therefore, all patients should be informed about the risk of this complication before the injection procedure. Minor complications such as globus, cough, neck pain, hemorrhage, and swelling were also observed during the follow-up period, and none of these conditions required special treatment. In fact, symptoms such as globus, mild pain, and cough were recorded for almost all patients, with severe symptoms documented for only one patient, who complained of a severe globus sensation until 6 months after injection. Material removal was considered for this patient, but the condition resolved after the next follow-up visit.

Failure and major complications occurred in 15 patients (1.6%) and were not recorded after 2015. This can be attributed to the difference in the number of injections each year, but an improvement in the injection technique over time cannot be ruled out. Procedures that were previously considered difficult were performed more easily as time passed, so the incidence of major complications gradually decreased.

In the present study of 955 procedures, the incidence of failure was 0.5%, the rate of switching to general anesthesia was 0.4%, and the incidence of major complications (excluding failures) was 1.0%. DeFatta et al. reported 10 major complications after 22 vocal fold injections with CaHA paste under general anesthesia at three institutions. These included four vocal folds with adynamic mucosa, six with a severely decreased wave, and two granulomas affecting the vibratory margin. Gillespie et al. also evaluated 39 transoral CaHA injection laryngoplasty procedures under general anesthesia and reported five, two, and one case of superficial injection, overinjection, and inflammation, respectively; the complication rate was 21%. Rosen et al. reported the surgical removal of superficially injected material from one of 63 cases involving different CaHA injection laryngoplasty techniques, whereas Carroll et al. reported the surgical removal of superficially injected material from three of 108 cases involving transoral CaHA injection laryngoplasty. Although the incidence of major complications varies widely among these previous studies, Carroll and Rosen’s large-scale study showed that the major complication rate for CaHA injection laryngoplasty performed via the transoral or percutaneous approach was 1% to 3%; this was similar to the rate in the present study, which evaluated only the cricothyroid approach. These findings indicate that office-based CaHA injection laryngoplasty via the cricothyroid approach is a safe procedure.

The present study has some limitations. First was its retrospective design. Among the 955 injections, 65 injections, excluding those for patients with terminal cancer, were not followed up beyond the day of injection laryngoplasty, and we could not assess complications for these cases. In addition, we could not identify the duration of complications because of the irregular follow-up...
pattern and the retrospective study design. Second, voice outcome after injection laryngoplasty, which can affect the follow-up, was not analyzed. But the long-term benefit of CaHA as an injection laryngoplasty material was already proven, which last an average of 18.6 months. This result shows the same result as our previous study. Thus, we believe that the findings of our long-term, large-scale analysis of the safety of office-based CaHA injection laryngoplasty via the cricothyroid approach performed by a single practitioner at a single institution are clinically significant because all the injections were performed by a single physician, who by the nature of the very large number is experienced in this procedure. The safety results described herein may not be applicable to physicians who perform many fewer procedures. Future large-scale prospective studies are required to further clarify our findings.

**CONCLUSION**

The findings of this study suggest that office-based CaHA injection laryngoplasty via the cricothyroid approach is a safe procedure with a complication rate comparable to that for conventional transoral injection laryngoplasty. As observed with most surgeries and procedures, increased complications primarily occur early in the learning curve. CaHA is safe and effective as a long-term injection material if the associated complications are managed in an adequate and timely manner.

**BIBLIOGRAPHY**