# Hyaluronidase Injection in the Vocal Folds for Vocal Hemorrhage, Reinke Edema, and Hyaluronic Acid Overinjection: A Novel Application in the Larynx

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**Summary:** Hyaluronidase (HAase) injection into the vocal folds is an off-label use of an enzyme for liquefaction of hyaluronic acid (HA). HAase injection was performed in 14 cases in 13 patients. Office and operative injections of HAase were performed. The indications were five cases of overinjection of HA, six cases of Reinke edema and polypoid corditis, and three cases of acute vocal hemorrhage with early fusiform polyp formation. All the patients tolerated the HAase without complications. Significant voice improvements were noted between pre- and postinjection procedures as evaluated by a self-rating of voice by the Voice Handicap Index-10. A marked decrement in the mass on the side of the injection of HAase was noted in all groups successfully injected upon viewing by videostroboscopy. HAase prevented an additional operative phonosurgery in 10 patients. In conclusion, HAase injection can be used in the vocal folds with good effect in patients. The indications are polypoid corditis with overproduction of HA, acute vocal hemorrhage, and correction of iatrogenic HA overinjection.

**Key Words:** Hyaluronidase–Hyaluronic acid–Polypoid corditis–Vocal hemorrhage–Reinke edema.

## INTRODUCTION

Hyaluronidase (HAase) is a preparation of proteolytic enzyme.[1] The exact chemical structure of this enzyme is unknown. HAase injection is supplied as a sterile, nonpreserved, colorless solution. It is marketed as Amphadase, Hylenex, and Vitrase. The mechanism of action is by enzymatic degradation of hyaluronic acid (HA).

HAase injection is indicated as an adjuvant in subcutaneous fluid administration for achieving hydration. HAase injection is used in improving the dispersion and the absorption of injected drugs,[2] and has been used as an adjuvant in subcutaneous urography for improving the reabsorption of radio-opaque agents. The absorption and the dispersion of other injected drugs may be enhanced. Ovine HAase is approved for the treatment of vitreous hemorrhages.[3] Off-label use of this drug for the treatment of overinjection of HA in the facial cosmetic literature has been reported.[4]

HA is an important extracellular matrix (ECM) protein that is important in vocal fold biomechanics.[5] HA is an important regulator in wound healing and inflammation. Both HA synthase and HAase are increased in the wound healing and scar process.[6] Although most of the literature on HA in the vocal folds relates to a reduction or a lack of HA in pathologic conditions such as scar and work is ongoing in adding HA as a biogel in improving vocal vibratory function,[7] there are conditions where an HA may be redundant and overproduced. We hypothesize that the application of HAase reported in the general medical literature may be applied to the vocal fold.

Conditions in the vocal folds where there is an overabundance of HA may occur when HA is used as a tissue filler[8] and results in overinjection. This situation is similar to cosmetic complications after HA injection for teardrop deformities of the eyelids.[9] In certain conditions where excess HA is overexpressed in the lamina propria,[10] surgical intervention is performed to remove the extracellular matrix. This may not be necessary if HAase is injected, thereby avoiding surgery. When there is acute vocal fold hemorrhage, the situation is similar to vitreous hemorrhage where HAase use is indicated to improve absorption. We postulate that the use of HAase may be a useful adjunct in the conditions of (1) correction and rapid reduction of HA overinjection in the vocal fold, (2) correction of Reinke edema and polypoid cordites without the need for microphonosurgical removal, and (3) possible reduction by HAase of the duration of voice disturbance because of acute vocal fold hemorrhage and avoidance of vocal hemorrhage complications.

We carried out HAase injection as an off-label use of this product 14 times in 13 patients for the previously mentioned indications and report on their results. This is the first report of the application of HAase use in the human vocal folds.

## MATERIALS AND METHODS

From October 2015 through April 2017, this author has injected HAase in 14 cases in 13 patients. The HAase used was Vitrase (Alliance Medical Products Inc., Irvine, CA). The concentration used was 200 units/1 mL.

There were five subjects with HA overinjection. All presented with unacceptable voice after HA injection. On laryngoscopy, all had unilateral vocal fold bulging. All had unilateral bulging of one fold greater than 2 months after a prior injection of Restylane or Perlane (Nestle Skin Health, New York, NY) as an HA filler.

There were three subjects with a unilateral acute vocal fold hemorrhage with early vocal fold polyp formation. Two patients were professional singers. The two professional singers underwent

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**TABLE 1.**
**Tabulation of Patients' Demographics, Diagnosis, Route of Injection, and VHI-10**

| Case number | Age | Sex | Reason/Diagnosis | Route | Units | VHI-pre | VHI-po | Follow-up (mo) |
|---|---|---|---|---|---|---|---|---|
| 1 | 57 | M | Overinjection of HA | Transcervical | 20 | 27 | 7 | 19 |
| 2 | 75 | F | Overinjection of HA | Office transoral | 20 | 11 | 11 | 16 |
| 3 | 82 | F | Overinjection of HA | Office transoral | 40 | 39 | 31 | 3 |
| 4 | 65 | F | Overinjection of HA | Office transoral | 20 | 6 | 7 | 19 |
| 5 | 67 | F | Overinjection of HA | Office transoral | 20 | 24 | 25 | 15 |
| 6 | 56 | F | Hemorrhage with early polyp | OR | 20 | 10 | 4 | 12 |
| 7 | 48 | M | Hemorrhage with early polyp | Office transoral | 20 | 25 | 19 | 9 |
| 8 | 37 | F | Hemorrhage with early polyp | Office transoral | 40 | 34 | 15 | 2 |
| 9 | 57 | M | Bilateral Reinke edema | Office transnasal | 60 | 19 | 15 | 15 |
| 10 | 48 | F | Bilateral Reinke edema | Office transoral | 100 | 22 | 20 | 8 |
| 11 | 46 | F | Bilateral Reinke edema | OR | 40 | 25 | 22 | 4 |
| 12 | 63 | M | Bilateral Reinke edema | OR | 40 | 15 | 1 | 3 |
| 13 | 50 | M | Bilateral Reinke edema | OR | 80 | 18 | 11 | 14 |
| 14 | 58 | F | Bilateral Reinke edema | OR | 20 | 31 | 7 | 4 |

*Abbreviations:* F, female, HA, hyaluronic acid; M, male; OR, operating room; po, postoperative; pre, preoperative; VHI, Voice Handicap Index.

injection under anesthesia, whereas the third elected for office injection alone.

Six injections were done in five patients with bilateral Reinke edema with polypoid degeneration. The first four patients had a traditional removal of one side using the microlaryngoscopy technique with the contralateral side treated with HAase injection only. The fifth patient had severe cervical spine disease and had an injection in the office alone. The sixth patient is a patient who underwent prior surgery and HAse injection and presented 6 months after surgery with voice complaints and elected to undergo a bilateral HAase injection in the office rather than an operative laryngoscopy. This was the only patient who had two procedures using HAase. Four patients in this group had unilateral injections, whereas the other two had bilateral injections of HAase for Reinke edema.

The age, sex, the indication for the procedure, the number of units, the method of injection, and the duration of follow-up are tabulated in Table 1.

The patients were examined immediately before injection and 1 week after injection of HAase by videostroboscopy. Additional reviews were made of the long-term videostroboscopy results. The Voice Handicap Index (VHI)-10 was administered immediately before and approximately 6 weeks after intervention and was tabulated. We also noted the patients' clinical course as to whether they felt their voice quality improved and whether any return to surgery was necessary.

A chart review of all patient data was obtained after institutional review board (IRB) approval. IRB approval from Mount Sinai Hospital was obtained. No separate human IRB for the use of HAase was obtained for the present study, but a separate consent for the off-label use of an existing pharmaceutical was obtained from each subject. Before the office or operative procedure, operative consent for injection laryngoplasty procedure was obtained after a discussion with the patient and the surgeon (PW). The specific rationale for the use of HAase as an off-label use of Food and Drug Administration-approved medication in the larynx was discussed and documented as a separate consent document. The risks and benefits of HAase use were explained to each patient based on the known literature regarding HAase. The use of HAase as an off-label use of the product in the vocal fold was explained, and as part of the consent process, the patient was given the option of nonuse of the product.

The HAase was supplied in 200 USP units/mL single-use vials. HAase was used in a concentration of 20 units/0.1 cc.

For all injections, the site of injection was the midmembranous vocal fold into the superficial layer of the lamina propria.

Technique of transoral injection: The oral pharynx and the larynx were anesthetized by 2% lidocaine spray. The endolarynx was coated with a 2% lidocaine-soaked cotton ball. With the rigid endoscope coupled to the camera as a guide, a curved needle with Vitrase was drawn into a 1-cc needle used for vocal fold injection under endoscopic control.

Technique of transcervical injection: Transcervical injection using a 30-gauge needle was performed by drawing the desired amount of HAase into the 1-cc syringe. The needle was placed below the thyroid cartilage on the affected side and aimed cephalad to the target. Visible bulging affirmed the accurate placement of HAase by laryngoscopy.

Technique of direct injection: At the time of microlaryngoscopy, the HAase was placed through a 25-gauge butterfly needle. The needle was bent forward 2–3 mm at the distal end so as to ensure the injected HAase was not extruded through the needle puncture site. The site of injection was in the superficial layer of the lamina propria.

## RESULTS

The clinical information on the 14 cases is tabulated in Table 1. There were five men and nine women. The median and the standard deviations of the duration of follow-up for the group were 10.5 ± 6 months. The age ranged from 37 to 82. The route of injection was performed in the operating room in five cases. The other nine injections were performed in the office setting, with seven

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