Interarytenoid Botulinum Toxin Injection for Recalcitrant Vocal Process Granuloma

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Objectives/Hypothesis: This study evaluated the efficacy of botulinum toxin type A injected into the interarytenoid muscle to treat recalcitrant vocal process granulomas.

Study Design: Retrospective clinical review at a tertiary care center.

Methods: Eight patients with vocal process granulomas refractory to a variety of prior treatments including surgical resection, proton pump inhibitor therapy, and voice therapy underwent percutaneous injection of botulinum toxin type A into the interarytenoid muscle, performed in an office setting. Doses ranged from 5 U to 25 U in one to two injections.

Results: One patient demonstrated no improvement, two patients demonstrated partial resolution, and five patients demonstrated complete resolution of their granulomas. Four patients noted transient breathiness. There were no other side effects. All patients tolerated the injections without difficulty.

Conclusion: Botulinum toxin injection into the interarytenoid muscle appears to be a safe and effective modality for treating recalcitrant vocal process granuloma.

Key Words: Botulinum, botox, granuloma, vocal process.

Level of Evidence: 4.

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INTRODUCTION

Granulomas of the vocal process of the larynx are benign lesions of the posterior glottis generally centered over the tips of cartilaginous vocal processes. Clinically, they are associated with odynophagia, throat clearing, globus, and otalgia.

These lesions were first described by Chevalier Jackson in 1928 as superficial ulcerations along the posterior border of one or both sides of the larynx. At the time, he hypothesized that “vocal abuse” was the etiology. In 1935, Jackson and Jackson went on to describe a “hammer-and-anvil” action of one vocal process striking the other in the setting of vocal abuse. In 1932, Clausen described the first postintubation granuloma. In 1968, Cherry and Margulies used fluoroscopy to identify the association between reflux and vocal process granuloma. In 1989, Hillman et al. noted high vocal-fold closure velocities and closure forces present in granuloma patients that were notably absent in nodule and polyp patients. More recently, Carroll et al. presented evidence for glottic insufficiency and consequent hyperfunction as a possible etiology. As discussed by Hoffman et al., multiple factors often are contributory.

Regardless of etiology, vocal process granulomas share similar clinical presentation and histopathologic findings.

The treatment of vocal process granulomas can range considerably. The otolaryngologist generally attempts to determine the underlying etiology and treat accordingly, though this can prove challenging. Conservative therapies have included topical and systemic steroids; antiinflammatory, antiallergy, antibiotic, and antacid regimens; voice rest, and voice therapy. Resolution with these modalities is time-consuming, with average time to resolution with laryngopharyngeal reflux treatment being 5.7 months, and average time with voice therapy being 8 months. Surgical treatment has historically been plagued by recurrence rates from 20% to 60%.

Nasri et al. first used botulinum toxin to treat vocal process granulomas in 1994. They injected botulinum toxin type A into the thyroarytenoid muscle (TA) of six patients with vocal fold granulomas, noting complete resolution in all six. Orloff and Goldman also reported success in eight of eight patients with vocal fold granulomas using TA botulinum toxin injections. Pham et al. noted a 50% or greater decrease in the size of granulomas within 2 weeks of TA botulinum toxin injections in five of six patients, also noting conservative measures generally required months for a response. Damrose and Damrose used botulinum toxin in the TA muscle in seven patients with recalcitrant vocal fold granulomas, noting good response in seven patients.

Thyroarytenoid botulinum toxin injections have been shown to be useful in multiple case series. However, in...
our clinical experience, we have noted a high degree of recurrence and patient dissatisfaction with the side effects of breathy voice and difficulty swallowing from bilateral TA injections. As has been demonstrated by Nasri et al. in a canine model, the interarytenoid muscle serves mainly to adduct the posterior true vocal fold, most specifically the vocal process of the arytenoid.16,17 Thus, we hypothesized that chemodenervation of the interarytenoid muscle with botulinum toxin might provide the same therapeutic benefit of decreasing vocal fold trauma posteriorly while improving the side effect profile.

MATERIALS AND METHODS

This study was approved by the Massachusetts Eye and Ear Infirmary Institutional Review Board.

Eight patients, all with unilateral vocal process granulomas, were treated with botulinum toxin injection into the interarytenoid muscle. All patients had been treated previously with surgical excision (4/8), speech therapy (3/8), proton pump inhibitors (8/8), or some combination thereof (Table I). Three patients underwent simultaneous steroid injection into the granuloma at the time of botulinum toxin injection (Table II).

Pre- and posttreatment examinations were performed using flexible distal-chip nasolaryngoscopy to assess size and location of granulomas. All patients received percutaneous interarytenoid botulinum toxin injection via the trans-thyrohyoid membrane approach, as initially described by Amin et al.18 Patients were seated upright in the examination chair, and the nares and oropharynx were topicaly anesthetized with 1% oxymetazoline hydrochloride and 3% lidocaine spray. A transtracheal injection of 2 cc of 4% lidocaine was given to further anesthetize the airway. A 25-gauge needle was then used to inject 1 cc to 2 cc of 1% lidocaine with 1:100,000 epinephrine diluted into the soft tissues overlying the thyrohyoid membrane and thyroid notch. After an appropriate time had elapsed, a flexible, distal-chip endoscope was passed transnasally and positioned to visualize the glottis. A syringe was then filled with the appropriately mixed botulinum toxin type A and attached to a 25-gauge, 1.5-inch needle (see Table II for dosages). The needle was passed just above the thyroid notch and through the subcutaneous tissues and preepiglottic space to enter the larynx at the level of the petiole of the epiglottis. The needle was then advanced into the superficial tissue of the interarytenoid region under direct endoscopic visualization (Fig. 1). Laryngeal electromyography (EMG) was used to confirm placement in the two initial injections to confirm muscle activity. Subsequent injections were performed without the laryngeal EMG.

RESULTS

All eight patients were successfully injected with botulinum toxin in the clinic. Patient follow-up time ranged from 1.5 to 16 months (mean 6 months). Five of eight patients experienced complete resolution of granuloma, and two of six patients experienced partial resolution (Table II). Two patients received booster injections performed by the same technique, after reporting no voice changes from the first injection. Both of these injections were performed 2 to 4 weeks after the initial injection. The range of time to total resolution was 1.25 to 3 months (mean 3.5 months) for those who saw complete resolution. Four patients received simultaneous steroid injections into the granulomas. One patient underwent simultaneous surgical excision with botulinum toxin type A injection secondary to airway concerns. One patient underwent concurrent injection into the thyroarytenoid and cricothyroid muscles.

No serious adverse effects were noted. All patients tolerated the injection well. Four of eight patients did note mild to moderate breathiness. No patients missed

| Number of Patients | Botulinum Dose (U) | Steroid | % Improved | Time to Resolve (wks) | Follow-up (wks.) | Adverse Affects
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<tbody>
<tr>
<td>1</td>
<td>15 +10 booster</td>
<td>no</td>
<td>100</td>
<td>12</td>
<td>52</td>
<td>Weak voice, mildly breathy</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>yes</td>
<td>100</td>
<td>10</td>
<td>10</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
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<td>100</td>
<td>12</td>
<td>12</td>
<td>Breathy voice</td>
</tr>
<tr>
<td>4</td>
<td>12.5 + 7.5 booster. Concurrent SML with cold excision.</td>
<td>yes</td>
<td>0</td>
<td>n/a</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>5 with TA/CT</td>
<td>yes</td>
<td>100%</td>
<td>5</td>
<td>64</td>
<td>Breathy voice</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>no</td>
<td>90%</td>
<td>90% at 6 wks</td>
<td>6</td>
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</tr>
<tr>
<td>7</td>
<td>7.5</td>
<td>yes</td>
<td>L-100%</td>
<td>9 wks</td>
<td>28</td>
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</tr>
<tr>
<td>8</td>
<td>7.5</td>
<td>no</td>
<td>100%</td>
<td>28 wks</td>
<td>28 wks</td>
<td>Breathy voice</td>
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work. No patients noted dysphagia or required alteration in diet. No patients experienced local complications at the injection site. In the patients who only required one injection, the vocal processes of the larynx were noted not to touch after the injection. In the remainder of the patient population, they were noted not to touch after the booster.

DISCUSSION

Chemical denervation in the larynx using botulinum toxin was first used as a modality for the treatment of laryngeal spasms observed in spasmodic dysphonia (SD) in 1985. Since that initial report, botulinum toxin injections have been implemented for an ever-widening circle of laryngeal problems. In 1994, Nasri and Berke began using botulinum toxin injections for granulomas, followed by a series of others.

Granulomas are inflammatory lesions, requiring not just an initial traumatic insult, but also altered healing secondary to chronic irritation or inflammation. In recurrent vocal process granulomas, there may be multiple primary factors. Irritation or inflammation may be from acid reflux, infection, exposure of cartilage, or recurrent physical trauma in the form of chronic cough and throat clearing. It appears likely that reducing the amount of trauma to the vocal folds at the point of contact along the vocal process of the arytenoid cartilage aids in the healing of granulomas. This has been shown in multiple studies in which botulinum toxin injections into the thyroarytenoid muscle have allowed recalcitrant granulomas to heal, generally at a rate faster than that reportedly required with medical therapy. Despite these favorable reports, in our clinical practice the response of granulomas to this treatment is highly variable.

The multifactorial etiology of granulomas may be responsible for this variability. In the case of addressing vocal hyperfunction, our ability to "figure out what is wrong" or which muscles are hyperfunctioning is inadequate. Clinical examination and visualization during phonation is a rough guide to laryngeal activity. Visualization of the larynx with the endoscope allows for a single angle of view, which limits evaluation of inferior and deeper structures. In the case of muscle tension dysphonia and vocal hyperfunction, the true vocal folds are often obscured by the function of the supraglottic structures.

This case series reflects an evolution of our current model for the treatment of recalcitrant vocal process granulomas with botulinum toxin injections. Initially, we used thyroarytenoid injections for recalcitrant granulomas as an adjunctive treatment, in combination with resection and steroid injections for patients who had failed voice therapy, medication, and surgery. The incorporation of interarytenoid injections were made after observations that the posterior vocal folds still were able touch after thyroarytenoid injections alone. In our series, several of our patients recurred after undergoing injections into the thyroarytenoid muscle, which was one of the reasons that the interarytenoid region was then injected. As we began using the modality, we used it in conjunction with other treatments, as noted in Table I. As we noted its efficacy in maintaining separation between the vocal processes, as well as in resolution of granuloma, we began to use it in isolation.

An advantage of this approach is that the botulinum toxin injections can be performed without expensive EMG equipment for localization. The interarytenoid muscle is easily identified and accessed through the thyrohyoid space using a traditional 1.5 inch 25-gauge needle. This makes this technique available to much broader patient base.

We postulated that by injecting the interarytenoid muscle in lieu of the thyroarytenoid muscle, we could decrease trauma at the level of the vocal process of the arytenoid, with decreased effect on the anterior glottis. As such, we felt it might be possible to maximize the effect of the injection while simultaneously limiting the breathiness after injections. In reviewing our patients’ data, we found that four of our eight patients reported breathy voice after injection, one of whom received concurrent injection of 5 U to both the right and left thyroarytenoid muscles.

In Nasri and Berke’s initial description of TA injections for six patients with 10 U to 15 U of botulinum toxin type A, all suffered from breathiness for 2 to 5 months. Orloff and Goldman used 5 U to 20 U of botulinum toxin type A and noted mild to moderate breathiness in seven of eight patients. Four of their patients did require re-injection for persistent vocal process contact. Damrose and Damrose injected seven patients with 10 U to 25 U of botulinum toxin type A. They noted that all seven participants suffering from breathy voice. Interestingly, Pham et al. noted breathiness in only one of six participants, despite injecting 15 U of botulinum toxin type A into the ipsilateral true vocal fold.

CONCLUSION

While this study does present a promising technique, it is subject to several limitations. This was a retrospective review of a novel technique, initially employed with other treatments to solve a recurrent or recalcitrant
problem. As such, only four of eight patients had interarytenoid botulinum toxin injections alone. We believe that future trials will be necessary to assess the efficacy of interarytenoid injection alone, to better understand which granulomas have the best response to injection, and to quantify breathiness objectively will be necessary. We also believe that a trial comparing the efficacy of thyroarytenoid versus interarytenoid injections in granuloma resolution and quality of life, particularly as regards breathiness, will be useful.

BIBLIOGRAPHY