Treatment of Vocal Fold Granuloma Using Botulinum Toxin Type A

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Contact granuloma of the vocal folds has been associated with abnormal use of the voice, and acid reflux may exacerbate the inflammatory process. Treatments have included voice therapy and antireflux measures. Surgical excision is considered in patients who do not respond to medical management.

Localized injections of botulinum toxin type A (BOTOX®) have been effective in patients with disorders of muscular control in the head and neck. In this study, granulomas resolved in six patients who underwent injection of the affected vocal folds. Botulinum toxin type A is probably successful because it prevents forceful closure of the arytenoids during phonation and coughing. Localized injection of this neurotoxin is promising both as an initial treatment and as an alternative treatment in patients who do not respond to standard therapy or who are poor surgical candidates.

INTRODUCTION

Vocal cord granulomas are benign growths of hypertrophic granulation tissue, most often occurring at the vocal processes. Bilateral involvement is common. Granulomas are thought to begin as ulcerations of the laryngeal mucosa (contact ulcers). Continued inflammation and repeated injury produce granulation tissue. Granulomas frequently develop following mucosal injury caused by endotracheal intubation. These benign growths also occur in persons who abuse their voices and in individuals with gastroesophageal reflux. Granulomas are prone to recurrence because phonation or coughing places them in contact with the opposite arytenoids, which causes repeated injury.

Therapies for vocal cord granulomas include treatment of the underlying source, resting of the voice, and surgical resection. The primary surgical approach has been excision of the lesions using a carbon dioxide laser. However, current treatment modalities are not effective in all granulomas. This study describes the use of botulinum toxin type A (BOTOX®) in the treatment of vocal fold granulomas. Localized injection of this toxin can be used as the initial treatment for vocal fold granuloma or as an alternative treatment when standard approaches are ineffective.

Botulinum toxin type A is a neurotoxin produced by the anaerobic gram-positive bacterium, *Clostridium botulinum*. Its site of action is the neuromuscular junction, and the end result is blockage of the neurotransmission by acetylcholine. Scott, *et al.*[1–3] pioneered the use of botulinum toxin type A injections in the treatment of strabismus. After demonstrating that the neurotoxin had no systemic effects in either animals or humans, these investigators began using it to treat blepharospasm. Many other clinical applications of botulinum toxin type A have since been described.

In this article, the authors report their initial experience in treating vocal fold granulomas with injections of botulinum toxin type A. Unlike in other applications, the neurotoxin was injected to achieve a particular physiological effect, rather than to prevent an abnormal muscle action.

PATIENTS AND METHODS

The characteristics of the six patients in this study are summarized in Table I. Three of the patients were chosen because of their failure to respond to traditional treatments and their willingness to try an alternative modality. The other three patients received injections of botulinum toxin type A as the primary treatment for vocal cord granuloma.

While electromyography is most often used for the placement of botulinum toxin type A in the larynx, the point-touch technique first described by Green, *et al.*[4] was used in this study. The injection is performed with the patient seated in an examination chair. The thyroid and cricoid cartilages are outlined with a marking pen, and the injection site is prepared with alcohol. A 27-gauge needle with a 2-mL syringe is used to inject botulinum toxin type A. The needle is inserted through the thyroid cartilage into the ipsilateral thyroarytenoid muscle at a 90-degree angle and then directed posteriorly. Once the injection pressure changes from high to low, the needle is assumed to be in the muscle and the neurotoxin is released from the needle. The injection affects the ipsilateral thyroarytenoid and lateral cricoarytenoid muscles.

If extensive ossification of the thyroid lamina is pres-

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TABLE I.
Patients Treated for Vocal Fold Granuloma With Injections of Botulinum Toxin Type A.

Patient No.	Age (Years)	Etiology	No. of Injections	Time of Response (Months)	Time Since Injection (Months)
1	67	R, V, I	1	2	24
2	41	V, T, R	1	3	24
3	63	V	2	2	20
4	72	I, V	1	3	6
5	57	V, R	1	2	5
6	65	R, V	1	3	5

R = gastroesophageal reflux; V = voice abuse; I = intubation; T = tobacco.

ent, the technique is altered and the cricothyroid membrane is perforated just below the lower edge of the thyroid cartilage, 1.5 cm lateral to the midline. The needle is directed superiorly, medially, and posteriorly, and its placement is monitored through a nasopharyngoscope. Once the needle is positioned in the thyroarytenoid muscle, the botulinum toxin type A is injected. In the six patients in this series, the dosage of neurotoxin varied from 10 to 15 U.

PATIENT REPORTS

Patient 1

In May 1992, a 67-year-old male financial consultant was referred to the voice clinic at the University of California, Los Angeles (UCLA) for the evaluation of recurrent vocal fold granuloma. At the time of presentation, the patient had a persistent sore throat that became more painful when he coughed or shouted. The patient, a nonsmoker, had been intubated 1 year previously for an uncomplicated abdominal procedure. Subsequently, he developed a vocal fold granuloma. He was started on steroids and histamine H_2 blocker therapy, and the granuloma was excised in March 1992. Shortly thereafter, the vocal fold granuloma recurred.

Stroboscopic examination of the larynx showed complete glottal closure, minimal restriction of wave motion, and symmetrical movement of the folds. The granuloma was noted on the posterior free margin of the right vocal fold (Fig. 1, top). Except for a slightly breathy, harsh voice, no vocal abnormalities were noted. The patient chose the option of botulinum toxin type A injection over other available treatments. The right thyroarytenoid and lateral cricoarytenoid muscles were injected with 12 U of the neurotoxin.

When the patient was seen 2 months after the injection, the granuloma could no longer be identified (Fig. 1, bottom). He continued to complain of a breathy voice for approximately 6 months; thereafter, his voice returned to normal. In the 2 years since the injection, the granuloma has not recurred.

Patient 2

A 41-year-old male radio announcer was referred to the UCLA voice clinic because of intermittent weakening of his voice and hoarseness. The patient had a history of moderate alcohol intake and a 30 pack-year smoking history. Over the previous 2 years he had noticed a change in his voice, which had become substantially worse in the 2 months before presentation. He also described a history of allergic rhinitis and a duodenal ulcer, which was treated in 1984.

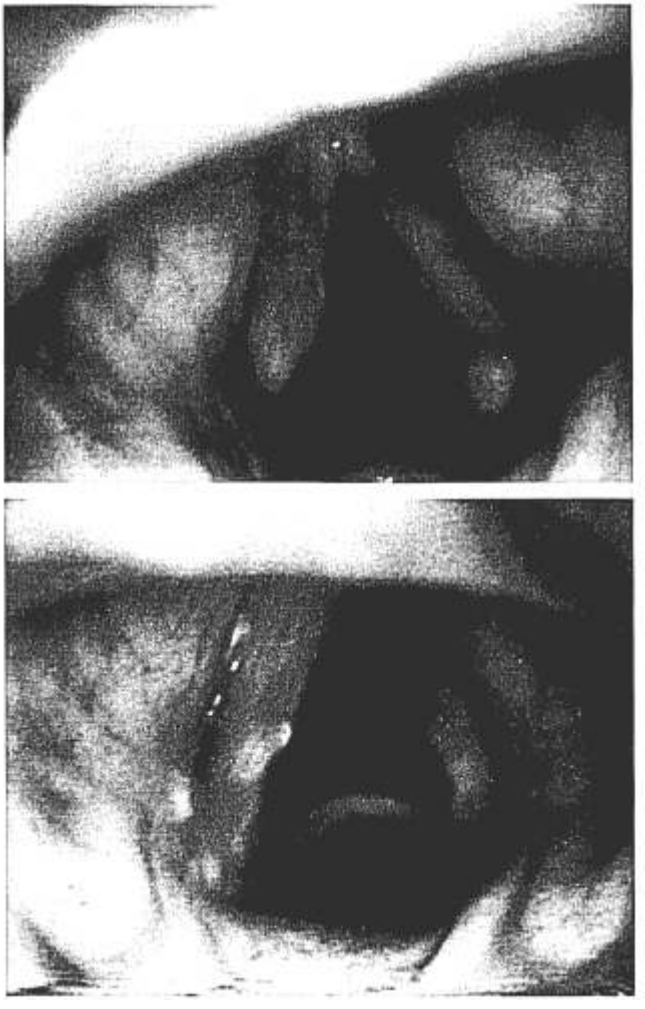

Fig. 1. View of the larynx in patient 1, obtained using a 90-degree Karl Storz laryngoscope. **Top.** Right posterior vocal fold granuloma before treatment. **Bottom.** Resolution of granuloma 2 months after the injection of botulinum toxin type A.

Laryngeal stroboscopy revealed complete glottal closure, no restriction of wave motion, and symmetrical movement of the folds. A granuloma was identified on the right posterior vocal fold. On January 16, 1992, the patient underwent surgical excision of the lesion. Postoperatively, he was treated by a speech therapist.

The patient continued to have inflammation and voice weakness in the early postoperative period, and he was found to have a recurrent granuloma in February 1992. The right vocal fold was injected with 10 U of botulinum toxin type A in June 1992. Slight improve-

ment was noted in the following visits. By September 1992, the patient had full return of voice, and laryngoscopy detected no granulomas.

Patient 3

A 63-year-old male engineer presented to the UCLA voice clinic for the first time in August 1992. He had received various treatments for a left vocal fold granuloma that was first diagnosed in August 1990. The patient had been treated by a speech therapist and had undergone two carbon dioxide laser excisions of the granuloma. However, the lesion persisted; when he was evaluated at the UCLA voice laboratory, the granuloma was larger than in the original report. During this visit, he complained of a breathy, hoarse voice.

The patient had no history of gastroesophageal reflux. He was given 2 weeks of tapering prednisone therapy, but no improvement occurred. On October 21, 1992, the lesion was excised using a carbon dioxide laser. In subsequent visits, the granuloma was smaller, but it did not resolve. The patient was treated with cimetidine (Tagamet®) and antacids, without resolution of the granuloma.

In December 1992, the patient's left thyroarytenoid and lateral cricoarytenoid muscles were injected with 10 U of botulinum toxin type A. By May 1992, the granuloma was smaller in size, but still present. At this time, 13 U of botulinum toxin type A was injected into the muscle. Three months later, the granuloma had resolved completely. Follow-up examinations have revealed no recurrence of the lesion, and the patient has had a normal voice.

Patient 4

A 72-year-old man presented to the UCLA voice clinic with a 2-month history of hoarseness following coronary artery bypass surgery in November 1993. The patient had no history of tobacco and alcohol use or heartburn and indigestion. However, he did have a history of excessive voice use. Physical examination revealed bilateral vocal fold granulomas.

The patient's vocal folds were injected with botulinum toxin type A, 10 U on each side. Three months later, both granulomas had completely resolved. The lesions have not recurred, and the patient's hoarseness has completely resolved.

Patient 5

In December 1993, a 57-year-old man presented to the UCLA voice clinic with a 4-month history of laryngeal pain and a 2-month history of dysphonia. His medical history was significant for voice abuse and gastroesophageal reflux. Physical examination revealed a left posterior vocal fold granuloma.

The patient's left thyroarytenoid and lateral cricoarytenoid muscles were injected with 15 U of botulinum toxin type A. Two months after the injection, the granuloma had completely resolved. The patient has been on ranitidine (Zantac®) and antacids since the initial symptoms appeared. He has remained free of disease, pain and dysphagia.

Patient 6

A 65-year-old man first presented to the UCLA voice clinic in December 1993 with a 6-month history of hoarseness. His medical history was significant for gastroesophageal reflux and voice abuse. The physical examination revealed bilateral granulomas of the posterior vocal folds.

The patient's posterior vocal folds were injected with botulinum toxin type A, 10 U in each side. At a follow-up examination 2 months after the injection, the patient's voice was no longer hoarse, and the granulomas had completely resolved. The lesions have not recurred. Since June 1993, the patient has been taking ranitidine and antacids.

DISCUSSION

The results of this preliminary study suggest that botulinum toxin type A may be helpful in many patients with vocal fold granulomas. The beneficial effect of the toxin is that it prevents the forceful adduction of the arytenoids that perpetuates the granuloma. The toxin can be used in patients who have failed other therapeutic modalities, as well as in those who have received no prior treatment.

Jackson[5] first described contact ulcers of the posterior larynx in 1928. The etiology of vocal fold granuloma may be multifactorial. In some patients, trauma to the arytenoid mucosa from intubation initiates the process of injury and repair that leads to a granuloma. In other patients, gastroesophageal reflux and voice abuse initiate the lesion. The mechanical trauma that occurs with repeated coughing and throat clearing may contribute to the persistence of granuloma.

The results of surgical therapy for granulomas have been mixed and recurrence rates have generally been high, even with the use of the carbon dioxide laser. Jaroma, *et al.*[6] reported that 54% of surgically treated patients returned with recurrent granulomas. In their study, nine patients with small granulomas responded to nonsurgical treatment. Conservative management included voice therapy and treatment of infections, allergies and gastroesophageal reflux. Nevertheless, the conclusion from this study is that surgery should be reserved for granulomas that are causing significant voice or airway problems. In a study of 17 granuloma patients treated with voice therapy, Bloch, *et al.*[7] reported that granulomas resolved in 12 patients; the other 5 patients terminated treatment early. This suggests that conservative therapy may be effective in a subset of patients with granuloma. Although the carbon dioxide laser is commonly used for the resection of granulomas, a prospective study has

not been conducted to compare laser treatment with other forms of therapy.

In the larynx, botulinum toxin type A has most commonly been used to treat hyperadduction disorders. In adductor spasmodic dysphonia, paralysis of the thyroarytenoid muscle helps prevent the development of the high subglottic pressure that is associated with vocal spasms. Botulinum toxin type A causes a chemical denervation, which results in an impressive relief of symptoms with minimal or no side effects.[8–10] Injections of this neurotoxin have even been effective in patients previously treated with recurrent nerve section.[11] More recently, Blitzer, *et al.*[12] described their experience with posterior cricoarytenoid muscle injection for abductor spasmodic dysphonia.

Botulinum toxin type A has also been used in the head and neck to treat other diseases of muscular control. Blitzer, *et al.*[13] used injections of the neurotoxin to treat oromandibular dystonia, a disease marked by focal spasms of one or more facial muscle groups. Although many of the patients in this study needed multiple injections, most experienced relief of symptoms when the spasms were limited to a single group of muscles. In another study, Saeed and Brookes[14] successfully treated palatal myoclonus with botulinum toxin type A injections of the levator and tensor veli palatini muscles.

Botulinum toxin type A has also been used in facial plastic surgery for glabellar frown lines and hyperfunctional lines of the face.[15] In addition, many authors have described the use of this neurotoxin in various hemifacial spasms. For example, Flanders, *et al.*[16] reported treatment of 65 patients with varying degrees of spasm. Although only 51 of the 65 patients elected to continue the therapy after the first injection, all described improvement after this injection.

The effectiveness of botulinum toxin type A in the treatment of vocal fold granulomas is probably related to the cause of these lesions. Because granuloma formation is initiated by mucosal injury and perpetuated by repeated forceful closure of the glottis, injection of the neurotoxin into the thyroarytenoid and lateral cricoarytenoid muscles can prevent continuous injury to vocal folds resulting from adduction of these muscles and forceful contact of the cords. Three of the six patients in our series have not been followed longer than 1 year. For the treatment to be termed successful, at least a 1-year follow-up is required. Therefore, we consider our data to be preliminary, pending further follow-up.

One serious possible complication of this treatment is diffusion of the neurotoxin into surrounding tissues. This could result in a generalized weakness similar to the clinical syndrome of botulism, except milder. This complication has not been reported in other studies, and it was not seen in our series. Dysphagia, local pain, and breathiness of the voice are possible with injection of the adductory muscles of the larynx. With the exception of breathiness, no significant morbidity occurred in our series. Breathiness lasted 2 to 5 months, with a mean of 3 months. None of the patients complained of breathiness lasting longer than 5 months after the injection.

It is crucial to emphasize the significance of silent gastroesophageal reflux disorder in many patients with vocal fold granuloma. The weakness of the vocal fold closure may result in aspiration. Therefore, all patients with granuloma need to be fully evaluated for reflux disease. If the disorder is identified, it needs to be aggressively treated.

In this report, we have described a new clinical use of botulinum toxin type A. This neurotoxin provides an alternative to current management protocols for vocal fold granulomas. In our small series, the efficacy of this treatment is clear. A study to prospectively compare botulinum toxin type A, surgery, and conservative therapy for granulomas would further define the merits of this approach.

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