

Double-Blind Controlled Study of Botulinum Toxin in Adductor Spasmodic Dysphonia

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The treatment of adductor spasmodic dysphonia using botulinum toxin A was conducted in 13 patients as a double-blind, placebo-controlled study. Patients were diagnosed independently by an interdisciplinary team consisting of speech pathologists, an otolaryngologist, and a neurologist. The toxin or saline was injected into each thyroarytenoid muscle under electromyographic and laryngoscopic guidance. Botulinum toxin A markedly reduced perturbation, decreased fundamental frequency range, and improved the spectrographic characteristics of the voice. Fundamental frequency and phonation time remained unchanged. Patients injected with botulinum toxin A noticed significant improvement in their voices in comparison with the placebo-treated group. Excessive breathiness of the voice occurred in two patients, and mild bleeding in one patient in the botulinum toxin A-treated group. Injection with saline resulted in edema of the vocal cord in one patient. Botulinum toxin A proved to be an effective and safe treatment of adductor spasmodic dysphonia.

INTRODUCTION

The neuromuscular blockade produced by botulinum toxin A (BOTOX) has been shown to be effective in the treatment of various ophthalmic conditions,¹⁻³ blepharospasm,⁴ oromandibular dystonia,⁵ and torticollis.⁶ In adductor spasmodic dysphonia, spasmodic hyperadduction of the vocal folds interferes with free-flowing speech. Involuntary hyperadduction of the vocal fold blocks the air flow and production of laryngeal sound, resulting in a characteristic strained hoarseness or voice arrests. Encouraging result has been reported in open studies using BOTOX.⁷⁻⁹ We report in this paper the results of a double-blind, placebo-controlled study of BOTOX in 13 patients.

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MATERIALS AND METHODS

All patients gave informed written consent prior to their entry in this study. BOTOX was obtained from Oculinum Inc. (San Francisco). The toxin was reconstituted with normal saline to a concentration of 50 mouse units/mL.

Patients

Thirteen patients with voice problems diagnosed as spasmodic dysphonia participated in the study. They were evaluated by an interdisciplinary team consisting of speech pathologists, an otolaryngologist, and a neurologist. The diagnosis of adductor spasmodic dysphonia had to be agreed upon by each member of the team; it was based on the presence of those characteristic staccato, glottal stop, and effortful cessations of phonation that occurred during attempts at communication. Patients complain of a choking feeling with difficulty getting vowels out and a tendency for words to cut off.¹⁰⁻¹¹

The 13 patients underwent voice analysis using a Kay Elemetrics Visi-Pitch,* Model 6387 with a laryngeal contact microphone as well as a Kay Elemetrics SonaGraph Spectrum* analyzer, Model 6061B. The following measurements were obtained: fundamental frequency (the speed of vocal cord vibration); phonation time (the ability to sustain an isolated vowel as long as possible); fundamental frequency range (the variation in fundamental frequency when a subject attempts to produce a sustained vowel); perturbation (the irregularity of vocal cord movement); and spectrographic analysis (the assessment of specific frequency, intensity and duration characteristics of the voice).

Steady-state /AH/ vowels were used for the above acoustic analysis procedures to reduce the variables in connected speech. This approach was thought to be sensitive to intermittent adductor spasms, as it was observed to be so in the clinical environment. In all cases, the means of three vowel samples were analyzed for each condition.¹²⁻¹⁶ The patients were also videotaped reading aloud a standard text. We repeated voice analysis and videotaping approximately 4 days after treatment.

The patients were randomly assigned to either group A or B and received either saline or BOTOX. Only this part was used in data analysis. In the second phase of the study, the patient who received saline would receive BOTOX, and the patient who received BOTOX would receive saline. Although this was not part of the evaluation, to protect the integrity of the investigation, neither the examiner nor the patient were aware of what the patient received in the second phase.

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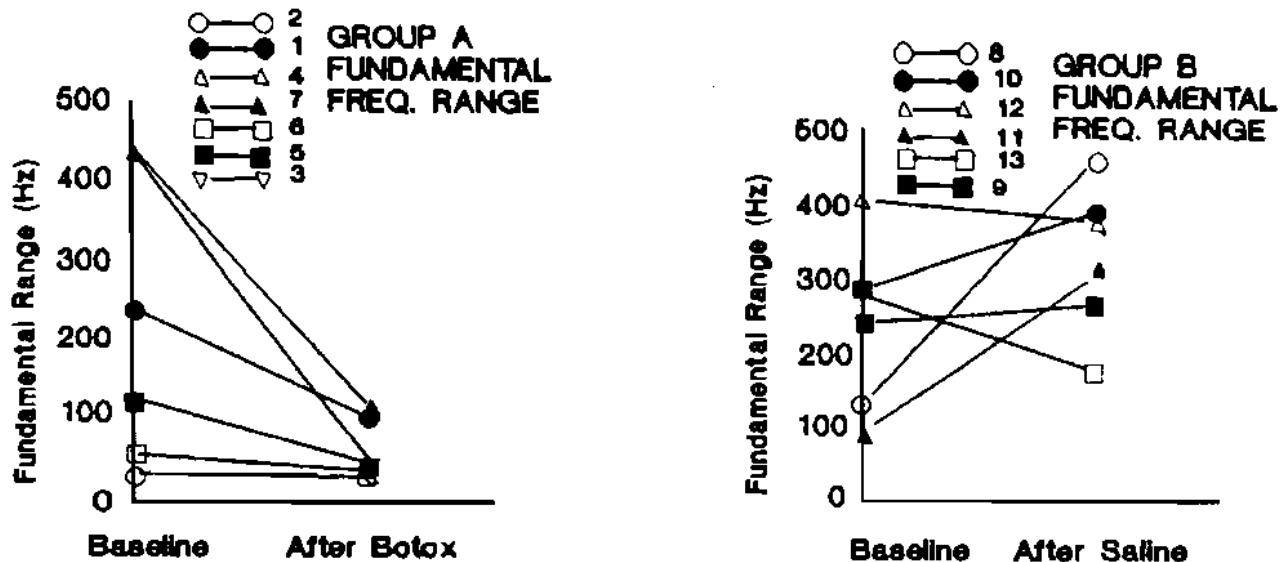


Fig. 1. Effects of BOTOX or saline on fundamental frequency range. Patients in group A were injected with BOTOX. Group B patients received saline. BOTOX decreased fundamental frequency range, but saline did not.

Injection Technique

The injection technique has been previously described.⁹ With the patient in a sitting position, 2 mL of 2% lidocaine was injected into the trachea to induce topical anesthesia in the trachea, glottis, and supraglottis. A fiberoptic laryngoscope was inserted through the nostril and into the endolarynx to a level just above the true cords. A 25-gauge Teflon[®]-coated needle attached by an alligator contact to an electromyograph was passed through the cricothyroid membrane in the midline. After perforating the membrane, it was angled sharply upward and laterally into the body of the true vocal fold until a crisp sound was picked up by the electromyograph when the patient phonated a long /i/. Toxin solution 0.1 cm³ (5 mouse units) or saline was injected into each thyroarytenoid muscle. Mild bulging of the vocal fold by the injected volume was seen through the laryngoscope. Both thyroarytenoid muscles were injected at one sitting.

Four days after the injection, voice analysis was repeated for each patient. Another videotape was also made at this time, and a patient's self-evaluation was obtained.

Rating Scales

The sound spectrograms were rated by a speech pathologist according to the following rating scale. All spectrograms analyzed a 2.4 second sample of a sustained vowel production:

1. Normal periodicity and lack of random high-frequency energy (breathiness) with no evidence of aperiodic vocal breaks (spasms).
2. Normal periodicity with minimal random high-frequency energy (breathiness), with no evidence of aperiodic vocal breaks (spasms).
3. Minimal aperiodicity with moderate high-frequency energy (breathiness), with no evidence of aperiodic vocal breaks (spasms).
4. Minimal to moderate aperiodicity with moderate

high-frequency energy (breathiness) and with one or two aperiodic vocal breaks (spasms).

5. Moderate to severe aperiodicity with moderate high-frequency energy (breathiness) and with three or more aperiodic vocal breaks (spasms).

Videotaped recordings of patients prior to injection and after treatment were rated by a single rater who was highly skilled in diagnosing and treating dysphonia. A 7-point rating scale as previously described and validated was used.¹⁶ In this scale, the higher score represented the more severe condition.

Patients rated themselves after treatment according to the following scale:

0. No improvement;
1. Mild improvement, still has severe difficulty with phonation;
2. Moderate improvement, moderate difficulty with phonation;
3. Marked improvement, only mild difficulty with phonation; and
4. Normal speech.

Patient self-assessments were analyzed using the Mann-Whitney-U test for ranked data. Fundamental frequency measurement, perturbation, fundamental frequency range, and phonation time were converted to percent of initial results and were then analyzed by unpaired Student's *t* tests. Ranked data from spectrographic analysis and videotaped patients' speech samples were also converted to percentages of pretreatment phase but analyzed by Mann-Whitney-U test for nonparametric data.

RESULTS

Fundamental frequency measurement did not

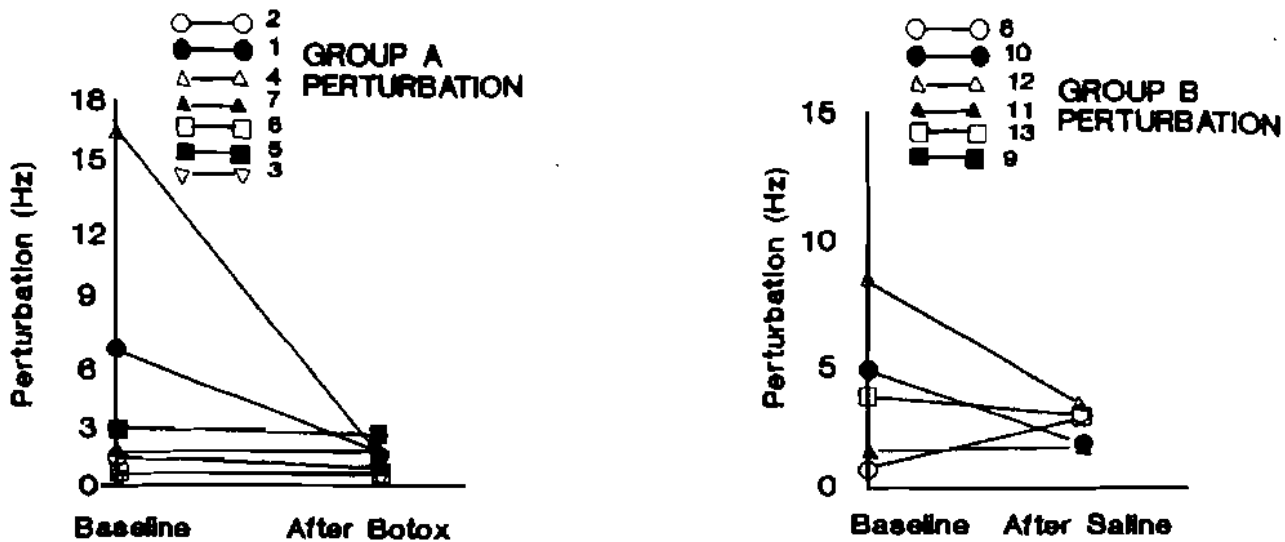


Fig. 2. Effects of BOTOX or saline on perturbation. Patients in group A were injected with BOTOX. Group B patients received saline. Perturbation scores decreased after BOTOX injection, but not after saline.

differ between BOTOX- and placebo-treated patients ($88.91\% \pm 7.00\%$ vs. $102.11\% \pm 8.37\%$). The phonation time measurements did not differ between the two groups ($90.75\% \pm 22.89\%$ vs. $83.24\% \pm 5.96\%$). The vocal fundamental frequency range decreased in patients treated with BOTOX when compared with the placebo, $28.73\% \pm 6.43\%$ vs. $183.86\% \pm 48.30\%$ ($P < 0.01$; unpaired Student's *t* test) (Fig. 1). In the BOTOX-treated group, the perturbation scores improved significantly, $48.28\% \pm 10.14\%$ vs. $122.79\% \pm 42.08\%$ ($P < 0.05$; unpaired Student's *t* test), in the placebo-treated group (Fig. 2). Spectrographic analysis of the BOTOX-treated group improved significantly, $58.33\% \pm 10.46\%$, comparing with $97.14\% \pm 2.85\%$ ($P < 0.05$; Mann-Whitney-U test) in the placebo-treated group.

After treatment with BOTOX, group A patients had a speech rating of $45.24\% \pm 5.63\%$ of their initial rating scores versus $117.86\% \pm 21.83\%$ in group B patients after receiving saline ($P < 0.005$; Mann-Whitney-U test) (Fig. 3).

Subjectively, patients injected with BOTOX noticed a mean improvement of 2.83 ± 0.63 versus 0.0 for the placebo group ($P < 0.01$ by Mann-Whitney-U test).

Side effects included excessive breathiness of the voice in two patients and mild bleeding in one patient in the BOTOX-treated group. Injection with saline resulted in edema of the vocal cord in one patient.

DISCUSSION

Our results showed that BOTOX is effective for the treatment of adductor spasmodic dysphonia and confirms previous open studies.^{7,8} Improvements were seen in the overall rating of speech and a number of specific vocal characteristics.

Perturbation measurements of sustained vowel

sounds improved significantly in the BOTOX-treated group. This acoustic measurement relates to the irregularity of vocal cord movement and is an important factor in spasmodic dysphonia. One would expect high perturbation readings during vocal cord spasms and lower scores if the spasms were lessened. Indeed, this was the case for the toxin-treated group.

For patients with spasmodic dysphonia, there is much intermittent fluctuation of vocal fundamental frequency. This apparently occurs as the vocal cords suddenly tighten uncontrollably and are unable to maintain a steady rate of vibration. The significant lowering of the fundamental frequency range measurements after BOTOX injection is a reflection of the diminished spasmodic movements of the vocal cords.

Broad-band spectrograms of steady-state vowels display a representation of regularity of vocal cord movement, amount of breathiness in the voice, and the existence of spasmodic vocal breaks. The ratings of the spectrograms improved significantly in the BOTOX-treated group, as most of these vocal characteristics would be expected to improve without the sudden tightening of the vocal cords.

It is not surprising that phonation time measurements did not improve in the BOTOX-treated group. The ability to produce a lengthy vowel tone is affected by vocal cord spasms as well as by weakened vocal cords. Our protocol required voice analysis 4 days after the injection. At this time, some patients in the BOTOX-treated group still experienced inadequate vocal cord approximation, which also reduced phonation time.

The fundamental frequency, or rate of vibration of the vocal cords, was not significantly raised or lowered as a consequence of the BOTOX injections. While

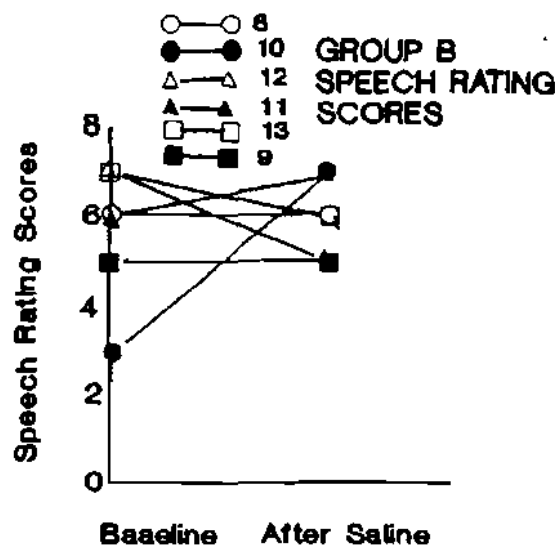
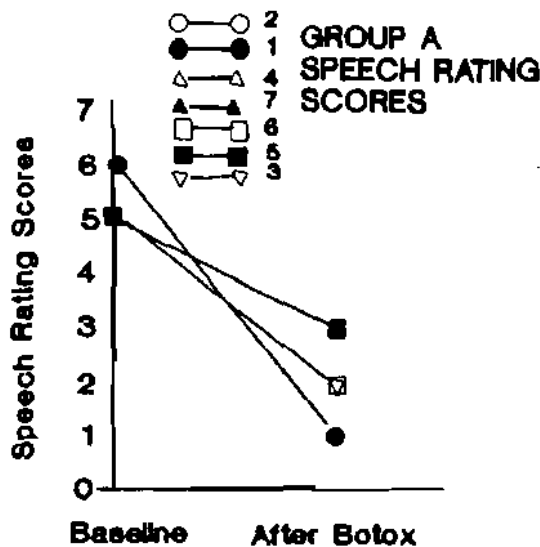


Fig. 3. Effects of BOTOX or saline on speech rating scale. Patients in group A were injected with BOTOX. Group B patients received saline. Videotape recordings of patients prior to injection and after treatment were rated by a rater on a 7-point rating scale, with the higher score representing a more severe condition. BOTOX improved the speech rating scores; saline did not.

it may be expected that weakened or parietic vocal cords would vibrate at a lower rate, this was not observed in our study.

The patients' rating scale analysis showed that saline-treated patients noticed no improvement, in contrast with the results achieved by BOTOX. This was also observed in the rating of speech quality, as assessed by an experienced speech pathologist. Although the rating was done by a single clinician, a previous report has shown this method to be reliable.¹⁶

The use of bilateral injection with BOTOX is safe and reliable, as is evidenced by the few side effects observed in our study population. Ludlow, *et al.*⁷ tried to reproduce the paralysis of the recurrent nerve action. Our results and those of Blitzer, *et al.*⁹ showed that paralysis is not a prerequisite to improving the voice. Moreover, a mild bilateral weakening may provide a more natural condition for voice production. It was noteworthy that none of our patients reported reduction in speed of swallowing, comparing with 80% as reported by Ludlow, *et al.*⁷ This may be explained by the difference in injection techniques and the lesser amount of toxin used for this study.

Excessive breathiness was noted in two of our patients and lasted for about 2 weeks. An average improvement for nearly 3 months is seen in our patients. Similar length of improvement has been reported by others with markedly higher doses of the toxin.⁷ We propose a lower starting dose, which would decrease the amount of initial aphonia or excessive breathiness. Furthermore, electrophysiologic and serological evidences of distant effects of BOTOX injection in other parts of the body have been re-

ported.¹⁷⁻¹⁹ These side effects may be avoided by a lower dose of the toxin.

Treatments for adductor spasmodic dysphonia are often less than satisfactory. Medications are often unsuccessful. Recurrent laryngeal nerve resection offers relief in some patients, but the long-term result is sometimes disappointing.²⁰ BOTOX may offer a better alternative until causative treatment can be found.

SUMMARY

BOTOX treatment is effective and safe in the treatment of adductor spasmodic dysphonia. Good results can be achieved with bilateral injection of small doses of the toxin.

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