Botulinum Toxin for Essential Tremor of the Voice With Multiple Anatomical Sites of Tremor: A Crossover Design Study of Unilateral Versus Bilateral Injection

Christopher Dromey
Brigham Young University, dromey@byu.edu

Paul Warrick
University of Toronto

Jonathan C. Irish
University of Toronto

Lisa Durkin
University of Toronto

Anthony Parkiam
University of Toronto

See next page for additional authors

Original Publication Citation

Warrick, P., Dromey, C., Irish, J., Durkin, L., Pakiam, A. & Lang, A. (2000). Botulinum toxin for essential tremor of the voice with multiple anatomical sites of tremor: A crossover design study of unilateral versus bilateral injection. Laryngoscope, 110, 1366-1374

The Laryngoscope
Lippincott Williams & Wilkins, Inc., Philadelphia

Botulinum Toxin for Essential Tremor of the Voice With Multiple Anatomical Sites of Tremor: A Crossover Design Study of Unilateral Versus Bilateral Injection

Paul Warrick, MD; Christopher Dromey, PhD; Jonathan C. Irish, MD, MSc, FRCSC, FACS;
Lisa Durkin, MSc; Anthony Pakiam, MD, FRCPC; Anthony Lang, MD, FRCPC

Objectives/Hypothesis: **To evaluate the relative efficacy of unilateral and bilateral injections of botulinum toxin injection (BOTOX) in the treatment of essential tremor of the voice (ETV).** ***Study Design:*** **Prospective open-label crossover study.** ***Methods:*** **Patients referred to the Neurolaryngology Clinic at Toronto General Hospital with a diagnosis of ETV were eligible for the study. Patients were sequentially assigned to receive BOTOX as either a bilateral 2.5-U or a unilateral 15-U electromyography-guided injection, followed by the alternative injection 16 to 18 weeks later. Acoustic, aerodynamic, and nasopharyngoscopic data were collected approximately 2, 6, 10, and 16 weeks after each injection. Patients were asked to provide a perceptual evaluation of BOTOX effects at the conclusion of the study.** ***Results:*** **Three of 10 patients demonstrated an objective reduction in tremor severity with bilateral injection, and 2 of 9 with unilateral injection. However, 8 of 10 patients wished to be re-injected at the conclusion of the study. A reduction in vocal effort appeared to be coincident with reduction in laryngeal airway resistance after BOTOX injection.** ***Conclusions:*** **Using objective acoustic measures, only a small proportion of patients achieved benefit from BOTOX injection for ETV. However, a majority of patients in our study benefited from a subjective reduction in vocal effort that may have been attributable to reduced laryngeal airway resistance.** ***Key Words:*** **Essential tremor, botulinum toxin.**

***Laryngoscope*, 110:1366–1374, 2000**

INTRODUCTION

Essential tremor of the voice (ETV) refers to the periodic contraction of antagonistic adductor-abductor and/or superior-inferior laryngeal muscles in an alternating or synchronous fashion. Periodic tremulous voice is the most important characteristic that differentiates ETV from other conditions. The tremor is exacerbated in situations of emotional tension (55%), use of the telephone (16%), and fatigue (13%), and may improve with the use of alcohol (13%).[1] Risk factors for ETV include advancing age and a positive family history. Essential tremor is marked by a bimodal age distribution, peaking in the second and sixth decades.[2] Prevalence estimates for essential tremor of any anatomical site range from 0.4% to 5.6% of the population older than 40 years of age, making it the most common movement disorder.[3] Approximately 25% of patients with essential tremor will have ETV,[2,4] but only a minority of these cases present clinically. Most patients present with several tremulous muscle groups, including the palate,[5] hyoglossus,[6] strap muscles,[7] rectus abdominus, and diaphragm.[7,8] One study suggests that the incidence of intralaryngeal and extralaryngeal muscle tremor involvement is as follows: thyrohyoid, 100%; thyroarytenoid, 80%; sternothyroid, 66%; and cricothyroid, 63%.[7] In the largest review of ETV (31 patients), Brown and Simonson[1] found that 6 patients (19%) had isolated voice tremor, and the remaining 25 had associated tremors with the following frequency: upper extremity (77%), lower extremity (13%), head (52%), face (10%), and tongue (3%). Sixteen (52%) had a positive family history for tremor. Familial clustering of essential tremor ranges from 17% to 100%, with autosomal dominance being the suspected mode of inheritance.[9] Essential tremor is thought to result from overactivity of the cerebellum[10–12] and does not correlate

Presented in part at the 52nd Annual Meeting of the Canadian Society of Otolaryngology—Head and Neck Surgery, Montreal, Quebec, Canada, June 14–17, 1998.

From the Departments of Otolaryngology (P.W., C.D.) and Speech-Language Pathology (L.D.), and the Division of Neurology (A.P., A.L.), Toronto General Hospital/Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada.

Funded in part through the Spasmodic Dysphonia Research Fund, The Toronto General Hospital, University Health Network, a Burroughs-Wellcome Medical Research Council Scholarship, and a Center of Excellence Grant from the National Parkinson Foundation in Miami.

Editor's Note: This Manuscript was accepted for publication April 27, 2000.

Send Correspondence to Jonathan C. Irish, MD, Princess Margaret Hospital, Room 3-952, University Health Network, Toronto, Ontario M5G 2M9, Canada.

well with a subsequent diagnosis of Parkinson's disease;[13] contradictory evidence exists, however.[2,14] The frequency of tremor gradually decreases with age, from the physiological frequency range of 8 to 12 Hz to the pathological and visually perceptible 5- to 7-Hz range among those older than 60 years.[15] These findings suggest that voice tremor is an intention tremor, likely associated primarily with speech-related adduction of the vocal folds.

The diagnosis of ETV often requires the experience of a tertiary referral center. In our experience with 175 consecutive patients referred to The Toronto General Hospital Neurolaryngology Clinic for suspected spasmodic dysphonia, 17% had a diagnosis of isolated ETV, 15% had overlap of ETV with adductor spasmodic dysphonia (ADSD), and 37% had isolated ADSD (unpublished observations). Important to note is the particular difficulty in differentiating overlap disease from true ETV. For this purpose, acoustic analysis can identify periodic oscillation in both frequency and amplitude among patients with ETV,[16] which differentiates ETV from ADSD and overlap disease, which involve less rhythmic oscillation of the voice tremor. Patients suffering from ETV may therefore have a predominantly amplitude or a predominantly frequency tremor, and these components may respond differently to treatment.[17]

Pharmacological management of ETV has demonstrated disappointing results, with response rates ranging from 24% to 40%. Agents tested include β-adrenergic antagonists (propranolol),[18–20] anticonvulsants (primidone),[21] benzodiazepines (clonazepam, diazepam),[20] and carbonic anhydrase inhibitors (methazolamide).[17,22]

Botulinum Toxin

Botulinum toxin type A (BOTOX, Allergan, Irvine, CA) is a potent inhibitor of acetylcholine release from the neuromuscular junction. Since its introduction as a therapeutic agent in 1983, BOTOX has become the treatment of choice for managing blepharospasm,[23] hemifacial spasm,[24] oromandibular dystonia,[25] torticollis,[26] limb dystonias,[27] and spasmodic dysphonia.[28,29] Recent evidence suggests that BOTOX may be useful in managing ETV. Jankovic and Schwartz[30] have reported the use of BOTOX in 51 patients having head and/or hand tremors of various etiologies, including essential tremor, dystonia, and parkinsonism. Koda and Ludlow[7] noted that the high incidence of thyroarytenoid muscle involvement in their study suggests that patients with voice tremor should respond well to BOTOX injection. Ludlow and colleagues have reported preliminary results on the use of BOTOX in idiopathic voice tremor,[31,32] but neither of these reports commented on the diagnosis or categorization of patients with voice tremor or attempted to isolate patients with ETV.

Study Objectives

We have used BOTOX in patients with ETV in our neurolaryngology clinic for the past 5 years with favorable anecdotal experience. We wanted to evaluate the efficacy of BOTOX to attenuate ETV with multiple anatomical sites of tremor using objective acoustic and aerodynamic data, perceptual measures derived from audio and endoscopic data, as well as patient perception of the benefit of effect. We present the results of a crossover design open-label comparison study of unilateral versus bilateral injection with BOTOX for ETV with multiple sites of tremor. This study represents the first scientific evaluation of BOTOX for ETV to our knowledge.

MATERIALS AND METHODS

Patients

After institutional ethics board approval and informed written consent, 10 patients of Northern European descent who received diagnoses of ETV or ETV-ADSD overlap from both the neurolaryngology (J.C.I., L.D.) and movement disorders (A.L., A.P.) clinics were asked to take part in the study. Each patient was questioned about the nature of his or her symptoms of tremor, the degree of disability caused by the tremor, family history of tremor and other neurologic disease, and expectations of treatment with BOTOX. No patient underwent concurrent speech-language therapy as part of the treatment regimen. The patients underwent hearing screening to ensure thresholds of less than or equal to 40 dB at each of 0.25, 0.50, 1, 2, and 4 kHz.

Treatment Regimen

Patients received percutaneous electromyography-guided injection of BOTOX according to the method described by Ludlow et al.[33] Patients received either bilateral injection at the time of enrollment followed by unilateral injection 16 to 18 weeks later, or vice versa, according to the order of their enrollment. Odd-numbered patients were designated to receive bilateral injection first and even-numbered patients were scheduled for unilateral injection first. (Patients 4 and 7 were enrolled in a coincident longitudinal study of BOTOX by the same authors and for this reason both received bilateral injection first, despite the fact that patient 4 was scheduled according to our protocol to receive unilateral injection first.)

BOTOX treatment was standardized. Bilateral treatment consisted of 2.5 units of BOTOX reconstituted in normal saline injected into each vocalis muscle and unilateral treatment consisted of 15 units of BOTOX injected into the left vocalis muscle. All but one of the patients were re-injected with the alternative injection of BOTOX at 16 to 18 weeks of follow-up. Patient 4 declined repeat injection after experiencing prolonged breathiness after bilateral injection. He received voice therapy from the speech-language pathologist in our group (L.D.) to circumvent any maladaptive strategies he might have developed during the process after his first injection with BOTOX.

Data Collection

Data were collected before injection and approximately 2, 6, 10, and 16 weeks after each injection. During each visit acoustic and aerodynamic recordings were made of the patient's voice. All patients were also asked to undergo direct nasopharyngoscopy and videostroboscopy at each visit. Collection of the endoscopic component of our data were subject to patients' tolerance of the procedure.

Instrumentation

Recordings were made in a sound booth using a head-mounted microphone (AKG C-420) positioned 4 cm from the patient's mouth. Sound pressure level was measured with a sound level meter (CEL 254) placed exactly 50 cm from the patient's lips. Acoustic and sound pressure level signals were recorded into a digital audio tape recorder (Panasonic SV-3800). During each recording session, the vowel /a/ was produced three times at normal pitch and loudness for about 5 seconds, and was also sustained maximally three times to record the maximum phonation time. A standardized reading passage (The Rainbow Passage) was recorded. Signals were later digitized using the Computerized Speech Lab (CSL) (Kay Elemetrics Model 4300B, Lincoln Park, NJ). The Motor Speech Profile module of CSL provided magnitude, rate, and periodicity measures of both amplitude and frequency tremor in vowel phonation. For each recording, the three normal pitch and loudness vowels were analyzed by selecting a 2.0-second window starting 500 milliseconds into each vowel.

Aerodynamic data were digitized on-line using a pneumotachograph mask (Glottal Enterprises MS100-A2, Syracuse, NY) that transduced oral airflow and intraoral air pressure. The flow signal was low-pass filtered at 4.5 kHz (Frequency Devices 901) and digitized at 10 kHz (Data Translation 2801A) on a Pentium PC using C-SpeechSP software (Milenkovic, Madison, WI). This system was calibrated before each recording session using flowmeter and a manometer. Three trains of at least five /pae/ syllables were produced. This task allowed measures of oral airflow, intraoral air pressure, and sound pressure level. Estimated laryngeal airway resistance was calculated by dividing the estimated subglottal pressure by the mean mid-vowel airflow from the middle syllable from each of the three trains on each date, according to the method described by Smitheran and Hixon.[34]

Laryngoscopic data were acquired before injection and approximately 2, 6, 10, and 16 weeks thereafter and were recorded to S-VHS videotape (Kay Elemetrics videostroboscope system). Flexible nasopharyngoscopy was used to assess tremor of the palate during rest breathing, prolonged /a/ phonation and /second/ fricatives. Using flexible nasolaryngoscopy with halogen light, the oropharynx, hypopharynx, and larynx were viewed for their degree of tremor during rest breathing, and prolonged /i/ phonation with pitch and loudness variation. Videostroboscopic data were collected throughout the study, but too often, due to the fluctuation in frequency secondary to the tremor, this part of our data proved to be an unreliable marker of voice tremor and did not undergo detailed analysis.

Perceptual Analysis

Perceptual analysis of acoustic data was obtained using selected reading tasks in random order before and approximately 2, 6, 10, and 16 weeks after injection of BOTOX. Six speech-language pathologists blindly rated randomized samples of the first two sentences of the Rainbow Passage. Perceived vocal effort, tremor, and quality were evaluated by moving a computer display pointer along a visual analogue scale with a mouse. The values obtained were converted to their equivalent visual analogue scale (VAS, 10 cm) ratings. The Appendix at the end of this manuscript explains the values assigned to 0 cm and 10 cm for each VAS used in the study. The raters listened to the recordings in a sound-treated booth and were allowed to hear samples more than once. Alpha coefficients were calculated for intrarater reliability; only the data from those raters whose alpha coefficients were greater than 0.9 were included in the perceptual analysis.

Perceptual analysis of nasopharyngoscopy data was obtained using randomized silent video samples from the same time intervals as the perceptual acoustic data. Three blinded raters (C.D., J.C.I., L.D.) provided VAS assessments of abductor-adductor and superior-inferior tremor, supraglottic hyperfunction, and vocal fold adduction during phonation.

Patients were asked at the conclusion of the study to provide their retrospective opinion about BOTOX treatment. Patients completed VAS for overall satisfaction, subjective voice improvement and reduction in tremor. We inquired about the incidence and severity of swallowing problems, breathiness, and coughing. Patients were asked to compare the efficacy of bilateral versus unilateral injection and whether they would like to continue with future BOTOX injections.

RESULTS

Table I presents patient demographic data. These data concur with other published data regarding the epidemiology of ETV. Patients were in their fifth to eighth decade and were of Northern European (British, Irish,

TABLE I.
Patient Demographics.

Patient No.	Age (y)	Sex	Diagnosis	Occupation	Vocal Hobbies	Duration (y)	Prior Treatment or Consultation: SLP	Neurology	Otolaryngology	Family History
1	73	F	ETV	Banker	Singing†	2	0	0	0	—
2	75	F	ETV-ADSD overlap	Homemaker	None	20	1	1	0	—
3	48	F	ETV-ADSD overlap	Teacher	None	12	1	1	0	—
4	62	M	ETV	Professor	None	15	1	1	1	Parkinson's (aunt)
5*	70	F	ETV-ADSD overlap	Office manager	Volunteer†	5	1	1	1	Parkinson's (father)
6	46	F	ETV-ADSD overlap	Marketing†	None	22	1	0	2	—
7	65	M	ETV	Architect	Singing†	12	1	1	1	Hand tremor (twin brother)
8	70	F	ETV	Secretary	Volunteer	6	0	2	1	—
9	77	F	ETV	Office worker	None	14	0	2	1	Voice tremor (mother)
10	57	F	ETV	Homecare nurse†	None	10	0	1	1	Parkinson's (father) Head tremor (brother)
Mean	64.3					11.8	0.6	1.3	1.1	
SD	10.9					6.4	0.5	0.5	0.4	

*Patient had multiple sclerosis; full examination in the movement disorders and neurolaryngology units determined that this disease was distinct from her laryngeal essential tremor and did not contribute to her voice tremor.

†Patient is retired from stated occupation or no longer pursues vocal hobby.

"Previous treatment" indicates the number of consultants the patient had seen in the respective specialties shown. ETV = essential tremor of the voice; ADSD = adductor spasmodic dysphonia; SLP = speech-language pathology.

Scandinavian, Lithuanian, and German) extraction. Five of the 10 patients had previously decided to give up either their original employment or a hobby that they found pleasurable because of the speech impairment caused by vocal tremor. Patients had experienced the symptoms of ETV for approximately 12 years on average by the time they had enrolled in the study. Two of the 10 patients had a diagnosis of overlap (ETV-ADSD) disease. Patients attested to worsening of their voice tremor in association with increased emotional stress (5/10), physical fatigue (4/10), or caffeine ingestion (7/10). Improvement of voice tremor was reported to be associated with alcohol ingestion (4/10) or good hydration (2/10). Five patients reported having a family history of tremor in a first-degree or second-degree relative, three of whom attributed this tremor to a diagnosis of Parkinson's disease.

Patients had consulted with an average of one neurologist and one otolaryngologist before presenting to the neurolaryngology clinic for evaluation. Six of 10 had consulted with a single speech-language pathologist before our assessment. All had reported little to no benefit from previous attempts at voice therapy. Five of the 10 patients had been treated previously with BOTOX injection, of whom only 3 had received BOTOX injection in the 3 months before commencing the study. A single patient already enrolled in the study received a unilateral injection without any attendant breathiness, which she had experienced after previous injections. She was therefore re-injected 21 days later and the latter injection was followed for study purposes. Patients had on average three to four anatomical sites of tremor on clinical examination (Table II) that may have contributed to perceptible voice tremor. No patient in the current study had isolated vocalis muscle tremor.

Figure 1 depicts the measured percentage of modulation of amplitude and frequency of the patients over the course of the study after both unilateral and bilateral injections. A trend toward reduction in both aspects of tremor was noted with the unilateral injection, but only

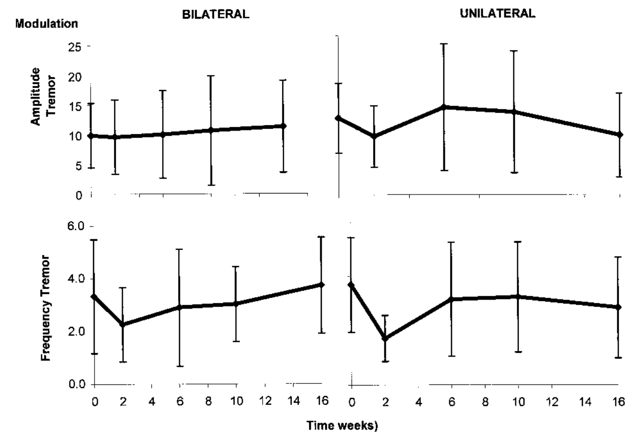

Fig. 1. Acoustic analysis of essential tremor of the voice treated with serial bilateral and unilateral BOTOX injections.

frequency tremor showed a trend toward reduction with bilateral injection. None of these reductions were sustained at the 6 week follow-up, so that limited long-term clinical benefit was derived from this effect. Only 3 of 10 bilateral injection patients and only 2 of 9 unilateral injection patients maintained frequency and amplitude tremor modulation values of less than half of baseline at the 6-week follow-up visit.

Figure 2 demonstrates the aerodynamic parameters (estimated subglottic pressure and laryngeal airflow) measured in this study. Sound pressure level, as measured at the same transducer for these parameters, is also included. Estimated laryngeal airway resistance was derived from the latter two measurements. Sound pressure level and estimated subglottic pressure remained relatively unchanged for both injection types throughout the study, suggesting that patients used a similar phonation strategy over the course of the study. As expected, laryngeal airflow increased after injection, as reduced adduction allowed greater air leak on phonation. Estimated

TABLE II.
Location of Tremor.

Patient No.	Ab/Ad	Sup/Inf	Strap	Pharyngeal	Tongue	Palate	Lip	Periorbital	Head	Total
1	1	1	0	0	0	0	0	0	0	2
2	1	0	0	0	0	0	0	0	1	3
3	1	0	1	0	0	1	0	0	0	3
4	1	1	0	1	0	1	0	0	0	4
5	1	0	0	0	0	0	0	0	0	2
6	1	0	0	0	1	1	0	0	0	3
7	1	1	0	0	0	1	0	1	0	4
8	1	0	0	0	1	1	1	0	0	4
9	1	1	0	1	1	1	0	0	0	5
10	1	1	0	0	0	0	0	0	1	4
Total	10	5	1	2	3	6	1	1	2	—
Mean ± SD	—	—	—	—	—	—	—	—	—	3.4 ± 0.9

Ab/Ad = abductor/adductor; Sup/Inf = superior/inferior.

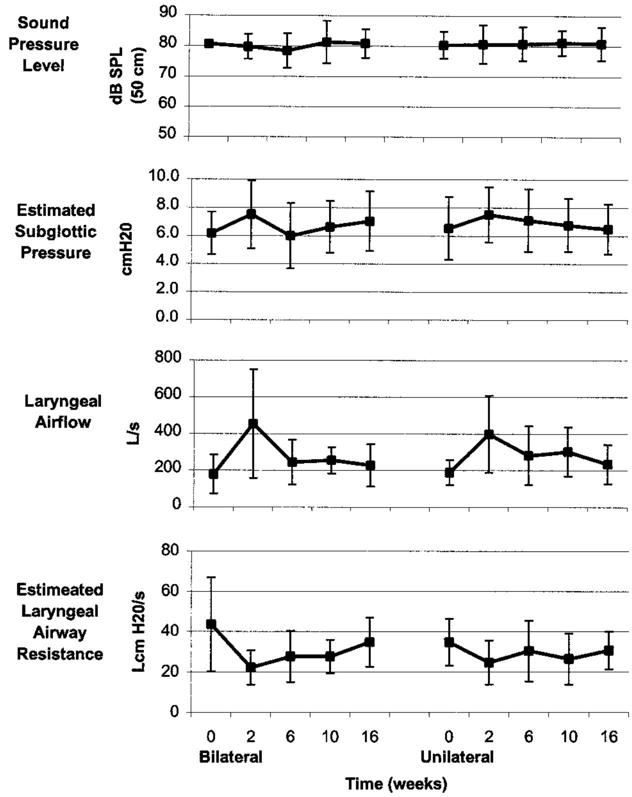

Fig. 2. Aerodynamic analysis of essential tremor of the voice treated with serial bilateral and unilateral BOTOX injections.

laryngeal airway resistance was reduced after injection, particularly in the case of bilateral injection, and gradually returned to pretreatment levels over the course of the 16- to 18-week observation period.

Table III illustrates the changes in perceived vocal effort, tremor, and quality at 0 and 6 weeks with unilateral and bilateral injection evaluated by the speech-language pathologists. Positive changes reflect an increase in VAS score over the interval and negative changes reflect a decrease. For the audio perceptual data, four of six raters produced alpha reliability coefficients greater than 0.9 and were included in the analysis. Intraclass correlation coefficients for the four raters are as follows: tremor, 0.878; effort, 0.883; and quality, 0.861. Patient 4 declined to continue with the second arm of the study after experiencing profound and prolonged breathiness after the first injection. Mean VAS ratings demonstrated a trend toward improvement for all parameters with both forms of injection, but the variation of response was wide, and these differences are not statistically significant. One can extract more useful information by examining these patients individually. Patients 8, 9, and 10 demonstrated marked VAS reductions in all acoustic perceptual parameters with both bilateral and unilateral injections, and patient 7 did so with bilateral injection.

Similarly, perceptual evaluation of nasopharyngoscopy data by three expert blinded raters is shown in Table IV. All three raters produced alpha reliability coefficients greater than 0.9. The intraclass correlation coefficient for all video ratings was 0.866. Some data points are missing because some patients declined to allow nasopharyngoscopy for one or both of the two study arms. From these data, no obvious trend is apparent, again owing to the wide variability in response in this small study population. Patients 3, 7, 8, and 9 had the most marked reductions of laryngeal tremor with unilateral injection and patients 5, 7, and 8 responded well to unilateral injection. Patients 5 and 10 demonstrated reductions in supraglottic hyperfunction with unilateral injection and patients 5,7, and 8 responded well to bilateral injection. Vocal fold adduction, a measure of accurate placement of the injection, was reduced by 50% or more on all but 4 of 15

TABLE III.
Perceptual Acoustic Data.

Patient No.	Unilateral			Bilateral		
	Tremor	Effort	Quality	Tremor	Effort	Quality
1	6	1	2	3	−14	−7
2	−3	−20	−2	19	−3	3
3	−10	−1	7	−3	−17	−8
4	—	—	—	−48	−1	32
5	20	19	15	31	13	11
6	−17	−8	4	−9	−4	−3
7	−37	−3	20	−46	−25	−24
8	−36	−41	−26	−5	−25	−11
9	−20	−29	−21	−20	−27	−14
10	−22	−17	−17	−29	−35	−22
N	9	9	9	10	10	10
Mean	−13	−11	−2	−11	−14	−4
SD	19	18	16	26	15	17

TABLE IV.
Perceptual Nasopharyngoscopy Data.

Patient No.	Unilateral Tremor Sup/Inf	Unilateral Tremor Add/Abd	Unilateral Supraglottic Hyperfunction Ant/Post	Unilateral Supraglottic Hyperfunction Vent Fold	Unilateral Adduction	Bilateral Tremor Sup/Inf	Bilateral Tremor Add/Abd	Bilateral Supraglottic Hyperfunction Ant/Post	Bilateral Supraglottic Hyperfunction Vent Fold	Bilateral Adduction
1	1.0	1.8	0.3	0.5	−1.8	−0.4	0.3	−1.0	−0.1	−0.8
2	—	—	—	—	—	1.2	−1.4	3.0	2.8	0.0
3	−5.1	−4.6	1.9	1.4	−3.6	5.7	1.5	−2.8	0.7	−0.2
4	—	—	—	—	—	1.9	0.2	0.6	0.6	−2.1
5	3.1	1.7	−2.4	−4.4	−2.0	−1.9	−0.9	−3.5	−2.6	−0.9
6	—	—	—	—	—	—	—	—	—	—
7	−2.8	−5.1	−1.1	1.2	−4.6	−3.0	−3.1	−3.4	−0.6	−3.5
8	−3.0	−4.3	0.1	0.7	−2.2	−0.4	−3.0	−1.7	−0.7	−1.3
9	−1.7	−1.3	0.1	−0.2	−0.9	—	—	—	—	—
10	1.2	−1.2	−2.9	−2.1	−0.7	0.3	−0.1	4.7	1.6	0.5
N	7	7	7	7	7	8	8	8	8	8
Mean	−1.0	−1.8	−0.6	−0.4	−2.3	0.4	−0.8	−0.5	0.2	−1.0
SD	2.9	2.9	1.7	2.1	1.4	2.7	1.6	3.1	1.6	1.3

Add/abd = adductor/abductor; Ant/Post = anterior/posterior; Sup/Inf = superior/inferior; Vent Fold = ventricular fold.

samples, suggesting that good infiltration of the vocalis muscle was achieved.

Table V outlines patient retrospective perceptual assessment of BOTOX injection. The mean overall satisfaction with BOTOX injection was high, with a mean VAS rating of 7.2 ± 2.7. The mean ability of BOTOX to reduce tremor, by both the unilateral and bilateral injection routes, was rated by patients as 7.3 ± 2.3. A fairly equal number of patients felt that their best overall result was obtained with unilateral injection[4] versus bilateral injection.[3] Two patients felt that the two injections had equal efficacy. Note that 8 of 10 patients wished to be re-injected with BOTOX at the conclusion of the study. The most bothersome side effect was breathiness (6.1 ± 2.3), followed by coughing/choking (3.0 ± 2.1) and swallowing problems (2.5 ± 1.7). One patient did experience pneumonia that occurred 2 to 4 weeks after unilateral (second) injection of BOTOX and may have therefore been related to aspiration secondary to the injection. Patients felt that overall experience with side effects was just as likely to be more severe with unilateral injection (5 of 9) as with bilateral injection (4 of 9). Patient 4 did not complete both arms of the study and was not included in this part of our analysis.

TABLE V.
Patient Satisfaction Survey.

Patient No.	Visual Analogue Scale: Overall Satisfaction	Improved Voice	Reduced Tremor	Swallowing Problems	Breathiness	Coughing/ Choking	Best Result: Unilateral	Bilateral	Equal	Most Side Effects: Unilateral	Bilateral	Would Continue
1	9.8	9.5	9.1	0.3	2.9	0.8	1	0	0	0	1	1
2	7.0	6.8	6.5	4.9	8.8	5.0	0	1	0	0	1	1
3	7.7	7.8	9.3	1.7	5.5	3.8	1	0	0	1	0	1
4*	—	—	—	—	—	—	—	—	—	—	—	—
5	9.8	9.8	9.5	2.1	2.6	0.3	1	0	0	1	0	1
6	8.8	7.9	8.0	3.3	9.0	2.6	0	0	1	1	0	1
7	1.1	0.4	1.9	0.5	8.0	0.5	0	1	0	1	0	0
8	6.8	6.3	6.9	2.9	5.5	5.4	0	1	0	1	0	1
9	8.1	6.9	6.9	5.3	6.3	5.4	1	0	0	0	1	1
10	5.9	5.1	7.7	1.9	6.1	2.9	0	0	1	0	1	1
Total							4	3	2	5	4	8
Mean	7.2	6.7	7.3	2.5	6.1	3.0						
SD	2.7	2.8	2.3	1.7	2.3	2.1						

*No data were obtained for this patient, who did not complete study.

DISCUSSION

Quantitative data regarding the use of botulinum toxin A injection in cases of ETV have not been reported previously. Given the low prevalence of ETV severe enough to cause patients to seek out medical attention, even major referral centers have difficulty assembling large case series. Therefore, we designed the current crossover study of unilateral versus bilateral BOTOX injection to maximize the amount of data generated by our study.

The major objective of this study was to evaluate the efficacy of BOTOX to attenuate ETV. BOTOX demonstrated remarkable effectiveness in reducing ETV in certain patients in our study. Moreover, most patients reported substantial subjective benefit from having received BOTOX injection. BOTOX appears to provide these patients with a tangible improvement in vocal effort and a measurable decline in laryngeal airway resistance. A reduction of laryngeal resistance after BOTOX injection has also been observed in the spasmodic dysphonia population; this effect may represent a universal effect of BOTOX.[35] Importantly, this reduction in laryngeal airway resistance occurred in the absence of any concurrent voice therapy. One would hypothesize that the benefits of voice therapy would be additive beyond the effect of BOTOX and would further reduce vocal effort and laryngeal airway resistance. In fact, the mean VAS for overall satisfaction with BOTOX injection for the nine patients who finished the study was 7.2 ± 2.7 of a possible 10. Given that 3 of 10 patients demonstrated objective improvement of their symptoms with bilateral injection and 2 of 9 with unilateral injection, the level of patient satisfaction obtained with BOTOX in this study is substantial.

The open-label crossover design of this study had distinct advantages and disadvantages that need to be taken into account when evaluating our findings. Patients in this study underwent alternating group assignment to either bilateral followed by unilateral injection, or vice versa. Despite the inherent risks of bias with this design, we felt that such a design was necessary given that the nature of BOTOX injection renders single-blinded or double-blinded design challenging, and the need to provide incentive (through patient awareness of the treatments) to keep a sizeable sample size enrolled over a long 32-week study period. Importantly, evaluation of our data shows no clear order effect or evidence that this aspect of our study design substantially influenced our findings. Moreover, all acoustic, aerodynamic, and audio and video perceptual data were evaluated in a randomized fashion by blinded raters, which should eliminate many of the biases that might be encountered in studies of this type.

The dosing of botulinum toxin chosen in this study reflects two factors that we considered at the outset of the study. First, the BOTOX literature in the spasmodic dysphonia population is not in agreement as to whether unilateral (range, 5–20 U) or bilateral (range, 2.5–5 U) injection is more effective.[36–40] Several comparative studies have demonstrated equivocal benefits of each modality,[36,38,40] or a marginal advantage with bilateral[37] or unilateral[39] injection. Second, as we had no dose-ranging study in the voice tremor population on which to base the dosing for the current study, our dosing was based on 5 years of anecdotal experience injecting these patients, as well as generally accepted and peer-reviewed dosing for spasmodic dysphonia used at our institution.[37,39]

The side effect profile of BOTOX did prove to be a limiting factor in the administration of this agent to our study population. A total of three patients rated the breathiness they experienced with BOTOX injection as greater than 8.0 on our VAS scale, in which 10 represented "worst possible breathiness." A further four patients gave ratings for this parameter of higher than 5.0. No difference in the incidence of breathiness was noted between unilateral and bilateral injection. Clinicians need to be aware that the more elderly patient population with ETV may be at increased risk of experiencing adverse effects (especially aspiration) from BOTOX injection and more careful follow-up of these patients may be warranted, for example, for patients with comorbidities.

No placebo group was included in our study, which involved an open-label crossover design. While some critics might view this as a limitation of our study, we believed this design was essential to extract a large amount of data from a small number of patients in this relatively uncommon disease. Had we employed a placebo crossover design, using saline as the placebo (such as that employed by Truong et al.[28] in an ADSD population, patients may well have been able to guess whether they had received BOTOX, which routinely causes marked breathiness in the 2 to 6 weeks after injection, thereby nullifying the benefits of such a design. Furthermore, without an obvious benefit from injections, our 32-week evaluation period would likely have proved too long for some patients who drove long distances to undergo multiple acoustic, aerodynamic, and video perceptual evaluations.

We have made several important observations that may clarify the apparent disparity in the efficacy of BOTOX one notes when comparing the objective and subjective data in this study.

1) Patient perception of vocal effort correlated with the aerodynamic estimate of laryngeal airway resistance. Patients with ETV may benefit from the fact that BOTOX effectively reduces airway resistance by limiting vocal fold adduction, which may have the subjective effect of reducing vocal effort during phonation. Because patients were not undergoing concurrent voice therapy, this subjective reduction in vocal effort experienced by many of the patients in this study appears to be due to BOTOX injection.
2) The objective response rates obtained in this study with ETV[10–12] were lower than those usually observed in patients with ADSD, which is likely attributable to the significant differences in pathophysiology between these two diseases. For ADSD, neurological dysfunction is usually limited to the thyroarytenoid muscle and is associated with high response rates to BOTOX injection.[28,29] Conversely, in ETV the neurological dysfunction is rarely limited to the thyroarytenoid muscles.[1] Often ETV involves muscles throughout the upper aerodigestive tract, such as the levator veli palatini,[5] hyoglossus,[6] sternothyroid, thyrohyoid,[7] rectus abdominus, and

diaphragm.[7,8] With increasing numbers of tremulous muscles, less benefit of injecting BOTOX only into the thyroarytenoid muscle would be expected.

3) The patient population for ETV tends to be elderly, and are likely at higher risk of side effects and intolerance to them. The incidence of side effects, such as prolonged breathiness, coughing, choking, and dysphagia has been higher in our experience as compared with patients with ADSD, who tend to be middle-aged and tolerate BOTOX injection better. This may be attributable in part to coincident presbylarynx in this population of patients. In particular, prolonged breathiness, ranging from 2 to 10 weeks in this study, must be considered when evaluating BOTOX for use in this population. The relatively increased duration of these side effects likely impairs the benefit derived from BOTOX, both from a subjective and an objective point of view. Although a reduction in the administered dose of BOTOX may be considered, this would likely be at the expense of efficacy.

CONCLUSION

Using objective acoustic measures, only a small proportion of patients achieved benefit from BOTOX injection for ETV. However, a majority of patients in our study benefited from a subjective reduction in vocal effort that may have been attributable to reduced laryngeal airway resistance.

BOTOX, given by either unilateral or bilateral intrathyroarytenoid electromyography-guided injection, should be regarded as a viable treatment for patients with ETV and deserves further study to elucidate subgroups of patients who will most benefit from this therapy. More side effects can be anticipated with these patients, as opposed to the ADSD population. The mechanism and therapeutic significance of the association of perceived vocal effort with estimated laryngeal airway resistance noted in this study need to be clarified. The potential additional benefit of speech therapy combined with BOTOX injection, as compared with BOTOX alone, should be addressed in future studies.

BIBLIOGRAPHY

1. Brown JR, Simonson J. Organic voice tremor: a tremor of phonation. *Neurology* 1963;13:520–525.
2. Lou J-S, Jankovic J. Essential tremor: clinical correlates in 350 patients. *Neurology* 1991;41:234–238.
3. Rautakorpi I, Marttila RJ, Rinne UK. Epidemiology of essential tremor. In: Findley LJ, Capildeo R, eds. *Movement Disorders: Tremor*. Toronto: Oxford University Press, 1984:211–218.
4. Koller WC, Busenbark K, Miner K, the Essential Tremor Study Group. The relationship of essential tremor to other movement disorders: report on 678 patients. *Ann Neurol* 1994;35:717–723.
5. Findley LJ, Gresty MA. Head, facial and voice tremor. *Adv Neurol* 1988;49:239–253.
6. Andran G, Kinsbourne M, Rushworth G. Dysphonia due to tremor. *J Neurol Neurosurg Psychiatry* 1966;29:219–223.
7. Koda J, Ludlow CL. An evaluation of laryngeal muscle activation in patients with vocal tremor. *Otolaryngol Head Neck Surg* 1992;107:684–696.
8. Hachinski VC, Thomsen IV, Buch NH. The nature of primary vocal tremor. *J Can Neurol Sci* 1975;2:195–197.
9. Louis ED, Ottman R. How familial is familial tremor? *The genetic epidemiology of essential tremor. Neurology* 1996;46:1200–1205.
10. Llinas R, Yarom Y. Oscillatory properties of guinea pig inferior olivary neurones and their pharmacological modulation: an in-vitro study. *J Physiol* 1986;376:163–182.
11. Jenkins IH, Bain PG, Colebatch JG, Thompson PD, Findley LJ, Frackowiak RSJ, Marsden CD, Brooks DJ. A positron emission tomography study of essential tremor: evidence for overactivity of cerebellar connections. *Ann Neurol* 1993;34:82–90.
12. Hallett M, Dubinsky RM. Glucose metabolism in the brain of patients with essential tremor. *J Neurol Sci* 1993;114:45–48.
13. Pahwa R, Koller WC. Is there a relationship between Parkinson's disease and essential tremor? *Clin Neuropharmacol* 1993;16:30–35.
14. Geraghty JJ, Jankovic J, Zetusky WJ. Association between essential tremor and Parkinson's disease. *Ann Neurol* 1985;17:329–333.
15. Elble RJ, Higgins C, Leffler K, Hughes L. Factors influencing the amplitude and frequency of essential tremor. *Mov Disord* 1994;9:589–596.
16. Winholtz WS, Ramig LO. Vocal tremor analysis with the vocal demodulator. *J Speech Hear Res* 1992;35:562–573.
17. Busenbark K, Ramig L, Dromey C, Koller WC. Methazolamide for essential voice tremor. *Neurology* 1996;47:1331–1332.
18. Koller W, Graner D, Mlcoch A. Essential voice tremor: treatment with propranolol. *Neurology* 1985;35:106–108.
19. Koller WC. Long-acting propranolol in essential tremor. *Neurology* 1985;35:108–110.
20. Massey EW, Paulson GW. Essential vocal tremor: clinical characteristics and response to therapy. *South Med J* 1985;78:316–317.
21. Hartman DE, Vishwanat B. Spastic dysphonia and essential (voice) tremor treated with primidone. *Arch Otolaryngol* 1984;110:394–397.
22. Muenter MD, Daube JR, Caviness JN, Miller PM. Treatment of essential tremor with methazolamide. *Mayo Clin Proc* 1991;66:991–997.
23. Dutton JJ. Acute and chronic effects of botulinum toxin in the management of blepharospasm. In: Jankovic J, Hallett M, eds, *Therapy with Botulinum Toxin*. New York: Marcel Dekker, 1994:199–209.
24. Biglan AW, May M, Bowes RA. Management of facial spasm with clostridium botulinum toxin, type A (Oculinum). *Arch Otolaryngol* 1988;114:1407–1412.
25. Brin MF, Blitzer A, Herman S, Stewart C. Oromandibular dystonia: treatment of 96 patients with botulinum toxin type A. In: Jankovic J, Hallett M, eds. *Therapy with Botulinum Toxin*. New York: Marcel Dekker, 1994:429–435.
26. Jankovic J, Orman J. Botulinum toxin A for cranial-cervical dystonia: a double blind placebo controlled study. *Neurology* 1987;37:616–623.
27. Pullman S. Limb dystonia: treatment with botulinum toxin. In: Jankovic J, Hallett M, eds. *Therapy with Botulinum Toxin*. New York: Marcel Dekker, 1994:307–321.
28. Truong DD, Rontal M, Rolnick M, Aronson AE, Mistura K. Double-blind controlled study of botulinum toxin in adductor spasmodic dysphonia. *Laryngoscope* 1991;101:630–634.
29. Blitzer A, Brin MF. The evaluation and management of abductor laryngeal dystonia. In: Jankovic J, Hallett M, eds. *Therapy with Botulinum Toxin*. New York: Marcel Dekker, 1994:451–459.
30. Jankovic J, Schwartz K. Botulinum toxin in the treatment of tremors. *Neurology* 1991;41:1185–1188.
31. Ludlow CL, Sedory SE, Fujita M, Naunton RF. Treatment of voice tremor with botulinum toxin injection [abstract]. *Neurology* 1989;39(Suppl. 1):353.

32. Stager SV, Ludlow CL. Responses of stutterers and vocal tremor patients to treatment with botulinum toxin. In: Jankovic J, Hallett M, eds. *Therapy with Botulinum Toxin*. New York: Marcel Dekker, 1994:481–490.
33. Ludlow CL, Rhew K, Nash A. Botulinum toxin injection for adductor spasmodic dysphonia. In: Jankovic J, Hallett M, eds. *Therapy with Botulinum Toxin*. New York: Marcel Dekker, 1994:437–450.
34. Smitheran JR, Hixon TJ. A clinical method for estimating laryngeal airway resistance during vowel production. *J Speech Hear Disord* 1981;46:138–146.
35. Adams SG, Durkin LC, Irish JC, Wong DL, Hunt EJ. Effects of botulinum toxin type A injections on aerodynamic measures of spasmodic dysphonia. *Laryngoscope* 1996;106: 296–300.
36. Langeveld TP, Drost HA, Baatenburg de Jong RJ. Unilateral versus bilateral botulinum toxin injections in adductor spasmodic dysphonia. *Ann Otol Rhinol Laryngol* 1998;107:280–284.
37. Adams SG, Hunt EJ, Irish JC, Charles DA, Lang AE, Durkin LC, Wong DL. Comparison of botulinum toxin injection procedures in adductor spasmodic dysphonia. *J Otolaryngol* 1995;24:345–351.
38. Zwirner P, Murry T, Woodson GE. A comparison of bilateral and unilateral botulinum toxin treatments for botulinum toxin treatments for spasmodic dysphonia. *Eur Arch Otorhinolaryngol* 1993;250:271–276.
39. Adams SG, Hunt EJ, Charles DA, Lang AE. Unilateral versus bilateral botulinum toxin injections in spasmodic dysphonia: acoustic and perceptual results. *J Otolaryngol* 1993;22:171–175.
40. Tsui JKC. Botulinum toxin as a therapeutic agent. *Pharmacol Ther* 1996;72:13–24.

APPENDIX.
Definition of Visual Analogue Scales.

Parameter	0 cm	10 cm
Audio Perceptual Data		
Tremor	No tremor	Worst possible tremor
Vocal effort	Minimal effort	Maximal effort
Quality	Excellent quality	Worst possible quality
Video Perceptual Data		
Superior/inferior tremor	No tremor	Worst possible tremor
Adductor/abductor tremor	No tremor	Worst possible tremor
Supraglottic hyperfunction: anterior/posterior	No supraglottic hyperfunction	Worst possible supraglottic hyperfunction
Supraglottic hyperfunction: ventricular fold	No supraglottic hyperfunction	Worst possible supraglottic hyperfunction
Vocal fold adduction	No adduction	Maximal adduction
Patient Perceptual Data		
Overall satisfaction	Not satisfied	Extremely satisfied
Voice improved on BOTOX	Not satisfied	Extremely satisfied
BOTOX reduced tremor	Not satisfied	Extremely satisfied
Swallowing problems	No swallowing problems	Worst possible swallowing problems
Breathiness	No breathiness	Worst possible breathiness
Coughing/choking	No coughing/choking	Worst possible coughing/choking