

The use of botulinum toxin in the treatment of adductor spasmodic dysphonia

R Whurr, M Lorch, H Fontana, G Brookes, A Lees, C D Marsden

Abstract

Botulinum toxin injections have been used to treat 31 patients with adductor spasmodic dysphonia. Injections of 3.00-3.75 units of botulinum toxin were performed bilaterally into the thyroarytenoid muscle. This treatment significantly decreased the standard deviation of the fundamental frequency of the speech sample, indicating a reduction in the variability of pitch amongst patients. A total of 96% of patients' subjective diary reports showed an improvement with a median of 7 days to peak effect and a 5 week duration of peak effect.

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Adductor spasmodic dysphonia (SD) is a chronic voice disorder of adult onset and unknown aetiology. SD is not a "spastic" disease, but is a focal laryngeal dystonia which should be differentiated from vocal tremor and myoclonus.¹⁻³ Although it is often erroneously labelled "spastic" dysphonia, no signs of spasticity have been found in the vocal folds of patients with spasmodic dysphonia.² This voice disorder is characterised by regular frequent breaks in phonation, staccato-like catches, pitch breaks and variations in pitch. Attempts to speak are usually accompanied by effortful, jerky, groaning, and strained phonation.

Spasmodic dysphonia was first described by Traube,⁴ who suggested that SD was an hysterical illness. A psychiatric aetiology was supported by Beck,⁵ Berendes,⁶ and Kiml,⁷ and this concept led to a variety of treatments, including psychotherapy, acupuncture, hypnosis, biofeedback, faradism and drug therapy, all of which had little benefit. A physical cause of SD was first proposed in 1874 by Schnitzler⁸ who described two patients with "cramping of the vocal cords and forced voice". He called this entity "spastic aphonia". In 1939, Critchley⁹ described two patients with a vocal disorder who had associated neurological signs and concluded that the site of the pathological process was likely to be the cerebellum or the basal ganglia.

More recent studies have linked SD with dystonia. The association of SD with Meige's syndrome led to the disorder being redefined as a focal form of dystonia, one of a group of movement disorders which are characterised by prolonged muscle contractions with twist-

ing spasms, which may have additional myoclonic or tremulous components.^{1 10 11}

Fibreoptic observations in patients with SD have shown rapid twitch-like movements and forceful spasm-like jerking of the vocal folds, and oscillations of the arytenoids. Forceful, rapid, jerking spasms are noted in the velum as well as in the superior pharynx and tongue. Such abnormal movements of the vocal folds may even be evident during quite respiration. These are exacerbated during phonation.¹²

The growing acceptance of the neurological aetiology of SD led to a change in approach to the treatment of the disorder. Dedo¹³ practised surgical resection of the recurrent laryngeal nerve. It was thought that unilateral vocal fold paralysis would result in compensation due to the strong adductive forces in the unparalysed contralateral side. Laryngeal nerve resection provided initial relief, but relapses were common. Long term results were disappointing, with reports in some cases of symptoms being made worse.¹⁴ The cause for the relapse was thought to be due to the hyperadduction of the non-denervated cord with exaggeration of the dystonic spasms, or reinnervation on the surgical side.¹⁶ Other forms of surgery have included arytenoid replacement, laser therapy, spinal cord stimulation, and even thalamotomy, all with no benefit or transient effects. Pharmacological intervention has included the use of anticholinergics, benzodiazepines, baclofen and carbamazepine.¹⁶ Only mild benefit from clonazepam and anticholinergics has been reported.

Recently, injections of botulinum toxin into targeted muscular sites have proved to be beneficial in the treatment of certain focal dystonias.^{17 19} Botulinum toxin acts pre-synaptically to block the calcium dependent release of acetylcholine. When injected in low doses the toxin causes local weakness in the muscle into which it is injected. This eliminates the abnormal muscle contractions while preserving functional ability. The effect of the toxin is temporary due to the re-sprouting of axons which form new neuro-muscular junctions.

The use of botulinum toxin treatment in spasmodic dysphonia of the adductor type is currently being tested in several centres.^{3 16 19 20-24} Table 1 summarises the various methods of botulinum toxin treatment currently being pursued. The potency of toxin being used in the UK (Dysport) differs from that being used in the USA (Oculinum)

The National Hospital for Neurology and Neurosurgery, London

R Whurr
M Lorch
H Fontana
G Brookes
A Lees
C D Marsden

**The Institute of Neurology
The National Hospital, London**
M Lorch
C D Marsden

Birkbeck College, University of London, UK

M Lorch
Correspondence to:
Dr Whurr, Speech and Language Therapy Department, The National Hospital, Queen Square, London WC1N 3BG, UK

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Table 1 Summary of studies of the use of botulinum toxin in the treatment of SD

Study	Number of Patients	Anaesthetic	Toxin	Needle	Site	Side	Dose/volume	Ratings	Re-injection
Blitzer <i>et al</i> ³ 1986 USA—New York	NS	NS	NS	NS	NS	Bilateral	NS	Video and audio recordings	NS
Miller <i>et al</i> ²³ 1987 USA—Houston	2	Lidocaine Hydrochloride	Botox A Oculinum	27 gauge teflon coated EMG needle	Thyro-arytenoid	Left	Pt1: 30/37U Pt2: 20U	Intra-thoracic pressure, Valsalva manoeuvre, subjective speech ratings, video and audio recordings	Yes
Blitzer <i>et al</i> ¹⁹ February 1988	5	NS	Botox A Lyophilised Oculinum	25 gauge monopolar teflon coated EMG needle	Vocalis thyro-arytenoid complex	Left or Right	2.5–7.5U varied concentration	Fibre-optic laryngoscopy, Video recordings EMG, brain stem evoked potentials, MRI scans	Yes
Blitzer <i>et al</i> ²⁰ June 1988 USA—New York	34	NS	Botox A Oculinum	27 gauge teflon coated EMG needle	Thyro-arytenoid	Unilateral also Bilateral	2.5U in 6 sites = 20–25U	Fibre-optic video laryngoscopy, speech therapist ratings, acoustic analysis, spectrography	Yes
Ludlow <i>et al</i> ²² 1988 USA—Bethesda	16	Xylocaine	Botox A Oculinum	27 gauge hollow teflon coated EMG needle	Vocalis thyro-arytenoid complex	Left	2.5–3.75U	Fibre-optic laryngoscopy, audio and video recordings, subjective ratings, patient self ratings	Yes
Brin <i>et al</i> ¹⁶ 1989 USA—New York	42	NS	Botox A Oculinum	Hollow mono-polar teflon coated EMG needle	Vocalis thyro-arytenoid complex	Bilateral	2.5–3.75U	Fibre-optic laryngoscopy, audio and video recordings, subjective ratings, patient self ratings	Yes
Jankovic <i>et al</i> ²¹ 1990 USA—Houston	24	NS	Botox A Oculinum	0.5" 30 gauge hollow teflon coated EMG needle	Vocalis thyro-arytenoid complex	Left	30U	Fibre-optic video laryngoscopy, rating scale, "peak effect" rating	Yes
Zwirner <i>et al</i> ²⁴ 1991 USA—San Diego	19	NS	Botox A Oculinum	Teflon coated hollow needle	Vocalis thyro-arytenoid complex	Left	15–30U	Laryngologist, speech therapist ratings, acoustic analysis	Yes

There are differences in the techniques reported for dose, site, and number of injections of botulinum toxin. In spite of these differences, all centres utilising botulinum toxin in the treatment of adductor SD claimed good results for improving the voice. Symptoms generally return after the restoration of vocal cord movement over a period of about 12 weeks. There have been no reports of patients becoming refractory to therapy. Brin *et al*¹⁶ found that there was a trend for a progressively longer period of benefit between injections.

The methods of evaluation of the results of botulinum toxin injections on vocal quality also have varied. Methods of assessment have included neurological, speech therapy/pathology, fibre-optic laryngoscopy, EMG, audio and video recording. Evaluation of results has commonly included subjective speech/video recordings, though Ludlow²² and Zwirner²⁴ included objective acoustic analysis of speech. Other methods have been patient diaries²⁶ and measures of interthoracic pressure and Valsalva manoeuvres.²³

This paper describes the procedure used to assess, treat and evaluate treatment of patients with spasmodic dysphonia using botulinum toxin.

Method

Subjects

Between December 1988 and April 1991, 49 patients with suspected spasmodic dysphonia of the adductor type were referred to the spasmodic dysphonia (SD) clinic. Eighteen patients were removed from the trial: 12 were found on assessment not to have SD, 3 patients were treated elsewhere (1 found the travel too far, 1 was too unwell and 1 patient died). Thirty one patients entered the trial, 11 male, 20 female with a mean age at the time of initial assessment of 57 years (range

31–82). The mean age of the male subjects was 46 years (range 31–65); that of females was 63 years (range 43–82). Mean duration of symptoms was 5 years 2 months (range 11 months–18 years). There was no difference in mean duration of symptoms for males and females.

Fourteen of the 31 subjects (45%) had associated neurological signs: 10 female (50%), 4 male (36%). These signs were: a) tremor (n = 5, female patients) of various types—2 had hand tremor, 2 had head tremor (including voice tremor), 1 head, voice and hand tremor; b) dystonias (n = 8, 3 male and 5 female) of various types—2 torticollis, 1 multifocal dystonia, 1 torticollis and writers cramp, 2 blepharospasm, 2 Cranial dystonia; c) Parkinsonism (n = 1, male) (see table 2).

Twenty two patients (71%) had had previous treatments including: recurrent laryngeal nerve crush, drugs, faradism, hypnotherapy/hypnosis, acupuncture, reflexology, chiropractic, herbalism, psychotherapy, speech therapy. All found the treatments to have had no lasting effect on the voice. Four patients were receiving drug treatment at the time of their initial injection of botulinum toxin, they reported that the drugs were having no effect on their voice.

No control subjects were studied, because of the remarkable efficacy of this treatment, shown not only by this study but also by other studies (see table 1). A placebo controlled trial would probably not be ethically justified.

Assessment Procedures

Each patient had initial assessment by a team of a neurologist, a neuro-otolaryngologist and a speech-language therapist. The laryngological assessment was performed using either a flexible fiberoptic or rigid endoscope connected to a video camera. The speech-language therapist assessed each patient on a voice pro-

Table 2 Patient characteristics

Sex	Age range	Duration of voice symptoms (range)	Associated neurological signs
Male n = 11	31–65 years	1–18 years	n = 4 1 cranial dystonia, 1 torticollis, 1 torticollis and writers cramp, 1 Parkinsonism.
Female n = 20	43–82 years	11 months–15 years	n = 10 2 head and voice tremor, 2 hand tremor, 1 head hand and voice tremor, 2 blepharospasm, 1 torticollis, 1 multifocal dystonia, 1 cranial dystonia.

tol which was audio and video recorded. This vocal protocol included the reading of a passage (*The North Wind and the Sun*) which would be used for later analysis. The audio recording was made using a UHER CR 160 AV stereo cassette recorder in conjunction with a UHER M534/A cardioid directional microphone. Filters were used to extract extraneous ambient background noise. All recordings were carried out in a video recording studio. Each patient was reassessed by the team at each follow up visit.

Botulinum toxin treatment procedure

The toxin *Clostridium Botulinum* toxin Type A (Dysport) is obtained from Porton Products Ltd as a freeze dried toxin-haemagglutinin preparation. Fifty nanograms is equivalent to 2000 mouse-units. To begin with we diluted in normal saline to a concentration of 25 units per ml. Now we use a concentration of 40 units per ml.

The injection procedure used followed that of Brin *et al.*¹⁶ A small dose of botulinum toxin was injected into *both* thyroarytenoid muscles (that is, left and right). Before the injection 2% lignocaine was injected down through the cricothyroid membrane to provide local anaesthesia. EMG recordings were employed to localise the thyroarytenoid muscle. A 26 gauge hollow monopolar teflon coated needle was used with a skin reference (clavicle) and a ground in position. The needle was advanced through the cricothyroid membrane in a superior and lateral direction until a crisp motor unit interference pattern was heard. When the monopolar teflon coated laryngeal EMG needle was in the correct position, the toxin was administered through the same needle which was then withdrawn.

The original injection dose was 3.75 units in 0.15 mls. Recently the dose was altered slightly to 3 units in 0.075 mls. The first 22 patients in the series received the original larger dose; 9 subsequent patients received the new smaller dose.

The procedure was tolerated well by the majority of patients, although at times coughing and gagging occurred. The use of Merocaine lozenges (benzocaine cetylpyridium chloride) sucked 30 minutes before the injection has proved useful to suppress the tendency to cough during the injection.

Follow up

After the injections the patients were requested to keep voice diaries recording the occur-

rence, quality, and duration of any negative side effects and of positive improvement in their voices after treatment. Speech samples were collected when patients returned to the SD clinic for follow up.

Patients were usually seen for a follow up assessment 2–3 months after their injection and, if appropriate, they were re-injected with the same dose bilaterally. Patients were again assessed by the speech-language therapist who recorded the vocal protocol. The interval between the recordings was not the same for every subject (mean interval = 10 weeks, range 2–30 weeks). As the SD clinic draws patients from great distances, many could only attend the clinic for follow up visits when their voices were beginning to deteriorate. Typically patients were found to require re-injection at this time. The post-injection recordings were most commonly made at the point when the voice was beginning to deteriorate and had passed the peak period of maximum benefit.

Speech analysis

The effect of botulinum toxin injections on the patients' vocal quality was investigated with two different measures: 1) objective acoustic speech analysis and 2) patients' subjective diary reports.

Acoustic analysis

The audio taped recordings of the patients' reading of *The North Wind and the Sun* were analysed using the Visispeech speech analysis package (RNID) on a BBC Master computer. The Visispeech speech analysis programme measures the fundamental frequency of the voice over the duration of the entire speech sample. The data are scaled into 85 "bins" or compartments, and measures of central tendency, variance and standard deviation are calculated.

The measures of standard deviation of the distribution of frequency in the entire speech samples were compared pre- and post-injection. This measure can be taken as an indication of regularity of pitch of voice. Thus a voice with many pitch breaks and variations in pitch has a high standard deviation value. The standard deviation values pre-injection and post-injection were compared using a Wilcoxon Signed-Ranked Test.

Patient diaries

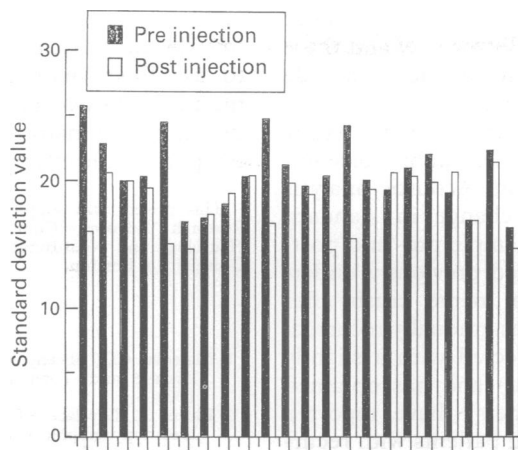
The analysis of the patients' diary records was carried out to determine: 1) the length of delay before the benefits of the injections were noted; 2) the duration of peak effect, that is, the length of time the voice was at its maximum improvement before any deterioration was noted, and 3) the duration of response, the length of time the patient received any benefit from the injection.

Results

Acoustic analysis

Of the 31 patients' audio recordings both pre- and post-injection only 22 were technically

Figure Values for standard deviation of fundamental frequency pre and post botulinum toxin injection for adductor spasmodic dysphonia.



acceptable for acoustic analysis. These 22 speech samples were analysed for the standard deviation of long term fundamental frequency. The measures of standard deviation of the speech samples recorded post-injection were found to be significantly lower than the pre-injection values ($p < 0.005$) using the Wilcoxon signed ranks test (see figure).

Beneficial effects

At the follow up visit the vast majority of patients (96%) in our study reported improvement in their voice, some reporting it "back to normal", and many gave very favourable reactions speaking of their increased confidence at work and socially since the change in their voices. Only a proportion of the 31 patients successfully kept voice diaries. The data available was analysed on diaries from 24 patients. The median time for onset of effects post-injection was 7 days ($n = 23$, range 1-18 days). The median duration of peak effects was 5 weeks ($n = 24$, range 1-12 weeks). The vast majority of our patients, at the time of their second injection, reported that their voice quality, though deteriorated from a peak level, was still an improvement on their pre-injection voice quality.

Beneficial vocal effects after injection reported by the patients included: reduced number of pitch and voice breaks, increased volume and increased overall ease of production (that is, reduced effortfulness).

Adverse effects

Temporary side effects were reported by 8 out of 22 patients (25%). These negative side effects included: some dysphagia for fluids (without aspiration) ($n = 5$), weak cough ($n = 2$) and slight pain at the site of injection ($n = 2$).

Discussion

This study shows that bilateral botulinum toxin injections into the thyroarytenoid provide an effective treatment for spasmodic dysphonia of the adductor type. This further confirms evidence of previous studies that have indicated the beneficial effects of botulinum toxin on this voice disorder.^{3 16 19-24 26}

At the time we started this study, the largest experience of botulinum toxin injections for adductor spasmodic dysphonia had used bilateral injections.¹⁶ Others, however, have employed unilateral injections. The relative merits of these two approaches have not been assessed formally. In theory, a unilateral injection might be safer, but bilateral injections might produce the same physiological result with smaller doses.

The analysis of standard deviation of fundamental frequency of a speech sample provided a useful objective assessment of the effects of treatment on the regularity of pitch, an important indicator of vocal quality. The finding of decreased standard deviation of frequency distributions after injection indicated an increase in regularity of the voice and a decrease in pitch breaks and variations in pitch. This objective acoustic measure confirmed the subjective assessment of the speech-language therapist and the patients' own reports. These findings on long term frequency measures substantiate those reported by Zwirner *et al*²⁴ comparing the standard deviation of fundamental frequency for a sustained vowel segment pre- and post-injection with botulinum toxin. They also found that standard deviation values were lower after injection.

As the post-injection assessments and recordings were not necessarily obtained during the peak period of maximum benefit, but at a time when the positive effects of the treatment were presumably already on the wane, this analysis can be taken conservatively. This evidence suggests that even when the peak period is over there is still a marked and lasting improvement in the voice compared with the voice pre-injection. This supports the findings reported by Brin *et al*¹⁶ that vocal symptoms do not recur after injection to the same level of strength and intensity as before botulinum toxin treatment.

Patients reports of vocal effects after injection indicated that onset of beneficial effects occurred at day 7 on average. The duration of peak voice benefit was typically 5 weeks. Only 25% of patients reported any negative side effects which were transitory in nature. Jankovic and Brin²⁵ state that a higher incidence of side effects have been reported when using the British toxin, Dysport, compared with the American toxin, Oculinum. They suggest that this might be accounted for by the higher potency of Dysport compared with Oculinum (1 nanogram of Dysport contains 40 units whereas 1 nanogram of Oculinum contains 2.5 units, where a "unit" is a standard measure of potency of commercially available toxin). However, when the incidence of side effects in the study by Blitzer²⁶ which utilised low dose bilateral injections (range of doses 1.25-3.75 units) was compared with the results obtained during this study it was seen that the incidence was very similar. Blitzer and Brin²⁶ reported 45% of patients with a short period of breathy dysphonia and 22% with mild dysphagia for fluids. For low dose bilateral injections for

adductor SD the results reported here concur with those obtained by Blitzer *et al* and there is no evidence for a higher incidence of side effects using the British toxin.

Only one of the 31 patients in the study failed to gain an improvement in his voice following the initial injection. Acoustic analysis revealed very minimal change in standard deviation of the speech sample pre- and post-injection. This patient had previously undergone recurrent laryngeal nerve crush after which the voice symptoms gradually recurred. He has since been reinjected with a slightly larger dose (5 units/cord) and has obtained an excellent result. Others¹⁶ have reported positive results in treating patients with recurrent nerve crushes.

Three patients had voice tremor in addition to SD. The injections of botulinum toxin alleviated the symptoms of SD but the voice tremor remained. Though the tremor did not markedly impede the speaker's intelligibility it was perceived by them as socially disabling.

In the present report, only data pertaining to the effects of the first injection have been analysed. All patients have, however, received follow up injections, and data from these suggests that the injection continues to have a beneficial effect. All 31 patients have continued with injections every 2–4 months, as appropriate, for periods of up to 3 years, with continued benefit.

The majority of treated patients derive the most dramatic improvement after the first injection of botulinum toxin. Most patients require subsequent multiple injections at varying intervals to maintain spasm-free vocal performance. Graded responses of muscle weakness can be obtained by using low doses of botulinum toxin. Once the patient's sensitivity to treatment is determined, an individualised protocol can be used for future injections, with small dose "top-ups" injected into one or both vocal cords. Low dose bilateral injections into the thyroarytenoid is suggested as the preferred method of treatment for SD of the adductor type.

Occasionally, patients report that they did not have any (positive or negative) effects following an injection, when previously (and subsequently) they have had a good response. At the outset it appeared that the botulinum toxin had not taken effect in these cases. However, these rare instances of failure of the injection to produce an effect may be linked to difficulties in the injection procedure itself, particularly if there have been problems obtaining a satisfactory EMG signal. Our experience therefore indicates the importance of using EMG to locate the thyroarytenoid muscle. Not every "failed" injection can probably be attributed to this factor, and further investigation of this problem is needed.

In conclusion, the use of botulinum toxin

in SD is an efficient method of treatment for this chronic voice disorder. It enables patients to use their voice effortlessly and to communicate easily—in some instances for the first time for many years, with very few and temporary side effects.

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