Botulinum toxin injections for the treatment of spasmodic dysphonia (Review)

Watts CCW, Whurr R, Nye C

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ABSTRACT

Background
The use of botulinum toxin for the treatment of spasmodic dysphonia is currently the treatment of choice for management of this neurological voice disorder. Over the past 20 years, botulinum toxin has been used to treat both adductor and abductor forms of the disorder, with vocal improvement noted after treatment for both. A large number of studies have attempted to document the efficacy of botulinum toxin for improvement of vocal symptoms in individuals with spasmodic dysphonia.

Objectives
To determine the effectiveness of botulinum toxin for treating spasmodic dysphonia.

Search strategy
Our search included the Cochrane Ear, Nose and Throat Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 2 2007), MEDLINE (1950 to April 2007), EMBASE (1974 to April 2007) and CINAHL (to April 2007). Reference lists for all the obtained studies and other review articles were examined for additional studies. The date of the last search was April 2007.

Selection criteria
All studies in which the participants were randomly allocated prior to intervention and in which botulinum toxin was compared to either an alternative treatment, placebo or non-treated control group were included.

Data collection and analysis
Two authors independently evaluated all potential studies meeting the selection criteria noted above for inclusion. One study met the inclusion criteria and was included in the final analysis.

Main results
Only one study in the literature met the inclusion criteria. This was the only study identified which reported a treatment/no treatment comparison. It reported significant beneficial effects for fundamental frequency (Fo), Fo range, spectrographic analysis, independent ratings of voice severity and patient ratings of voice improvement.

Authors’ conclusions
The evidence from randomized controlled trials does not allow firm conclusions to be drawn about the effectiveness of botulinum toxin for all types of spasmodic dysphonia, or for patients with different behavioral or clinical characteristics.

PLAIN LANGUAGE SUMMARY
Botulinum toxin has been shown to benefit some aspects of voice production in speakers with spasmodic dysphonia.
Botulinum toxin is currently the gold standard of treatment for patients with spasmodic dysphonia. It has been used over the past two decades to treat both adductor and abductor forms of the disorder. The results of this review of randomised controlled trials indicate that botulinum toxin is effective for some aspects of voice production, including perceptual measures of improvement post-injection, variability of fundamental frequency, vocal intensity and subglottal air pressure. These benefits may be dependent on certain subject variables, such as the amount of voice use immediately post-injection and treatment variables such as dosage and location of injection. These results should currently be interpreted with caution, however, as studies have used small sample sizes and have methodological differences which prevent between-study comparisons.

BACKGROUND

Spasmodic dysphonia is a voice disorder resulting from disrupted laryngeal motor control which causes involuntary movements of the laryngeal musculature during phonation. These involuntary movements may cause the vocal folds to inappropriately hyperadduct (close) (adductor spasmodic dysphonia) or abduct (open) (abductor spasmodic dysphonia), or in some cases do both (Aronson 1990; Cannito 1981). Adductor spasmodic dysphonia is the more common form of the disorder and is characterized by laryngeal muscle strain, a strained-strangled and harsh voice quality, pitch breaks, and abnormally low fundamental frequency (glottal fry). Abductor spasmodic dysphonia is characterized by intermittent glottal widening and a transient breathy voice quality (Blitzer 1991; Aronson 1990; Cannito 1981). The severity of symptoms and disabling nature of the disorder can vary from patient to patient.

Understanding of the etiology of spasmodic dysphonia has evolved over time from theories of underlying psychological causes to current opinion which emphasizes a primary neurological cause (Whurr 1993; Brin 1998a; Cannito 2001). As a type of dystonia, spasmodic dysphonia has been characterized as a chronic neurological disorder of central motor processing causing action-induced muscular spasms (Blitzer 2001). On average the first signs of spasmodic dysphonia are seen in individuals of around 40 years (Brin 1998a). The disorder appears to occur more often in females, with familial involvement in approximately 12% of all cases (Brin 1998a; Cannito 2001).

Primary behavioral treatment for spasmodic dysphonia is relatively ineffective (Boone 2000; Cannito 2001). When combined with pharmacological therapy, however, behavioral treatment may assist in improving voice quality and prolonging the benefit of pharmacological effects (Stemple 2000; Murry 1995). In this regard, a number of complementary behavioral management strategies for spasmodic dysphonia have been suggested, including laryngeal tension-reducing exercises, breath flow regulation, decreasing effort during phonation and co-ordination of the speech subsystems (Stemple 2000; Cannito 2001; Murry 1995).

Botulinum toxin is generally regarded as the primary pharmacological treatment for adductor spasmodic dysphonia, and may also be beneficial in cases of abductor spasmodic dysphonia or mixed spasmodic dysphonia (Cannito 2001; Bielamowicz 2001). Botulinum toxin inhibits the release of acetylcholine at the motor end plates, resulting in a temporary paresis or paralysis of the injected muscle (Langeveld 1998; Blitzer 2001). Botulinum toxin is administered either unilaterally (injected into the left or right vocal fold muscle) or bilaterally (injected into the vocal fold muscles on both sides), with smaller dosage levels reported for effective bilateral injections (Adams 1995; Bielamowicz 2000; Bielamowicz 2001). There are also different injection techniques that may be utilized, including an electromyographic guided percutaneous technique, and a nasolaryngoscopic guided technique (Rhew 1994; Bielamowicz 2001).

Over the past 20 years, a large number of articles have been published which have described the use of botulinum toxin for the treatment of spasmodic dysphonia. A recent search of the literature revealed over 100 published articles that investigated this topic, characterized as either clinical studies, review articles, animal studies or non-clinical studies. The majority of these manuscripts were clinical studies that attempted to document the effectiveness of botulinum toxin for the treatment of vocal symptoms secondary to spasmodic dysphonia. The methodology used in these studies is extremely variable. As an example, the independent (manipulated) variables selected for examination in the published literature have included injection type (unilateral versus bilateral, in both separate groups and in series), injection procedure, disorder type (adductor-type versus abductor-type), injection location, patient characteristics and treatment combinations (botulinum toxin with voice therapy or acupuncture) among others (Adams 1993; Bielamowicz 2002; Drost 1998; Green 1992; Ford 1990; Ludlow 1992; Blitzer 1998; Ford 1992; Lundy 1998; Schonweiler 1998). Dependent (measured) variables studied have included perceptual, electroglottographic, electromyographic, acoustic, endoscopic, stroboscopic, duration of benefit, aerodynamic, and subjective rating measures (Zwirner 1991; Sapienza 2002; Fisher 1999; Rodriguez 1994; Mehta 2001; Wong 1995a; Lundy 1998; Papathanasiou 1997; Whurr 1998). The exact method in which independent and dependent variables have been studied is rarely consistent between any two investigations. However, the collective literature has provided ample evidence of the positive effectiveness of botulinum toxin for treating spasmodic dysphonia.

To date there have been one systematic review (Whurr 1997) and
two meta-analyses in the literature that have considered the effectiveness of botulinum toxin for spasmodic dysphonia (Whurr 1998; Boutsen 2002). However, the ability to draw conclusions from these studies is limited as data from randomized control studies were combined with data from a variety of research designs. Numerous questions still need to be answered by randomized clinical trials:

- Is botulinum toxin treatment of spasmodic dysphonia more effective in providing temporary symptomatic relief of vocal spasms (e.g. improving voice quality) than no treatment?
- Are bilateral injections more effective for improving voice quality than unilateral injections?
- Is botulinum toxin more effective for improving voice quality in abductor spasmodic dysphonia, adductor spasmodic dysphonia, or mixed spasmodic dysphonia?
- Are bilateral injections associated with more frequent adverse events compared to unilateral injections?
- Are different dosage levels associated with differences in the frequency of reported adverse events?
- Is botulinum toxin alone more effective for improving voice quality compared to behavioral voice therapy alone, or in conjunction with post-injection voice therapy?
- Is one type of botulinum toxin product more effective for improving voice quality than another?

There have been no systematic reviews evaluating the effectiveness of botulinum toxin treatment for spasmodic dysphonia using only randomized trials. Thus the purpose of this review is to assess the effectiveness of the use of botulinum toxin for the treatment of spasmodic dysphonia using only randomized controlled trials as the standard for summary and analysis.

**OBJECTIVES**

To assess the effectiveness of botulinum toxin in the treatment of spasmodic dysphonia using data from randomized controlled trials.

**SEARCH METHODS FOR IDENTIFICATION OF STUDIES**

See: Cochrane Ear, Nose and Throat Disorders Group methods used in reviews.

The following databases were searched: the Cochrane Ear, Nose and Throat Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 2 2007), MEDLINE (1950 to April 2007), EMBASE (1974 to April 2007 ), CINAHL (to April 2007), mRCT, NRR (National Research Register), LILACs, KoreaMed, IndMed, PakMediNet, Zetoc, ISI Proceedings and Cambridge Scientific Abstracts. The date of the last search was April 2007.

The following details the search strategies that were used in each of the main databases. Other databases were searched using freetext terms. In MEDLINE, EMBASE and CINAHL, the search strategy was used in conjunction with the randomized controlled trial filter validated by The Cochrane Collaboration. MeSH terms appear in upper case and free text terms appear in lower case.

The strategy used for CENTRAL and NRR was as follows:

#1 VOICE DISORDERS single term (MeSH)
#2 LARYNGISMUS single term (MeSH)
#3 spasm* NEAR dysphoni* or spastic NEAR dysphoni* OR flaccid NEAR dysphoni* OR hyperkinetic NEAR dysphoni* OR respiratory NEAR dysphoni* OR laryngospasm* NEAR dysphoni*
#4 phonation NEXT disorder* OR laryngeal NEXT dystonia* OR neurologic* NEXT voice NEXT disorder*

**Types of intervention**

Experimental interventions included any unilateral or bilateral injection of botulinum toxin into a muscle or muscles of the laryngeal mechanism. No restriction on dosage, number of treatments or time to outcome measure was set.

**Types of outcome measures**

The major outcome measures studied in the randomized controlled trials included:

1. Acoustic function, or instrumental measurement of the voice spectrum via computerized analysis (e.g. fundamental frequency, frequency and amplitude perturbation, signal-to-noise ratio);
2. Perceptual ratings, or subjective ratings of voice quality or ability (e.g. subjective voice improvement, spectrographic ratings of normalcy);
3. Aero-dynamic function, or instrumental measurement of the airflow and air pressure that is needed to vibrate the vocal folds (e.g. mean airflow, coefficient of airflow variation, air pressure).
Additional searching strategies included:

2. Universities/Hospitals/Centres where there were individuals who engaged in spasmodic dysphonia treatment using botulinum toxin were contacted for additional citations and details of ongoing research.
3. Conference proceedings were reviewed and we attempted to retrieve relevant citations from presenters.
4. The reference lists for all of the obtained studies were reviewed for additional studies.
5. Foreign language journals were searched.
6. Authors who have researched in this area were contacted and asked to provide any unpublished data or studies.

METHODS OF THE REVIEW

Study selection
Abstracts were obtained for all studies which were potentially appropriate for inclusion in the review. Two authors assessed whether or not the complete study should be retrieved. For all studies clearly appropriate to the review a complete copy of the study was obtained. For those studies in which the abstract was not clear regarding the appropriateness, a copy of the full study was obtained. Complete articles were collected and two authors read and evaluated each study independently for inclusion criteria (i.e. random allocation). Authors were not blind to author or source, and any differences in study selection were resolved by discussion between the authors.

Quality assessment
Each author independently assessed the methodological quality of the studies identified for possible inclusion. Any discrepancy was resolved by consensus discussion.

The categorization of the methodological quality included an assessment of each study according to the following categories:
A - adequate concealment
B - unclear concealment
C - inadequate concealment

Adequate concealment, category A, included any form of random assignment in which the individual participant’s group assignment was unknown prior to the actual assignment and an acceptable randomization procedure such as computer-generated allocation was used for group assignment. If the author(s) of the study indicated that participant assignment to the experimental and control conditions was accomplished using a randomized process but gave no specific information regarding the details of the randomizing process, that study would at best be classified in category B, as using an unclear concealment procedure. Only studies reporting adequate or unclear concealment were assigned to the included studies group. Studies reporting no randomizing procedure were automatically categorized as reflecting an inadequate concealment procedure, category C, and were not included for the review or analysis. No study reporting more than 20% attrition was assigned to the included studies group.

Data analysis
The data from the studies were collated using RevMan 4.2. Studies reporting binary outcomes were to be summarized using odds ratios with 95% confidence intervals. Studies reporting continuous outcomes were summarized using weighted or standardized mean differences with a 95% confidence interval. Where the outcome had been measured using the same measure, a weighted mean difference was to be used. Where different measures were used to measure the same outcome the standardized mean difference was to be calculated to allow comparison.

Sensitivity analyses were to be performed to investigate heterogeneity of results based on design quality.

It was planned that, where possible, sub-group analyses would be performed to look at the comparative efficacy. Areas of sub-group analysis were to include (if applicable):
1. Different types of intervention compared with untreated controls
2. Injection site
3. Dosage and dilution
4. Type of toxin used
5. Side effects and adverse events
6. First treatment versus subsequent treatment(s)

DESCRIPTION OF STUDIES
A total of 77 abstracts were identified via the electronic and hand search strategy. Of these, 70 were found to be ineligible for inclusion due to methodology (e.g. review article, non-clinical study) and lack of non-randomized control design. Of the seven randomized controlled trials, four articles did not report appropriate data.
for analysis and authors were either unable to provide the appropriate data or did not respond to contact attempts. Of the three remaining studies, two did not meet inclusion requirements due to the nature of the treatment protocol (Finnegan 1999; Wong 1995b). The remaining study (Troung 1991) met the inclusion criteria.

Troung 1999

Finnegan 1999 utilized a randomized, double-blinded cross-over design to study airflow measures as a function of injection site (intrinsic laryngeal muscle only versus intrinsic laryngeal muscle plus laryngeal strap muscles). Participants were randomly assigned to one of two treatment protocols. However, while both groups of participants received the 2.5 unit bilateral injection into the intrinsic muscle (thyroarytenoid), both groups received differing bilateral injections during the alternative intervention. One group received 2.5 units of saline in the thyroarytenoid and sternothyroid while the second group received 7.5 units of botulinum toxin. Thus, the effects of the botulinum toxin cannot be assessed.

Wong 1995b

Wong 1995b examined acoustic and aerodynamic measurements subsequent to botulinum toxin injection in two experimental groups of speakers with spasmodic dysphonia: a non-vocalization group who remained silent for 30 minutes after botulinum toxin injection, and a vocalization group who read aloud at normal conversational loudness for 30 minutes after the injection. Twenty subjects in total were randomly assigned to one of the two groups. Each subject received 2.5 units of botulinum toxin to the thyroarytenoid muscles, bilaterally. Acoustic measures were obtained from audio recordings of the subjects producing sustained vowel prolongation of /a/. Aerodynamic measures were obtained in the context of having each subject produce three trials of uttering the syllable /pi/ repetitively. Both acoustic and aerodynamic measures were obtained prior to injection (baseline), and at two and ten weeks post-injection.

Wong 1995b could not be included in the analysis because, although participants were randomly assigned to different groups, both groups received botulinum toxin injections as part of the treatment protocol. Thus, although each group received a different secondary intervention as part of the treatment protocol (i.e. vocalization or non-vocalization), it is not possible to compare directly the effects of the botulinum toxin for treatment of spasmodic dysphonia.

Troung 1991

Troung 1991 was the only study which could be included in the review. Troung utilized a double-blind, placebo-controlled study to examine the effects of botulinum toxin (Botox\textsuperscript{T M}) on voice quality (via spectrographic analysis), perceived voice improvement, and acoustic measures in subjects with adductor spasmodic dysphonia who received either drug or saline injection into the thyroarytenoid muscles. Thirteen subjects were randomly assigned to either the botulinum toxin or saline treatment groups. Perceptual and acoustic analyses were applied to recordings of each subject producing sustained vowel productions. Perceptual variables included a speech rating scale completed by the investigators that judged the normalcy of spectrograms generated from the vowel productions, related to periodicity, the presence of high frequency energy and voice breaks. In addition, experimental subjects completed a self-rating scale related to degree of improvement post-injection and an independent judge rated the degree of voice severity pre-injection and post-injection. Acoustic variables included fundamental frequency, phonation time, fundamental frequency range and perturbation measures.

Outcome measures revealed that subjects injected with botulinum toxin exhibited significantly decreased perturbation and fundamental frequency range compared to subjects who received saline. In addition, the botulinum toxin group exhibited a significant improvement in ratings of speech quality (spectrographic analysis) and perceived improvements compared to the subjects who received saline (for both self and independent ratings). The authors proposed that results demonstrated an effective outcome for botulinum toxin, both for perceptual ratings and objective measures of voice production, at least in the treatment of adductor spasmodic dysphonia.

METHODOLOGICAL QUALITY

Only one study (Troung 1991) was identified as meeting the inclusion criteria based on methodological quality and availability of appropriate data for analysis. Troung 1991 used a double-blind, randomly assigned placebo-controlled design. The precise method used to assign subjects randomly to the experimental and control groups was not described, and the study was therefore given a level B ‘unclear concealment’ rating for methodological quality.

RESULTS

Troung 1991 was the only study comparing treated and non-treated groups. A total of five measures were taken at four days post-injection for both groups. Data were analyzed using the non-parametric Mann-Whitney U test for ranked data which yielded significant between group differences for spectrographic analysis, fundamental frequency range, self rating of improvement and professional spectrographic rating. Non-significant group differences were reported for phonation time.

Effect sizes were calculated using the individual group means and standard deviations reported for the seven dependent variables. Results of these analyses yielded significant group differences for:

- Fundamental frequency (standardized mean difference (SMD) -1.60; 95% confidence interval (CI) = -2.92 to -0.29);
• Fundamental frequency range (SMD -4.39; 95% CI = -6.68 to -2.09);
• Perturbation (SMD -2.36; 95% CI = -3.90 to -0.82)
• Spectrographic analysis (SMD -4.28; 95% (CI) = -6.53 to -2.03);
• Professional rating of improvement (SMD -4.42; 95% CI = -6.72 to -2.11).

Non-significant differences emerged for phonation time (SMD 0.40; 95% CI = -0.70 to 1.51). Data provided for the self rating of improvement did not allow for a calculation of effect. A meta-analysis was not possible since data from only one study were available for each outcome measured.

DISCUSSION

Although three studies reported randomized participant assignment, only one study representing a total of 13 participants with spasmodic dysphonia could ultimately be included in this review. The study reported a positive effect of botulinum toxin on both physiological functioning and listener perception.

The outcomes measured included basic physiological performance and perceived vocal quality resulting from improvement in these parameters of vocal production. Troung 1991 found that botulinum toxin improved the basic efficiency of the physiological functioning of the vocal mechanism in four of the five physiologically related dimensions measured (fundamental frequency, fundamental frequency range, perturbation, spectrographic analysis). In addition, Troung showed that patient rating of their speech production and independent ratings of speech severity improved significantly as a result of treatment.

Also noticeably absent from this study is long-term follow up of effects and side effects. Others have reported that the effects of the botulinum toxin treatment typically last between 3 and 12 months. Troung 1991 assessed post-treatment measures after four days, and reported an average improvement lasting three months. Breathiness was reported as a side effect in two participants. No information was provided with regard to the measurement of vocal production beyond the four days. This is in contrast to some studies which have reported that positive effects of botulinum toxin may not be observed for up to two weeks post-treatment. Certainly it would be important to provide quantitative support for both the longer term effects and the severity of the side effects.

A major problem with any interpretation of the effects of botulinum toxin in the treatment of spasmodic dysphonia, based on this one included study, is the small sample size. While significant differences were observed, any attempt make a population generalization would be suspect, with only a single study representing the effects of intervention.

This does not imply that the use of botulinum toxin for the treatment of spasmodic dysphonia should be rejected. The paucity of outcome data should be considered in the context of certain methodological shortcomings and differences that should be addressed in future randomized controlled trials. However, although small sample sizes were utilized in included and excluded studies and the observed effects were relatively inconsistent for the measurements at the post-treatment times reported, the fact remains that the overwhelming clinical evidence suggests that botulinum toxin is very effective in treating spasmodic dysphonia. Of the 77 citations identified, none of the clinical reports, case studies, single subject design studies, or excluded group designs studies indicated a negative effect for botulinum toxin treatment. In fact, these excluded citations are noteworthy for the similarity in their report of positive effects related to length of treatment effect, degree of improvement, patient satisfaction and observed side effects. This is not to suggest that better evidence is not warranted but only to point out that the gold standard data reported in this review may not represent the current practice regarding effective use of botulinum toxin for treatment of spasmodic dysphonia.

Future studies should utilize larger sample sizes to increase power for detecting the presence of significant outcomes. In addition, the lack of uniformity in methodological design, not only in the randomized controlled trials cited in the literature, but also the entire corpus of clinical literature related to the topic of botulinum toxin for spasmodic dysphonia, points to the need for replication studies and research designs that will allow for data comparisons with previously published research.

AUTHORS’ CONCLUSIONS

Implications for practice

In the randomized controlled trials published in the literature, botulinum toxin has been shown to demonstrate a benefit with regard to subjective measures of voice production and select acoustic and aerodynamic variables. However, due to the small number of studies available for this review, and the methodological differences inherent in the studies, generalizations regarding the degree of effectiveness of botulinum toxin for all forms of spasmodic dysphonia or patients with different behavioral or clinical characteristics must be withheld at this point.

Implications for research

Of 77 articles published in the area of botulinum toxin treatment for spasmodic dysphonia, only seven articles reported randomized controlled clinical trials. Of these seven, only three published adequate data that could be further analyzed via a systematic review. However, on further inspection it was found that only one study presented an appropriate and analyzable randomized trial thus limiting any conclusions that might be drawn. There is a large
body of data from non-randomized clinical studies that, taken to-
gether, suggest a very positive clinical outcome from the use of
botulinum toxin for spasmodic dysphonia. However, well con-
structed randomized controlled trials are insufficient in this area.
In addition, methodological variation across all studies in the clin-
ical botulinum toxin literature make it difficult to compare one
study with another. In order to facilitate more valid, reliable and
specific decisions regarding treatment benefit, more randomized
controlled trials are needed that control for or investigate the fol-
lowing variables: dosage, injection location, spasmodic dysphonia
type, subject characteristics and time post-injection that depen-
dent variables are measured. These factors should be incorpo-
ated into methodologies that investigate a number of variables that are
of clinical relevance. These include subjective and objective mea-
sures of the degree and duration of effectiveness for post-injec-
tion vocal improvement and neuromuscular functioning, as well
as acoustic, aerodynamic and endoscopic measures of the effects of
botulinum toxin on laryngeal function in patients with spasmodic
dysphonia.

POTENTIAL CONFLICT OF INTEREST

None known.

SOURCES OF SUPPORT

External sources of support
• No sources of support supplied

Internal sources of support
• No sources of support supplied

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blind controlled study of botulinum toxin in adductor spasmodic

Troung 1991
Troung D, Rontal M, Rolnick M, Aronson A, Mistura K. Double-
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in adductor spasmodic dysphonia. *Journal of Otolaryngology* 1995;24
(6):345–51.

Adams 1996
Adams SG, Durkin LC, Irish JC, Wong DL, Hunt EJ. Effects of
botulinum toxin type A injections on aerodynamic measures of spasm-

Aronson 1993
Aronson AE, McCaffrey TV, Litchey WJ, Lipton RJ. Botulinum
toxin injection for adductor spasmodic dysphonia: patient self-rat-
ings of voice and phonatory effort after three successive injections.
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Ford 1990

Ford 1992

Galardi 1991

George 1992

Green 1992

Inagi 1996

Jankovic 1990

Klap 1991

Klap 1993

Kobayashi 1993

Koriwchak 1996

Langeveld 1998

Langeveld 2001

Lees 1992

Liu 1996

Loven 1993

Loven 1994

Ludlow 1988

Ludlow 1990

Ludlow 1991

Ludlow 1992

Lundy 1998

Maloney 1994

Marion 1992

Maurri 1992
Maurri S Barontini F. Botulinum toxin. A new therapeutic alternative in spastic dysphonia (laryngeal abductor dystonia) [Breve aggiorna-
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Mehta 2001

Meleca 1997

Miller 1987

Murry 1995

Papathanasiou 1997

Poungvarin 1995

Rhew 1994

Rodriguez 1994

Rontal 1991

Rosen 1999

Ruiz 1998

Sapienza 2002

Schonweiler 1998

Smith 2000

Teive 2001

Thomas 2006

Tish 2003

Whurr 1993

Whurr 1997

Whurr 1998

Wong 1995a

Wong 1995b

Zwirner 1991

Zwirner 1992
Zwirner P, Murry T, Swenson M, Woodson GE. Effects of botulinum toxin therapy in patients with adductor spasmodic dysphonia: acous-

Zwirner 1993a

Zwirner 1993b

Zwirner 1997

Additional references

Aronson 1990

Blitzer 2001

Boone 2000

Boutsen 2002

Brin 1998a

Cannito 1981

Cannito 2001

Drost 1998

Stemple 2000

TABLES

Characteristics of included studies

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<tr>
<td>Methods</td>
<td>Double-blinded cross-over, placebo-controlled, random assignment</td>
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<tr>
<td>Participants</td>
<td>13 adductor spasmodic dysphonia</td>
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<tr>
<td>Interventions</td>
<td>Bilateral TA injections of 2.5U Botox or 2.5U saline</td>
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<tr>
<td>Outcomes</td>
<td>Fo, MPT, Fo range, Perturbation, Spectrographic analysis, Perceptual ratings</td>
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Notes
Allocation concealment | B – Unclear

Characteristics of excluded studies

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<td>Thomas 2006</td>
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<td></td>
<td>Participants: Adult patients with adductor spasmodic dysphonia</td>
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<td></td>
<td>Interventions: Frozen versus fresh reconstituted botulinum toxin type A</td>
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<tr>
<td>Whurr 1993</td>
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<tr>
<td>Whurr 1997</td>
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<tr>
<td>Whurr 1998</td>
<td>Not randomized</td>
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<tr>
<td>Wong 1995a</td>
<td>Randomized</td>
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<tr>
<td></td>
<td>Participants: Adults with spasmodic dysphonia</td>
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<tr>
<td></td>
<td>Interventions: Botulinum toxin with vocalization versus botulinum toxin without vocalization</td>
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<tr>
<td>Wong 1995b</td>
<td>Randomized</td>
</tr>
<tr>
<td></td>
<td>Participants: Adults with spasmodic dysphonia</td>
</tr>
</tbody>
</table>
Characteristics of excluded studies (Continued)

Interventions: Botulinum toxin with vocalization versus botulinum toxin without vocalization

Zwirner 1991 Allocation: Not randomized
Zwirner 1992 Allocation: Not randomized
Zwirner 1993a Allocation: Not randomized
Zwirner 1993b Allocation: Not randomized
Zwirner 1997 Allocation: Not randomized

Additional Tables

Table 01. Search strategies

<table>
<thead>
<tr>
<th>MEDLINE/CINAHL</th>
<th>EMBASE</th>
<th>mRCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. VOICE-DISORDERS.DE.</td>
<td>1. LARYNX-DISORDER.DE.</td>
<td>((dysphoni% OR laryngospasm% OR voice disorder% OR laryngeal dystonia) AND (botulin% OR botox% OR dysport% OR oculinum% OR myobloc% OR neurobloc% OR borb% OR cs bot% OR vistabel%))</td>
</tr>
<tr>
<td>2. LARYNGISMUS.DE.</td>
<td>2. LARYNX-SPASM.DE.</td>
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<tr>
<td>3. (SPASM$4 OR SPASTIC OR FLACCID OR HYPERKINETIC OR RESPIRATORY OR LARYNGOSPASM$4) NEAR DYSFONIS2</td>
<td>3. LARYNX.DE. AND DYSTONIA.DE.</td>
<td></td>
</tr>
<tr>
<td>4. PHONATION ADJ DISORDERS$1 OR LARYNGEAL ADJ DYSTONIA OR NEUROLOGIC$2 ADJ VOICE ADJ DISORDERS$1</td>
<td>4. DYSPHONIA.DE.</td>
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<tr>
<td>5. (ABSD OR ADSD).TI,AB.</td>
<td>5. (SPASM$4 OR SPASTIC OR FLACCID OR HYPERKINETIC OR RESPIRATORY OR LARYNGOSPASM$4) NEAR DYSFONIS2</td>
<td></td>
</tr>
<tr>
<td>6. 1 OR 2 OR 3 OR 4 OR 5</td>
<td>6. PHONATION ADJ DISORDERS$1 OR LARYNGEAL ADJ DYSTONIA OR NEUROLOGIC$2 ADJ VOICE ADJ DISORDERS$1</td>
<td></td>
</tr>
<tr>
<td>7. BOTULINUM-TOXINS#.DE.</td>
<td>7. (ABSD OR ADSD).TLAB.</td>
<td></td>
</tr>
<tr>
<td>8. (BOTULIN$3 OR BOTOX$1 OR DYSPORT$1 OR OCULINUM$1 OR MYOBLOC$1 OR NEUROBLOC$1 OR BOTB$1 OR CS ADJ BOT$1 OR VISTABEL$1).TLAB.</td>
<td>8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7</td>
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<tr>
<td>9. 7 OR 8</td>
<td>9. BOTULINUM-TOXIN.DE. OR BOTULINUM-TOXIN-A.DE. OR BOTULINUM-TOXIN-B.DE.</td>
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<tr>
<td>10. 6 AND 9</td>
<td>10. (BOTULIN$3 OR BOTOX$1 OR DYSPORT$1 OR OCULINUM$1 OR MYOBLOC$1 OR NEUROBLOC$1 OR BOTB$1 OR CS ADJ BOT$1 OR VISTABEL$1).TLAB.</td>
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Analyses

Comparison 01. Fundamental frequency (Hz)

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 T v C at 4 days post</td>
<td>1</td>
<td>13</td>
<td>Standardised Mean Difference (Fixed) 95% CI</td>
<td>-1.60 [-2.92, -0.29]</td>
</tr>
</tbody>
</table>
### Comparison 02. Mean improvement post-injection

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Botox versus placebo at 4 days</td>
<td>1</td>
<td>13</td>
<td>Standardised Mean Difference (Fixed) 95% CI</td>
<td>Not estimable</td>
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### Comparison 03. Fundamental frequency range

<table>
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<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tbody>
<tr>
<td>01 Fundamental Frq Range at 4 days</td>
<td>1</td>
<td>13</td>
<td>Standardised Mean Difference (Fixed) 95% CI</td>
<td>-4.39 [-6.68, -2.09]</td>
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### Comparison 04. Perturbation

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
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<td>01 Perturbation at 4 days</td>
<td>1</td>
<td>13</td>
<td>Standardised Mean Difference (Fixed) 95% CI</td>
<td>-2.36 [-3.90, -0.82]</td>
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### Comparison 05. Spectrographic ratings (degree of normalcy)

<table>
<thead>
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<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
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<tbody>
<tr>
<td>01 Botox versus placebo at 4 days</td>
<td>1</td>
<td>13</td>
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<td>-4.28 [-6.53, -2.03]</td>
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### Comparison 06. Phonation time

<table>
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<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<td>01 Phonation time treatment</td>
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<td>13</td>
<td>Standardised Mean Difference (Fixed) 95% CI</td>
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### Comparison 07. Audio ratings (degree of severity)

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<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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</thead>
<tbody>
<tr>
<td>01 Perceptual audio ratings</td>
<td>1</td>
<td>13</td>
<td>Standardised Mean Difference (Fixed) 95% CI</td>
<td>-4.42 [-6.72, -2.11]</td>
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### INDEX TERMS

Medical Subject Headings (MeSH)
- Botulinum Toxins [*therapeutic use]; Spasm [*drug therapy]; Voice Disorders [*drug therapy]

MeSH check words
- Humans

### COV E R SHEET

**Title**
- Botulinum toxin injections for the treatment of spasmodic dysphonia

**Authors**
- Watts CCW, Whurr R, Nye C
All authors contributed to the collection and evaluation of included/excluded studies, and preparing the text. Watts and Nye were responsible for the data input and analysis.
### Analysis 01.01. Comparison 01 Fundamental frequency (Hz), Outcome 01 T v C at 4 days post

**Review:** Botulinum toxin injections for the treatment of spasmodic dysphonia  
**Comparison:** 01 Fundamental frequency (Hz)  
**Outcome:** 01 T v C at 4 days post

<table>
<thead>
<tr>
<th>Study</th>
<th>Treated</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Control</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Standardised Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>95% CI (%)</th>
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<tbody>
<tr>
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<td></td>
<td>7</td>
<td>88.91 (7.00)</td>
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<td>102.11 (8.37)</td>
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<td>-1.60 [-2.92, -0.29]</td>
<td>100.0</td>
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<td>Total (95% CI)</td>
<td></td>
<td>7</td>
<td></td>
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<td></td>
<td></td>
<td>100.0</td>
<td>-1.60 [-2.92, -0.29]</td>
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Test for heterogeneity: not applicable  
Test for overall effect: z=2.39  
p=0.02

### Analysis 02.01. Comparison 02 Mean improvement post-injection, Outcome 01 Botox versus placebo at 4 days

**Review:** Botulinum toxin injections for the treatment of spasmodic dysphonia  
**Comparison:** 02 Mean improvement post-injection  
**Outcome:** 01 Botox versus placebo at 4 days

<table>
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<tr>
<th>Study</th>
<th>Botox</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Placebo</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Standardised Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Troung 1991</td>
<td></td>
<td>7</td>
<td>2.83 (0.63)</td>
<td>6</td>
<td>0.00 (0.00)</td>
<td>0.0</td>
<td>Not estimable</td>
<td>0.0</td>
<td>Not estimable</td>
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<tr>
<td>Total (95% CI)</td>
<td></td>
<td>7</td>
<td></td>
<td>6</td>
<td></td>
<td></td>
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<td></td>
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</table>

Test for heterogeneity: not applicable  
Test for overall effect: not applicable
### Analysis 03.01. Comparison 03 Fundamental frequency range, Outcome 01 Fundamental Frq Range at 4 days post

**Review:** Botulinum toxin injections for the treatment of spasmodic dysphonia  
**Comparison:** 03 Fundamental frequency range  
**Outcome:** 01 Fundamental Frq Range at 4 days post

<table>
<thead>
<tr>
<th>Study</th>
<th>Treated</th>
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<th>Standardised Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Standardised Mean Difference (Fixed)</th>
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<tbody>
<tr>
<td>Troung 1991</td>
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<td>6</td>
<td>-4.39 [-6.68, -2.09]</td>
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<tr>
<td>Total (95% CI)</td>
<td>7</td>
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<td>-4.39 [-6.68, -2.09]</td>
<td>100.0</td>
<td>-4.39 [-6.68, -2.09]</td>
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Test for heterogeneity: not applicable  
Test for overall effect $z=3.75$ $p=0.0002$

### Analysis 04.01. Comparison 04 Perturbation, Outcome 01 Perturbation at 4 days

**Review:** Botulinum toxin injections for the treatment of spasmodic dysphonia  
**Comparison:** 04 Perturbation  
**Outcome:** 01 Perturbation at 4 days

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
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<th>Weight</th>
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<tbody>
<tr>
<td>Troung 1991</td>
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<td>-2.36 [-3.90, -0.82]</td>
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<td>-2.36 [-3.90, -0.82]</td>
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<tr>
<td>Total (95% CI)</td>
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<td>-2.36 [-3.90, -0.82]</td>
<td>100.0</td>
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</table>

Test for heterogeneity: not applicable  
Test for overall effect $z=3.01$ $p=0.003$

### Analysis 05.01. Comparison 05 Spectrographic ratings (degree of normalcy), Outcome 01 Botox versus placebo at 4 days

**Review:** Botulinum toxin injections for the treatment of spasmodic dysphonia  
**Comparison:** 05 Spectrographic ratings (degree of normalcy)  
**Outcome:** 01 Botox versus placebo at 4 days

<table>
<thead>
<tr>
<th>Study</th>
<th>Botox group</th>
<th>Placebo</th>
<th>Standardised Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Standardised Mean Difference (Fixed)</th>
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</thead>
<tbody>
<tr>
<td>Troung 1991</td>
<td>7</td>
<td>6</td>
<td>-4.28 [-6.53, -2.03]</td>
<td>100.0</td>
<td>-4.28 [-6.53, -2.03]</td>
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<tr>
<td>Total (95% CI)</td>
<td>7</td>
<td>6</td>
<td>-4.28 [-6.53, -2.03]</td>
<td>100.0</td>
<td>-4.28 [-6.53, -2.03]</td>
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</table>

Test for heterogeneity: not applicable  
Test for overall effect $z=3.72$ $p=0.0002$

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Botulinum toxin injections for the treatment of spasmodic dysphonia (Review)  
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### Analysis 06.01. Comparison 06 Phonation time, Outcome 01 Phonation time treatment versus control

**Review:** Botulinum toxin injections for the treatment of spasmodic dysphonia  
**Comparison:** 06 Phonation time  
**Outcome:** 01 Phonation time treatment versus control

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment N</th>
<th>Treatment Mean(SD)</th>
<th>Control N</th>
<th>Control Mean(SD)</th>
<th>Standardised Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Standardised Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troung 1991</td>
<td>7</td>
<td>90.75 (22.89)</td>
<td>6</td>
<td>83.24 (5.96)</td>
<td>100.0</td>
<td>0.40</td>
<td>[ -0.70, 1.51 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>7</td>
<td></td>
<td>6</td>
<td></td>
<td>100.0</td>
<td>0.40</td>
<td>[ -0.70, 1.51 ]</td>
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</table>

Test for heterogeneity: not applicable  
Test for overall effect $z=0.71$ $p=0.5$

### Analysis 07.01. Comparison 07 Audio ratings (degree of severity), Outcome 01 Perceptual audio ratings treatment versus control

**Review:** Botulinum toxin injections for the treatment of spasmodic dysphonia  
**Comparison:** 07 Audio ratings (degree of severity)  
**Outcome:** 01 Perceptual audio ratings treatment versus control

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment N</th>
<th>Treatment Mean(SD)</th>
<th>Control N</th>
<th>Control Mean(SD)</th>
<th>Standardised Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Standardised Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troung 1991</td>
<td>7</td>
<td>45.24 (5.63)</td>
<td>6</td>
<td>117.86 (21.83)</td>
<td>100.0</td>
<td>-4.42</td>
<td>[ -6.72, -2.11 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>7</td>
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<td>6</td>
<td></td>
<td>100.0</td>
<td>-4.42</td>
<td>[ -6.72, -2.11 ]</td>
</tr>
</tbody>
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Test for heterogeneity: not applicable  
Test for overall effect $z=3.75$ $p=0.0002$