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Efficacy of Laryngeal Botulinum Toxin Injection: Comparison of Two Techniques

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Abstract

Objectives—It is hypothesized that there is no difference in the effectiveness of botulinum toxin (BTX) injection between electromyography (EMG) guided and non-EMG guided ‘point-touch’ techniques in treatment of adductor spasmodic dysphonia (AdSD).

Study Design—Retrospective chart review.

Methods—Patients selected for evaluation underwent sequential treatment by one or both of the senior authors utilizing two different injection techniques with similar BTX dilution & preparation. Data gathered included dose injected, injection effect, presence and duration of breathiness and dysphagia after injection. Statistical analysis was performed using a generalized estimating equations model.

Results—Four hundred seventeen injections in sixty-four patients were analyzed. There was no difference in the rate of successful injections between the EMG guidance group and the non-EMG guidance group (94.4% and 93.2%, respectively; $p = 0.7$).

Conclusions—This unique study demonstrates that efficacy of BTX does not necessarily depend on the method of injection utilized. In experienced hands, excellent clinical results can be achieved with either EMG or non-EMG guided injection techniques.

Keywords

Larynx; Spasmodic Dysphonia; Botulinum toxin; Injection Technique

INTRODUCTION

Spasmodic dysphonia (SD) is an idiopathic focal dystonia that results in irregular, uncontrolled contraction of the laryngeal musculature during phonation. As in other focal dystonia, SD is task-specific and typically affects connected speech. The disorder can be subdivided, based on the clinical signs and symptoms, into adductor (AdSD), abductor, or mixed SD.¹ AdSD is the most common form, consisting of 80–90% of those with SD, and is characterized by a strained-strangled voice with phonatory breaks occurring during utterance of phonemes weighted with voiced consonants.

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Conflict of Interest: None

There are several options for treatment of AdSD including speech therapy, medical therapy with intramuscular injection of botulinum toxin (BTX), and operations including laryngeal adductor denervation and reinnervation procedures and thyroplasty.¹ Currently, the preferred treatment modality is the injection of BTX type A into the intrinsic adductor muscle compartment of the larynx that includes the thyroarytenoid and lateral cricoarytenoid muscle.² BTX type A inhibits the release of acetylcholine at the neuromuscular junction and thus results in flaccid paralysis of the injected laryngeal musculature.³

There are several different techniques used to deliver BTX into the intrinsic laryngeal adductor compartment. No particular technique has been shown to be superior to another. The target muscle can be approached either percutaneously or permucosally; appropriate placement of the needle within the body of the target muscle may be guided by electromyography (EMG) or by visualization with flexible nasopharyngoscopy or indirect laryngoscopy.⁴⁻⁷ To our knowledge, there has only been one investigation that directly compared techniques of BTX injection for the treatment of AdSD.⁸ In this study, the investigators compared a percutaneous EMG guided technique with a permucosal endoscopic guided technique using two different preparations of BTX and found no difference in efficacy between groups. Of note, a nearly 30% rate of ineffective dosing was reported amongst the different groups in that study.

In the Division of Laryngology at the Medical College of Wisconsin, two laryngologists routinely treat AdSD with percutaneous BTX type A injections, one under EMG guidance⁹ and one using the 'point-touch' technique,⁷ a non-EMG technique based solely on laryngeal anatomy. Our observation has been that of overall stability in dose and dose effect between practitioners; it is hypothesized that there is no clinically significant difference in efficacy between the BTX injection techniques as determined by patient report of injection response.

MATERIALS AND METHODS

Subjects

A retrospective chart review was performed of patients treated with BTX in the laryngology clinic at the Medical College of Wisconsin from June 2001 to June 2009. Patients selected for analysis were those that had undergone treatment for AdSD by one or both of two laryngologists with BTX type A using preparations of the same dilution and preparation. Documentation within the patient's chart had to be adequate for interpretation of BTX effect. Each subject underwent a history and physical examination including laryngoscopy and in most cases videostroboscopy prior to treatment. Injections performed by an individual laryngologist using a specific technique were each divided into two groups for analysis.

Toxin preparation and administration

For each injection, BTX type A (Botox[®], Allergan Inc., Irvine, California) was reconstituted just prior to patient delivery in preservative-free saline, to give a dose concentration of 2.5 units/0.1 mL.

In Group 1, BTX was injected using the point-touch technique described by Berke in 1992.¹⁰ This technique has been slightly modified from the original description and is based purely on externally palpable laryngeal landmarks; no endoscopic guidance or verification is utilized. The reconstituted and diluted BTX was loaded into a tuberculin syringe that was attached to a 1.5-inch 27-gauge needle. This was then introduced percutaneously through the thyroid cartilage or cricothyroid membrane, depending on the degree of calcification, and into the laryngeal adductor compartment near the insertion of the thyroarytenoid at the anterior commissure. Adequate needle positioning was guided by palpation and external landmark visualization alone. The appropriate dose of BTX was then delivered.

The injections included in Group 2 were performed under EMG guidance. The patients were placed in a sitting position with their neck slightly extended. A 37mm 27-gauge monopolar, hollow-bore, Teflon-coated EMG needle (TECA MyoJect, Nicolet Biomedical, Madison, WI) was inserted percutaneously through the cricothyroid membrane and into the area of the thyroarytenoid muscle. The patient was asked to phonate /i/ and the BTX dose was delivered into the portion of the muscle with the most active motor unit action potentials (MUAPs). A fellowship-trained neurologist provided EMG monitoring and interpretation for each injection.

Outcomes

The four outcome measures analyzed in the study are patient report of beneficial effect (presence and duration of fluent speech), negative effects (presence of breathiness for greater than one week and presence of dysphagia), and an alteration or modification of dose compared to the prior injection. All patients, receiving a therapeutic injection of BTX, were counseled about possible side effects associated with in the injection including the aforementioned measured outcomes. When the subject returned to the clinic for a new BTX injection, they were asked about the effectiveness, and the presence and duration of dysphagia or breathiness during the prior injection period; this was subsequently recorded in the medical chart of the subject. Questioning was obtained in a non-standardized fashion during the pre-injection interview with the patient at a given clinic visit. In general, questions are delivered open ended and answers were recorded in the patient's clinic chart. The dose was modified or left the same depending on the effect of the prior injection. Typically, a change in dose was made after discussion between patient and physician and would be made to either improve the beneficial effects or reduce the negative effects of a prior BTX injection. A change in dose was defined as either a change from bilateral to unilateral, unilateral to bilateral injection, or change in the quantity of BTX delivered. A change in dose or dosing strategy would imply that the prior injection was not ideal. Completely ineffective injections, determined by both the patient and the laryngologist, that required a repeat injection, were also recorded. Mean and maximal doses for each injection and patient were calculated for statistical interpretation.

Statistical Analysis

The association between each of the three binary outcomes variables (beneficial effect, breathiness, dose change) and the injection technique was assessed with the odds ratio. The generalized estimating equations (GEE) with LOGIT link function and exchangeable working correlation matrix were used to control for the effect of multiple injections per patient. The fourth outcome (the presence of dysphagia) was analyzed descriptively, because only four dysphagia cases were registered among all injection sessions. Since every injection session may formally consist of several injections with different doses, the maximum and average injection doses were used to represent the session injection dose. These two are the only continuous variables compared between the injection techniques, where the subject effect was accounted for via single predictor GEE models with the LOGIT link and the linear continuous predictors of the maximum and average injection dose variables. Due to exploratory nature of this study, tight control of the study-wise false discovery rate was not a goal. Student's t-tests and Fisher's exacts tests were incorporated into the analysis where appropriate. All findings with a p-value <0.05 were declared significant.

Records missing documentation of specific outcomes (7 missing beneficial effects, 7 missing breathiness, and 5 missing dysphagia) were dropped on a pair-wise basis when GEE based p-values were calculated.

RESULTS

During the study period, 1087 BTX injections were performed in 229 patients. Only those patients treated with BTX type A for a diagnosis of AdSD, by one or both of the two fellowship-trained laryngologists were included in this study. Those treated with BTX for other disorders were left out of analysis, as they were less frequent. Additionally, those without adequate documentation of dose effect could not be analyzed. Sixty-four subjects, undergoing a total of 417 BTX injections for AdSD were identified and included in this study. Twenty-one of these subjects were treated by both physicians and sequentially underwent injections using both techniques. Patients were separated into two groups. Group 1 was comprised of injections performed using the point-touch technique and Group 2 included injections performed under EMG-guidance and consisted of 220 and 197 injections, in 44 and 41 patients, respectively. Subject age at injection ranged from 25 to 82 years old; the average age was 56. In both groups, injections were performed both unilaterally and bilaterally into the adductor compartment with targeting of the thyroarytenoid muscle. Demographics and distribution of injections are shown in Table I. The average dose injected into each thyroarytenoid muscle for the bilateral injections was not significantly different for Groups 1 and 2 (1.9 units and 1.8 units, respectively; $p = 0.50$). Likewise, for unilateral injections, there was no difference in average dose between Groups 1 and 2 (1.7 units and 1.5 units, respectively; $p = 0.29$). These data are highlighted in Table II.

There were no statistically significant differences in the rate of effective injections, need to alter dose, breathiness, or dysphagia between study groups. These data are highlighted in Table III and displayed graphically in Figures 1 and 2.

A subgroup analysis was performed on the 21 subjects who underwent injections using both techniques. A total of 235 injections were performed in this group; 107 injections were performed using the point-touch technique and 128 injections were performed under EMG-guidance. Within this subgroup, there was no statistically significant difference in the rates of breathiness (19% for the point-touch group and 28% for the EMG-guidance group, GEE p -value = 0.157). Similarly, there was no statistically significant difference between the groups for the rate of ineffective injections (6.5% and 6.2%, respectively, GEE p -value = 0.961). Dysphagia was not statistically analyzed within this subgroup as only one injection resulted in post-injection dysphagia.

As expected, statistical analysis did reveal a trend for increasing dose to be directly related to increasing incidence of post injection breathiness (odds ratio = 0.4698 with 95% confidence interval of 0.1241 to 1.7785). This was seen with both the mean ($p = 0.0248$) and maximal dose ($p = 0.0465$). If the mean dose increased by 1 unit then the odds of having breathiness after an injection increased by 76%. Likewise, the odds of having breathiness after an injection increased by 23.4% when the maximum dose increased by 1 unit. The mean and maximum doses, however, were not significantly associated with the rate of ineffective injections or with incidence of requiring a dose change.

DISCUSSION

In this study, two techniques of intralaryngeal BTX injection were studied, essentially comparing the practices of two experienced laryngologists. There were no differences in the efficacy or incidence of negative effects using a percutaneous approach with EMG guidance versus a percutaneous approach without EMG guidance in a single cohort of patients. There was no difference in the incidence of a change in dose compared to the prior injection between the two techniques.

It has been previously demonstrated that BTX can be effectively delivered to the larynx using a variety of techniques, however, in the treatment of AdSD, a comparison of the efficacy of individual techniques has only been evaluated in limited numbers in a single publication.⁸ In that report, fifteen patients who were previously treated with a EMG guided percutaneous approach with BTX type A (Botox® - Allergan) were later treated with either a EMG guided percutaneous or a endoscopic guided permucosal approach with one of two types of BTX type A: Botox® (Allergan) or Dysport® (Ipsen). They found no difference in outcomes but noted a rather high rate of ineffective dosing with either medicine using either strategy.

Techniques of injection into the posterior abductor compartment of the larynx for treatment of abductor SD have also been evaluated. In a randomized controlled trial by Bielamowicz *et al*, two techniques used for BTX into the posterior cricoarytenoid muscle for abductor spasmodic dysphonia were compared.¹¹ There was no difference in benefit between an endoscopic approach with visual guidance and a percutaneous approach with EMG-guidance. Meleca *et al* found that both patients and practitioners preferred a transcricoid rather than a retrocricoid approach to the posterior cricoarytenoid muscle for injecting BTX in abductor SD.¹²

EMG can confirm placement of the needle within the thyroarytenoid muscle by showing distinct MUAPs with phonation, ensuring delivery of the exotoxin into the most active portion of the muscle. Using a non-EMG guided technique, placement of the needle into the vicinity of the muscle can be achieved but it is not possible to confirm placement within the body of the muscle or into the most active portion of the muscle. Does BTX need to be delivered to the electrically most active portion of the muscle to make it more effective, or is the EMG signal just an aid to direct the needle into the correct muscle? This question has already been explored and debated.^{13, 14} Arguments both for and against routine use of EMG guidance of BTX injection have been made in targeting of non-laryngeal muscles. Benefits of EMG guidance include the ability to target dystonic motor units and localize injection near the motor endplates. Additionally, a more accurately placed dose in a particular muscle should reduce any side effect of inappropriate dosing of an adjacent muscle. Cited disadvantages of EMG guidance include the possibility that EMG signal may be misleading, and the technique is more time consuming, redundant to anatomic localization, or even more uncomfortable due to additional needle positioning and maneuvering.

An evidence-based review of laryngeal EMG found that needle localization for BTX injection was 'possibly useful' with an evidence level of Class III.⁶ This assessment, however, does not suggest that other techniques of non-EMG guided laryngeal BTX delivery are inferior. In our experience, there are a few minor disadvantages to laryngeal EMG guided BTX administration. There may be more patient discomfort due to an inherent longer period of needle placement during the search for MUAPs. Although not specifically analyzed in this study, the point-touch technique, in experienced hands, can be performed quickly and is well tolerated. Additionally, there is not the need for specialized EMG equipment and coordination of injection time with another practitioner to monitor the EMG signal.

It has been demonstrated that BTX easily passes through muscle fascia and can disseminate to muscles nearby an injection site.¹⁵ Both increasing volume and concentration of injection will have a direct effect on the volume of muscle treated.¹⁶ In the current study, dilution of medicine was the same between groups and there were no significant differences in dosage or volume of delivered BTX solution. The intrinsic laryngeal muscles are physically small. It may be that once the needle is in the vicinity of the correct muscle, toxin delivered will

dose the entire muscle regardless of needle tip proximity to the most active MUAP. The operator only need be accurate enough to avoid collateral spread to an unintended target.

EMG guidance is useful in the management of AdSD. It may be also be valuable as a teaching tool. A teaching clinician can easily assess the accuracy of needle placement with a remote EMG monitor. The point-touch technique may be more difficult to learn. Although comprehensive knowledge of intrinsic laryngeal anatomy is necessary for both techniques, with the point-touch, the only feedback one receives regarding dosing accuracy is the feel of the needle, which one could argue is more vague than the audible tone and visible signals of a MUAP.

Both of the laryngologists in this study were fellowship trained and each have over 10 years of experience with percutaneous approaches to the larynx and have individual expertise in their chosen technique. Data from this study suggests one method cannot be recommended over another. The treating physician should choose an injection technique they are most familiar with and which suits their individual practice; EMG may not be necessary for a practitioner with years of experience with the point-touch technique, but may be very helpful to others.

CONCLUSIONS

Both point-touch and EMG guided delivery of BTX are effective techniques of treatment for AdSD. There seems to be no significant difference in patient outcome based on technique of injection, utilized in this cohort, treated by experienced clinicians.

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Figure 1. Number of effective and non-effective injections per group

Group 1 = point-touch technique; Group 2 = EMG guided technique.

Using Fisher's exact test, there were no statistical differences between the groups ($p = 0.69$).

Figure 2. Distribution of outcomes amongst groups

Group 1 = point-touch technique; Group 2 = EMG guided technique.

There were no statistical differences between groups in dose effect, presence of breathiness, dysphagia, or rate of change in dose (all $p > 0.05$).

Table I

Characteristics of subjects

	Group 1	Group 2
Total Subjects	44	41
Female Subjects	28	31
Male Subjects	16	10
Median Age	58	58
Mean Age	57	56

Group 1 = point-touch technique; Group 2 = EMG guided technique.

Data was analyzed from 64 patients. Twenty-one patients underwent treatment with both techniques and are thus included in each group for the data analysis.

Table II

Type of BTX injections for each group.

	Group 1	Group 2	p-value
Total # of Injections	220	197	
Bilateral injection	139 (63%)	113 (57%)	
Unilateral injection	81 (36%)	84 (42%)	
Average maximum dose for all injections	3.0 Units	2.8 Units	0.12
Average dose per side for bilateral injections	1.9 Units	1.8 Units	0.51
Average dose per side for unilateral injections	1.7 Units	1.5 Units	0.35

A Student's t-test was used to compare the two groups. There was no significant difference in dosing between groups.

Group 1 = point-touch technique; Group 2 = EMG guided technique.

Table III

Efficacy, dose change requirements, and side effects of BTX injections.

	Group 1	Group 2	p- value
Efficacy			
Effective injections	204 (93%)	180 (94%)	0.6895
Ineffective injections	15 (7%)	11 (6%)	
Breathiness			
No breathiness	170 (78%)	137 (71%)	0.1732
Breathiness	49 (22%)	54 (29%)	
Dysphagia			
No dysphagia	217 (99%)	191 (99%)	
Dysphagia	2 (1%)	2 (1%)	
Dose change			
Injection dose unchanged	117 (60%)	95 (59%)	0.8367
Injection dose changed	78 (40%)	65 (41%)	

Group 1 = point-touch technique; Group 2 = EMG guided technique.

There were no statistical differences noted between groups and rate of effective injection, need to change dose, or breathiness. (all $p > 0.05$). There was no difference between groups and the rate of dysphagia, though this was not statistically analyzed as there were too few events. The dose effect, presence of breathiness, and presence of dysphagia were not described in the hospital charts of 7, 7, and 5 subjects, respectively. These few were pair-wise dropped and the total number statistically analyzed are reflected in the table.

Total subjects in each subgroup have different totals (n) reflecting analysis of quantifiable data for the statistical model. For instance, even though 417 injections were available for analysis, only 355 (195 injections and 160 injections, Groups 1 & 2 respectively) were analyzed for dose change, as the final injection for each subject was not included because a subsequent dose change could not be determined.