Factors Influencing Botulinum Toxin Dose Instability in Spasmodic Dysphonia Patients

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Summary: Objective. Many patients with spasmodic dysphonia (SD) see consistent effects from botulinum toxin (BTX) injections of the same dose, whereas others require dosage changes over time. We sought to determine whether demographics (age and gender) or environmental factors (smoking) affect the long-term stability of BTX dosing in these patients.

Study Design. Retrospective review.

Methods. Charts of all patients undergoing BTX injection for adductor SD were reviewed. Dosage change, defined as whether there was any difference in total dosage used between two beneficial injections, was used as a measure of dosing stability. Beneficial injections were indicated by a voice rating score of at least three of four and any non-zero duration of improved voice. Logistic regression analysis was performed to determine whether age, gender, smoking status, or duration of treatment correlated with odds of having a dosage change.

Results. A total of 211 patients were ultimately included. Age, gender, and smoking status were all found to have no correlative effect on dosing stability. The only factor that was predictive of dose stability was the number of previous beneficial injections, as every additional injection led to decreased odds of a change in dosage for the next injection (odds ratio = 0.964; 95% confidence interval = 0.947–0.981).

Conclusions. Dosage of BTX injections for long-term treatment of SD has a significant propensity to remain stable over time. Factors such as age, gender, and smoking status do not appear to influence the dosage stability. These findings should allow for better patient counseling regarding expectations for their long-term treatment.

Key Words: Spasmodic dysphonia–Botulinum toxin–Dosage–Spastic dysphonia–Laryngeal spasm–Botox–Outcomes.

INTRODUCTION

Spasmodic dysphonia (SD) is a type of focal dystonia causing involuntary spasms of the laryngeal muscles during speech production.[1] This neuromuscular condition affects the ability of the vocal folds to properly coordinate adduction and/or abduction during speech, causing patients to have difficulty speaking and a poor voice quality. Depending on the subtype of the disease, SD can cause spastic activity of the muscles that close the vocal folds, the muscles that open them, or a mixture of both. The disorder is generally separated into two major types, namely adductor spasmodic dysphonia (ADSD), in which spasms cause the vocal folds to close and the voice has a strangulated quality; and the more rare abductor type (ABSD), in which spasms cause the vocal folds to open and the voice has a breathy quality.[1] However, there is much variation from patient to patient, and those who suffer from SD can have a combination of the two subtypes with or without a number of associated symptoms including difficulty speaking loudly, frequent pitch breaks, or an associated vocal tremor. This condition is often misdiagnosed or not diagnosed at all, and often leads to a very poor quality of life for afflicted patients because it can profoundly affect their ability to communicate.

The exact cause of SD is not known, and there is currently no cure for this condition. The gold standard of treatment that has been extensively described in the clinical literature is the direct injection of botulinum toxin (BTX) into the affected muscle of the vocal folds. This is done in an office setting, most commonly under electromyography guidance, and it has the effect of weakening the spastic muscles. This initially can cause adverse side effects such as breathiness or dysphagia to liquids, but these effects usually subside.[2] The beneficial effect of BTX is temporary and usually lasts for 2–5 months.[3] Some patients see more effective and longer lasting results than others, and patients with ADSD have been shown to gain better voice quality and for longer periods of time overall than patients with ABSD.[4]

The dosing of BTX is variable, and this is the focus of the present study. There is often some trial and error to find a dose that provides a suitable voice while not causing extensive initial breathiness. This initial effective dose can vary greatly among patients, and our group recently found that a lower initial dose maintains the positive voice effects while reducing the duration of breathiness.[5] Many patients see consistently positive effects from BTX injections and return routinely for injections at the same dose. Others, however, can gradually develop resistance and require increasingly higher doses over time. Still, others may require progressively lower doses.

One possible cause of dosing variability that has been investigated recently has been the effect of age. There have been retrospective reviews by our group, as well as by other groups, demonstrating that older patients suffer more severe SD symptoms and that these patients may also experience less benefit from BTX injection.[6–8] Tanner et al[8] recently performed

Accepted for publication August 14, 2014.
The authors report no external funding sources or relationships to disclose.
This study was presented at the Annual Symposium of The Voice Foundation; June 1, 2014; Philadelphia, PA.
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Journal of Voice, Vol. 29, No. 3, pp. 352-355
0892-1997/$36.00

http://dx.doi.org/10.1016/j.jvoice.2014.08.011

a case-control study that identified a variety of endogenous risk factors associated with SD, including age between 60 and 70 years, as well as exogenous exposures associated with increased risk, such as dust. Interestingly, although this study examined several exogenous exposures, including dust, chemical inhalation, and vaccinations, tobacco smoking was not explicitly examined. Tobacco smoke has a known inflammatory effect in the upper aerodigestive tract, and it has been hypothesized that laryngeal inflammation can trigger the afferent laryngeal neural circuit and potentially alter the symptoms of ADSD.[9] Smokers also are known to self-report higher dysphonia symptoms than their age-matched controls, which would suggest that these patients might not be as satisfied with their post-BTX injection outcomes.[10]

Our aim was to statistically test the hypothesis that certain demographic factors in ADSD patients influence the overall dose stability. We sought to prove this through logistic regression analysis rather than through descriptive group analysis. By taking this approach, we were able to assess whether the variable in question, BTX dose stability, was dependent on other independent variables—age of onset, age at time of treatment, smoking status, and gender.

METHODS

Approval was first obtained from the University of Miami Institutional Review Board for a retrospective chart review of all patients with ADSD treated at our tertiary care facility between 1990 and 2011. Patients underwent personalized BTX treatment by one of the two practitioners as described previously.[5] Patients self-reported their degree of voice improvement post-injection on a four-point noncontinuous scale. A retrospective review was conducted of all patients undergoing BTX injection for ADSD, and logistic regression analysis was performed to determine whether age, gender, smoking status, or duration of treatment correlated with the likelihood of having a dosage change. To be included in the analysis, patients had to have had at least two beneficial injections of BTX, indicated by a voice rating score of at least three and any non-zero duration of improved voice. Logistic regression analysis was performed using dosage change as the outcome, defined as whether there was any difference in total BTX dosage used between two beneficial injections. The first BTX dose was excluded from analysis owing to the lack of indication of dosage change status. The predictors used were age, number of visits/injections, and smoking status. Smoking status was categorized as "never," "former," and "current."

Descriptive statistics were first used to explore data distribution. Logistic regression with general estimating equations (GEEs) for estimating test variances was fit to the data to estimate the odds of dose change as a function of age and number of visits/injections. An interaction was incorporated to allow a differential effect of number of visits/injections by age. Effect of smoking status was also assessed in the model. All statistical analyses were performed using *SAS* 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Descriptive statistics showed a final sample of 211 patients, 78.2% of whom were female. Of these patients, there was equivalent gender breakdown of smokers and nonsmokers: 76.0% of the lifetime nonsmokers were women, and 74.2% of the patients with a history of smoking were female. The mean age of the sample was 55.5 years (standard deviation [SD] = 14.7). On average, each patient received 10.9 (SD = 10.4) injections and experienced a dosage change from their previous beneficial injection 1.9 (SD = 2.6) times (Tables 1 and 2). From the results of logistic regression with GEEs, first all interaction effects were assessed: age versus number of visits/injections, age versus smoking status, smoking status versus number of visits/injections, and age versus smoking status versus number of visits/injections. However, none of them was statistically significant ($P > 0.05$), thus they were removed from the model. Results of the remaining model, incorporating the main effects of time, age, and smoking status, reveal a significant association between number of visits/injections and dosage change (odds ratio [OR] = 0.964; 95% confidence interval [CI] = 0.947–0.981) controlling for age and smoking status (Table 3). Thus, the odds of having a dosage change decreased by about 4% with every additional visit/injection. Neither age (OR = 0.988; 95% CI = 0.975–1.002) nor smoking status was found to be significant predictors for dosage change (never smoker vs current smoker OR = 0.995; 95% CI = 0.544–1.821; former smoker vs current smoker OR = 1.063; 95% CI = 0.543–2.079).

DISCUSSION

As our statistical analyses show, the dosage of BTX injections for long-term treatment of ADSD has a significant propensity to remain stable over time. Factors such as age, gender, and smoking status do not appear to influence the dosage stability. The only factor that was predictive of dose stability was the number of previous injections, as every additional beneficial injection contributed to a slightly lower probability likelihood of dosage change. Presumably this is owing to the fact that the more times a patient has gone for BTX treatment, the more likely it is that the patient will have found an effective dose and thus will not need to change it. Although this finding may seem obvious on the surface, it does contradict some published studies, as well as the perception that long-term BTX treatment can lead to desensitization or antibody formation. Recent research in this area has painted a somewhat conflicting picture regarding BTX dose variability and the effect of age on dose and voice outcome.

TABLE 1.
Demographic Summary of Study Patients

Demographics	N (%)/Mean (SD)
Gender, n (%)	
Female	165 (78.2)
Male	46 (21.8)
Age	55.5 (14.7)
Number of injections	10.9 (10.4)
Number of dosage changes	1.9 (2.6)

Abbreviation: SD, standard deviation.