Longitudinal Effects of Botox Injections on Voice-Related Quality of Life (V-RQOL) for Patients With Adductory Spasmodic Dysphonia

Part II

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Objective: To investigate the longitudinal effects of botulinum toxin type A (Botox) injections on voice-related quality of life (V-RQOL) for patients with adductory spasmodic dysphonia.

Design: Prospective study.

Setting: Academic tertiary care referral center.

Participants: Forty-two patients who presented to our institution with dysphonia and were diagnosed as having adductory spasmodic dysphonia during a 38-month period.

Intervention: Patients received Botox injections into both thyroarytenoid muscles via the cricothyroid membrane. The typical starting dose was 1.0 U per vocal fold. If necessary, the dosage was adjusted in subsequent injections to reduce adverse effects or to enhance duration of benefit.

Main Outcome Measures: Patients filled out questionnaires, including the V-RQOL Measure and a self-assessed overall voice rating, before each injection. Postinjection questionnaires were completed 6 to 8 weeks after each treatment. Mean pretreatment and posttreatment scores were calculated for each treatment.

Results: The number of treatments per patient ranged from 1 to 7. Statistically significant improvements in mean total and domain V-RQOL scores were calculated for every injection (P < .01) (no postinjection questionnaires were available for the seventh injections). The magnitude of the effect remained constant for later injections. Eighty-two percent of the population recorded at least 1 category of improvement in overall self-assessed voice rating with each injection.

Conclusions: Botox has a significant beneficial effect on V-RQOL for at least 6 injection cycles. This study demonstrates the efficacy of Botox for treating patients with adductory spasmodic dysphonia and further illustrates the usefulness and validity of the V-RQOL Measure in evaluating patients with dysphonia.

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ADDUCTORY SPASMODIC DYSPHONIA (AdSD) is a focal dystonia of the laryngeal adductor muscles. It accounts for 80% of all cases of spasmodic dysphonia. Abductory and mixed spasmodic dysphonias also occur, but less frequently. Patients with AdSD present with a strained or pressed voice, resulting from spasms of the adductory laryngeal muscles during phonation. The disease can have dramatic emotional, functional, and social effects on patients and significantly reduce their quality of life.

Several techniques have been used to treat AdSD, including voice therapy, sectioning of the recurrent laryngeal nerve, laryngeal framework surgery, partial myectomy of the thyroarytenoid muscles, and chemodenervation using intramuscular botulinum toxin type A (Botox; Allergan Inc, Irvine, Calif) injections. Although Botox is the most widely accepted therapy today, treatment of AdSD remains an off-label application of this medication in the United States. Botox treatment is not curative, and repeated injections over time are necessary for continued therapeutic benefit.

Numerous methods have been used to evaluate the physiologic effects of AdSD and treatment for the disease, including acoustic and aerodynamic measures, electromyography, endoscopy, and perceptual analyses. None of these methods quantifies the effects that AdSD has on a patient’s quality of life. Quality of life is a uniquely personal outcomes measure that takes into account many different feelings and circumstances in a patient’s life.

In the present study, we examine voice-related quality of life (V-RQOL) out-
The goals of the present study were (1) to study the long-term effectiveness of Botox changes with repeated injections, and (2) to further expand understanding of the usefulness of the V-RQOL Measure (Voice-Related Quality of Life Measure). The number of patients receiving 3 or more injections for a cohort of patients with AdSD for at least 3 injections. The V-RQOL survey questions and day-to-day variation of the V-RQOL survey questions and day-to-day variation indicates greater degree of categorical improvement.

The data for this study are based on self-reported surveys. Measurement error in this study can arise from individual differences in patient responses, including Interpretation of the V-RQOL survey questions and day-to-day variation in patient symptoms. However, the survey used for this study has been shown to be reliable and valid across a population of patients with different symptoms (including nonvoice patients) and for test-retest consistency for the same patients. The Cronbach α coefficient for the overall V-RQOL survey was 0.89, while the physical functioning and social and emotional subscales had coefficients of 0.80 and 0.81, respectively. The intraclass correlation coefficients for the overall and domain scores were 0.92, 0.90, and 0.87, respectively. For these measures, scores above 0.80 are considered to demonstrate excellent reliability.

**METHODS**

**PATIENT POPULATION AND DATA ACQUISITION**

Forty-two new patients presenting with dysphonia to the University of Michigan vocal health program during a recent 38-month period were diagnosed as having AdSD. Twenty-seven of these patients were included in a previous 18-month investigation, and 15 presented since completion of the earlier study.

Continuing longitudinal data from the original group and data from the additional patients make up the present study. One of us (N.D.H.) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The project was approved by the institutional review board of the University of Michigan Medical Center.

Six of the 42 patients with AdSD chose not to have any Botox treatment. Their initial V-RQOL surveys are included in the population data. Thirty-six of the 42 patients underwent at least 1 cycle of bilateral thyroarytenoid muscle Botox injections and filled out a follow-up survey during the study. Thirty of these 36 patients are still being treated with Botox injections at our institution, while 6 are no longer receiving treatment. Only 1 of these 6 patients discontinued treatment because of equivocal therapeutic effect. The remaining 5 stopped receiving injections for reasons unrelated to treatment effectiveness.

Diagnoses of AdSD were made by experienced voice clinicians based on history, vocal capabilities, and laryngeal videostroboscopy findings. Typical diagnostic features have been previously described. Using electromyographic guidance, a fellowship-trained laryngologist (N.D.H.) performed the percutaneous Botox injections. After anesthetization of the skin and airway, Botox was injected via the cricothyroid membrane. The typical starting dosage was 1.0 U per vocal fold. If necessary, the dosage was adjusted in subsequent injections to reduce adverse effects or to increase the duration of benefit.

Patients filled out questionnaires, including the V-RQOL Measure (Figure 1) and a self-assessed overall voice rating, before each injection. Postinjection questionnaires were completed 6 to 8 weeks after each treatment. Patients were seen in the clinic 6 to 8 weeks after their first injection, and initial posttreatment surveys were completed during these visits. Any patient who still had breathy dysphonia as a Botox adverse effect was scheduled for a repeat follow-up assessment in an additional 6 weeks. Patients without significant adverse effects were instructed to call for a repeat injection when their vocal symptoms returned. Follow-up questionnaires for subsequent injections were mailed to patients and returned by self-addressed envelope.

Self-assessed overall voice quality categorical ratings were assessed as poor, fair, good, very good, or excellent. An improvement of 1 categorical rating (eg, from poor to fair) was given a score of +1. An improvement from poor to good was given a score of +2, and so forth. Greater numerical change indicates greater degree of categorical improvement.

**STATISTICAL ANALYSIS**

Survey responses were recorded from the pretreatment and posttreatment surveys. Demographic data and dates of treatment were recorded from clinical records. SAS version 6.12 for

**Figure 1.** Voice-Related Quality of Life Measure.

Because of my voice, How much of a problem is this?

1. I have trouble speaking loudly or being heard in noisy situations. 1 2 3 4 5
2. I run out of air and need to take frequent breaths when talking. 1 2 3 4 5
3. I sometimes do not know what will come out when I begin speaking. 1 2 3 4 5
4. I am sometimes anxious or frustrated (because of my voice). 1 2 3 4 5
5. I sometimes get depressed (because of my voice). 1 2 3 4 5
6. I have trouble using the telephone (because of my voice). 1 2 3 4 5
7. I have trouble doing my job or practicing my profession (because of my voice). 1 2 3 4 5
8. I avoid going out socially (because of my voice). 1 2 3 4 5
9. I have to repeat myself to be understood. 1 2 3 4 5
10. I have become less outgoing (because of my voice). 1 2 3 4 5

5 = Problem is as “bad as it can be”
4 = A small amount
3 = None, not a problem
2 = A small amount
1 = None, not a problem
0 = None, not a problem

**Statistical Analysis**

Survey data were analyzed using SAS version 6.12 (SAS Institute, Cary, NC) with the intraclass correlation coefficient determining interpatient and intrapatient reliability.**
The mean ± SD age for the entire study population was 51.5 ± 16.0 years, and 85% of the patients were female. One hundred three treatments were given, and 99 yielded follow-up surveys. Multiple posttreatment surveys for a single injection cycle were obtained from 2 patients. One of these patients returned for repeated follow-up because of continuing adverse effects (prolonged breathiness), and another presented to the injection clinic but did not yet require additional treatment. Inclusion or exclusion of these questionnaires did not significantly alter results. They are included in the data set.

The number of injections ranged from 1 to 7 (no follow-up surveys were available for the seventh treatment; hence, results include only treatments 1 through 6). The mean time between injection and follow-up survey was 7.3 ± 1.6 weeks. The mean time between treatments was 25.2 ± 10.7 weeks (range, 9.0-74.0 weeks).

The initial V-RQOL scores and standard deviations for the entire study population (N = 42) are given in Table 1. The mean total V-RQOL score of 32.7 ± 18.8 is low, and this magnitude is consistent with that determined in the initial 18-month study. Preinjection and postinjection V-RQOL data for all patients who underwent at least 1 injection are shown in Table 2. Improvements in overall and domain V-RQOL scores with the initial treatment were large. Changes in V-RQOL overall and domain scores were statistically significant, with P < .01. Table 3 and Table 4 show the pretreatment and posttreatment self-assessed voice ratings for all patients who received at least 1 treatment. Eighty-six percent of posttreatment surveys demonstrated at least a single categorical level of improve-
more than 58% of postinjection surveys had a change of +2 or more categorical levels in self-assessed voice quality rating. Table 5 gives pretreatment and posttreatment overall and domain V-RQOL scores for patients who received 2 to 6 treatments. Improvement in V-RQOL scores is calculated for each treatment. Significant improvements with each successive treatment were realized (P<.01). Improvement between preinjection and postinjection scores was significantly less with treatment 2 than with treatment 1 (P<.05). However, the longitudinal improvements between preinjection and postinjection scores with treatments 3 through 6 were not significantly different from treatments 1 or 2. That is, the treatment effects of injections 3 to 6 (as represented by change in V-RQOL scores) fell between those of injections 1 and 2.

Table 5. Voice-Related Quality of Life (V-RQOL) Scores*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>V-RQOL</th>
<th>Social and Emotional</th>
<th>Physical Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (n=23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>48.87 ± 19.66</td>
<td>52.17 ± 25.74</td>
<td>46.66 ± 18.18</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>73.57 ± 20.85</td>
<td>75.00 ± 22.22</td>
<td>72.61 ± 21.74</td>
</tr>
<tr>
<td>Improvement in score‡§</td>
<td>22.59 ± 25.00</td>
<td>21.47 ± 28.13</td>
<td>23.34 ± 26.51</td>
</tr>
<tr>
<td>3 (n=14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>44.94 ± 22.18</td>
<td>46.88 ± 28.67</td>
<td>43.65 ± 20.34</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>74.46 ± 22.26</td>
<td>75.45 ± 23.95</td>
<td>73.81 ± 22.49</td>
</tr>
<tr>
<td>Improvement in score‡</td>
<td>29.52 ± 23.95</td>
<td>28.57 ± 27.27</td>
<td>30.16 ± 24.47</td>
</tr>
<tr>
<td>4 (n=14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>41.07 ± 22.53</td>
<td>45.09 ± 26.54</td>
<td>38.39 ± 22.71</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>73.93 ± 24.47</td>
<td>73.21 ± 26.90</td>
<td>74.40 ± 24.34</td>
</tr>
<tr>
<td>Improvement in score‡</td>
<td>32.86 ± 28.75</td>
<td>28.13 ± 32.13</td>
<td>36.01 ± 28.05</td>
</tr>
<tr>
<td>5 (n=11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>45.68 ± 20.89</td>
<td>49.43 ± 24.76</td>
<td>43.18 ± 20.18</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>77.50 ± 16.84</td>
<td>78.98 ± 22.58</td>
<td>76.52 ± 16.06</td>
</tr>
<tr>
<td>Improvement in score‡</td>
<td>31.82 ± 29.48</td>
<td>29.55 ± 31.51</td>
<td>33.33 ± 28.99</td>
</tr>
<tr>
<td>6 (n=5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td>41.50 ± 25.16</td>
<td>33.75 ± 32.36</td>
<td>46.67 ± 22.90</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>80.50 ± 17.36</td>
<td>80.00 ± 28.44</td>
<td>80.83 ± 10.87</td>
</tr>
<tr>
<td>Improvement in score‡</td>
<td>39.00 ± 40.26</td>
<td>46.25 ± 57.04</td>
<td>34.17 ± 30.25</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD.
†Overall and domain scores significantly different from first treatment scores, P<.05.
‡Scores all significantly different from 0, P<.01.
§Change in overall and domain scores significantly different from first treatment change, P<.05.

Figure 3. Pretreatment and posttreatment scores for subset of population (n=11) who had at least 5 injections. V-RQOL indicates voice-related quality of life; SE, social and emotional; and PF, physical functioning.
The traditional clinical laryngologic examination cannot measure the quality-of-life impact of a voice disorder. Therefore, we used the V-RQOL Measure to quantify the detrimental effects of AdSD and the therapeutic effects of Botox.

It has previously been shown that untreated patients with AdSD have much lower overall and domain V-RQOL scores than normal subjects, and the present study corroborates this finding. The mean overall score of 32.7 at the time of initial contact is poor, but will not come as a surprise to clinicians familiar with this frequently devastating condition.

Equally striking as the severity of this disorder are the therapeutic benefits of Botox injections. The present data unequivocally demonstrate that this treatment remains effective over the longer term. Differences in pretreatment vs posttreatment V-RQOL domain or total scores remain significant and of unchanged magnitude when followed up to 6 injection cycles. This is one of the key findings, as the initial 18-month study suggested that the degree of improvement might diminish with each injection. The number of patients in the previous study receiving 3 or more injections was too small to draw any firm conclusions, and continued prospective data were necessary to answer this question.

This study and the previous study show that the improvement in V-RQOL from the second injection is significantly less than that from the initial treatment. This is despite the fact that the improvements with injections 3 through 6 are not significantly different from each other, nor are they different from either of the first 2 treatments. That is, these effects fell between those of the first and second ones. We believe, but cannot prove, that the most likely explanation is that patients’ expectations and perceptions begin to evolve after the initial treatment. They begin to consider their vocal capabilities relative to normal voices around them, as opposed to their original dysphonic voice. Therefore, they are more likely to present for their second treatment before becoming as severely dysphonic as they were originally. This hypothesis is supported by the fact that preinjection scores were higher for the second injection than for the first. Similarly, their assessment of the posttreatment voice becomes more critical. Ultimately, we conjecture that perceptions and expectations continue to evolve and likely stabilize after several injection cycles. The true magnitude of effect of Botox injections on V-RQOL in patients with AdSD may be most accurately represented by later injections. Evolving patient expectations are a positive clinical indicator, as it shows that patients begin to think of themselves as part of the “euphonic” world. A reasonable analogy is a patient who has undergone cochlear implantation pursuing life in the hearing rather than the deaf community and gauging his or her communication capabilities accordingly.

The effectiveness of Botox is also reflected in the categorical changes in self-assessed overall voice quality ratings with each treatment. More than 80% of treatments resulted in at least 1 categorical voice rating improvement. Fifteen percent of treatments did not result in a ratings change, and 4% resulted in a negative change. The most likely explanation for a zero or negative rating change is a degree of prolonged breathy voice adverse effect at the time of the follow-up questionnaire. Other possible explanations include underdosing of Botox, less than optimal response to Botox, or poor recall of earlier voice rating, leading to spurious data.

Given that outcomes research for voice disorders is a relatively new field of study, any opportunity to better understand the outcomes instruments themselves should not be overlooked. The present study is such an opportunity, as review of these prospective data provides additional insight into the validity and clinical significance of the V-RQOL Measure. The relationship between degree of categorical voice rating change and change in

Table 6. Self-assessed Voice Ratings Among 103 Treatments

<table>
<thead>
<tr>
<th>Pretreatment Rating</th>
<th>Poor (n = 50)</th>
<th>Fair (n = 22)</th>
<th>Good (n = 41)</th>
<th>Very Good (n = 22)</th>
<th>Excellent (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good (n = 3)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fair (n = 50)</td>
<td>3</td>
<td>11</td>
<td>21</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Poor (n = 50)</td>
<td>10</td>
<td>18</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Mean ±SD Change in V-RQOL by Change in Self-assessed Voice Rating in 99 Treatments

<table>
<thead>
<tr>
<th>Change in Rating</th>
<th>0 (n = 15)</th>
<th>+1 (n = 31)</th>
<th>+2 (n = 29)</th>
<th>+3 (n = 15)</th>
<th>+4 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in V-RQOL</td>
<td>14.8 ± 25.5</td>
<td>29.1 ± 22.2</td>
<td>36.1 ± 16.9</td>
<td>57.6 ± 14.8</td>
<td>72.2 ± 18.7</td>
</tr>
</tbody>
</table>

Abbreviation: V-RQOL, voice-related quality of life.

*Excludes 4 treatments in which rating declined (mean ± SD change in V-RQOL for these treatments was −2.8 ± 43.1).

Figure 4. Change in overall and domain voice-related quality of life (V-RQOL) scores by change in pretreatment and posttreatment self-assessed voice ratings (99 treatments). Change in self-assessed voice rating of +1 corresponds to a change of approximately 29.1 in overall V-RQOL score. Change in social and emotional and physical functioning domain scores closely approximates change in overall scores.
V-RQOL score (Table 7 and Figure 4) supports clinical validity in that increasing categorical changes corresponded to increasing numerical V-RQOL changes. Also, these data can help to interpret the clinical significance of changes in V-RQOL scores. That is, they can better answer the question, “What amount of numerical V-RQOL change constitutes a clinically significant difference between pretreatment and posttreatment?” A logical answer to this question would be the amount of change necessary to accomplish a single categorical level of improvement in rating. In the original V-RQOL Measure validation study, this value was 18.6, with 20 patients in the 1 categorical improvement group. In the present study, it is 29.1, among 31 patients. Given these data, a conservative estimate would be that a change in V-RQOL score of about 25 to 30 points constitutes a clinically significant difference.

**CONCLUSIONS**

Patients with AdSD have a poor V-RQOL. Botox has a significant beneficial effect on this value for at least 6 injection cycles. The magnitude of the effect does not diminish with repeated injections over time. This study demonstrates the long-term effectiveness of Botox for treating patients with AdSD. It further illustrates the usefulness and validity of the V-RQOL Measure in the assessment of patients with dysphonia and their treatment outcomes.

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**REFERENCES**