Quality of Life and Voice Changes After a Single Injection in Patients With ADSD Over Time

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Summary: Introduction. Adductor spasmodic dysphonia (ADSD) is one of the most disabling voice disorders with no permanent cure. Patients with ADSD suffer from poor voice quality and repeated interruption of phonation that leads to limitations in daily communication. Botox (BT) injection, considered the gold standard treatment for ADSD, reduces the amount of voice breaks and improves voice quality for a limited period. In this study, patients with ADSD were followed after a single BT injection to track the changes in QOL and perceptual voice quality over a 6-month period.

Method. This is a prospective and longitudinal study. Fifteen patients with ADSD were evaluated preinjection and 1, 3, and 6 months postinjection. They completed the Voice Activity and Participation Profile-Persian Version (VAPP) and read a passage at each recording period. Perceptual assessment was done by three expert speech-language pathologists with knowledge of ADSD using the grade, roughness, breathiness, asthenia, strain (GRBAS) scale. The data were analyzed using Friedman, Wilcoxon, and McNemar tests. The significance level was set at \( P < 0.05 \).

Results. The VAPP total score and each of the domain scores reached their peak scores at 3 months postinjection. At 6 months postinjection, the VAPP scores increased significantly in comparison with the 3-month scores and were lower than preinjection scores. GRBAS results also indicated that patients’ voices at 1 and 3 months postinjection were significantly less severe in terms of strain and roughness (\( P = 0.01; P < 0.001 \), respectively).

Conclusion. BT injection resulted in improvement of subjects’ QOL. The improvement was greatest at 3 months postinjection but remained above the preinjection values at 6 months after injection. The voice quality also improved but was not judged as normal.

Key Words: Adductor spasmodic dysphonia–VAPP–GRBAS–Perceptual assessment–Quality of life.

INTRODUCTION

Spasmodic dysphonia is defined as a laryngeal focal dystonia with no clear pathophysiology. However, evidence of neurological dysfunction in the central nervous system (CNS) and above the brainstem, and genetic basis have been suggested as causes of spasmodic dysphonia. Spasmodic dysphonia as a rare chronic condition with a prevalence of 14 per 100,000 is task-induced dystonia appearing in three primary types: adductor, abductor, and mixed spasmodic dysphonia. Adductor spasmodic dysphonia (ADSD) is more common than the other types, with a female predominance (2.5:1). Onset is usually between 30 and 50 years of age. ADSD is characterized by involuntary spasms of the true vocal folds. The spasms lead to voice breaks and the perception of hoarseness or a strained quality of phonation. In some cases, vocal tremor also can be heard.

There is no permanent cure for spasmodic dysphonia. Botox (BT) injection continues to be the most common treatment for ADSD, with treatment lasting 3–4 months. BT injection has been reported as a safe method to treat spasmodic dysphonia, with occasional mild side effects reported by patients such as liquid aspiration and a breathy voice that will disappear in a short time after injection. Several authors have also reported surgical options as treatment for ADSD.

Several studies have used perceptual and self-assessment tools to track voice changes in ADSD patients following BT injection. The general conclusions from these studies indicate that voice quality improves after injection although the normal voice is not achieved. Langeveld et al found that although patients with ADSD do not experience any normal voice, they speak much more comfortably in comparison with their voice quality before injection. Nonetheless, most patients return for follow-up injections in approximately 3 months.

Previous studies have shown that ADSD negatively affects quality of life (QOL) and attitudes to communication. Studies of QOL found that patients with ADSD treated with BT show improved QOL and speech-related attitudes. Patients have reported that ADSD limits their professional activities, resulting in lower socioeconomic status, and negatively affects self-perception.

Studies of ADSD using the Voice Handicap Index (VHI-30 or VHI-10) and Voice-Related Quality of Life to evaluate patients with ADSD after BT injection relate to findings from one injection to the next.

The Voice Activity and Participation Profile was developed by Ma and Yiu based on the World Health Organization’s International Classification of Impairments, Disabilities, and Handicaps. This questionnaire has focused on different parts of daily activity in terms of job, daily communication, social communication, and emotion in addition to participation and activity restriction, and provides a framework for the study of QOL.
Previous investigators have assessed patients 4–8 weeks postinjection, but some conducted longer term follow-ups even up to 11 years. Silverman et al followed 30 patients for 12 weeks and immediately before reinjection. We do not know the exact time of re-injection while it varies for each patient. Geneid et al evaluated 17 patients 2 years and 13 patients 11 years after discontinuation of the treatment. They stated that after eleven years of the treatment, patients’ voices continued to improve. They did not state how many injections patients received before stopping the treatment. In another longitudinal study, Kim et al followed 30 patients 1, 3, and 6 months postinjection, but they focused more on the injection procedure than on how VHI scores changed over time. Rojas et al also completed a longitudinal study and reported that VHI scores were improved 37 and 137 days postinjection in 16 ADSD patients, suggesting that positive effects of BT injection continue over time.

To examine how QOL and perceptual voice quality change over time after a single injection, we followed Iranian patients with ADSD 1, 3, and 6 months postinjection, the point at which the pharmacological effects of BT were likely to have worn off. We also examined the severity of voice symptoms and patients’ feelings about their voice. Of note, this is the first report of the effects of BT injections on an Iranian population and the first to use the Voice Activity and Participation Profile—Persian version (V APPP) for ADSD patients.

The purpose of this prospective study was to determine the effects of BT injection on QOL and activities of daily living at 1, 3, and 6 months after injection. Of specific interest was to determine if improvement in aspects of daily living and voice quality were maintained after the typical period of BT effects ended.

METHOD
The Research Ethics Committee of Iran University of Medical Sciences approved the study procedures. This is a prospective, longitudinal study. The dependent variables were V APPP total score, all of seven V APPP domain scores including severity of the voice disorder, job, daily communication, social communication, emotions, the total score of the Activities Limitation Score (ALS) and the total score of the Participation Restriction Score (PRS), and finally, the perceptual voice quality scores based on grade, roughness, breathiness, asthenia, strain (GRBAS) judged by three experienced speech-language pathologists.

PARTICIPANTS
A total of 28 participants with spasmodic dysphonia were enrolled in the study from November 2016 until November 2017. Of these patients, 24 were diagnosed as ADSD and 3 as abductor SD. Differential diagnosis of ADSD was made based on previous protocols.

In short, an otolaryngologist and speech pathologist conducted video stroboscopic examinations and perceptual assessments at each of the time periods. Patients were selected if they had vocal symptoms 6 months or longer. Patients with any history of comorbid voice pathologies or diagnosed degenerative neurological disorders were excluded. Patients with previous BT injection, any surgical treatment, and voice therapy for treating ADSD were also excluded to control probable confounding biases.

All of the injections were performed by the otolaryngologist of the team (PD). The amount of 2.5 U was injected bilaterally in thyroarytenoid muscles. Among 24 patients who were diagnosed as ADSD, 8 patients chose not to receive BT injection because of personal or some medical issues, and 1 was not able to complete the V APPP form. The final sample of this study consisted of 15 patients. All patients signed a consent form and were aware that they were free to withdraw from the study without any adverse effects to their treatment.

SAMPLING AND OUTCOME MEASUREMENT
Perceptual assessment
Each participant completed the assessment battery (V APPP) before the injection and 1, 3, and 6 months post-BT injection. In every session of assessment, they read a standard Persian passage and prolonged vowel /a/. The voice samples recorded by Zoom Sound Recorder XYH5 (Zoom Company, Tokyo, Japan) equipped with two condenser microphones. Three expert voice therapists with at least of 3 years of experience in treatment and evaluating the patients with dysphonia assessed the voice samples based on GRBAS scale. Based on GRBAS scoring method, 0 was used for normal voice, 1 for mild, 2 for moderate, and 3 for severe voice disorder, in all five parameters including general voice quality, roughness, breathiness, asthenia, and strain. The examiners were blind to the purpose of the study and the order of the voice samples.

Voice Activity and Participation Profile
The Voice Activity and Participation Profile was developed based on the World Health Organization’s International Classification of Impairments, Disabilities, and Handicaps model by Ma and Yiu. There are two different parts that are based on the individual test parts, the ALS and PRS. These two elements evaluate the impact of a voice disorder based on limitation in activity and participation in communication. This tool was standardized for Finnish, Brazilian, and Italian population. The Persian version (V APPP) was standardized for Persian speakers in 2017.

Patients completed the V APPP questionnaire at each assessment session. The examiner provided the needed instructions on how to fill in the survey. The V APPP total score differs from 0 to 280 based on visual analogue scale (VAS). The overall rating was composed of 10 for severity of the voice disorder (1 item), 40 for the job (4 questions), 120 for daily communication (12 questions), 40 for social interaction (4 questions), and 70 for emotions (7 questions). Both ALS and PRS domains included 10 questions for each one and their scores varied from 0 to 100.

Statistical analysis
The Statistical Package for the Social Sciences, version 22.0 (SPSS, Inc., IBM Corp., Armonk, NY) was used for analysis of descriptive data and for comparison of the V APPP and GRBAS scores from the preinjection to 1, 3, and 6 months postinjection time points. For tracking the changes and analyzing the V APPP scores in all time points, the Friedman test applied because a
normal distribution could not be established. The Wilcoxon signed-rank test was applied as post hoc test for Friedman results provided the differences between each of the two time points. The perceptual data derived from GRBAS were analyzed by using McNemar test to compare each of the two time points.

RESULTS

A total of 28 participants with spasmodic dysphonia were enrolled in the study. Of these, 24 were diagnosed with ADSD and 3 as abductor spasmodic dysphonia. Out of 24 ADSD patients, there were 8 females and 16 males. The average age of ADSD participants was 47.71 (standard deviation [SD] = 13.83) with a range of 26–74 years. There were 15 (3 female) patients with ADSD who participated in the study. The mean (SD) of age and years from onset were 49.53 (13.29) and 3.1 (1.83), respectively. Of the 24 patients diagnosed with ADSD, 8 did not receive BT injection because of personal or medical issues. One patient was not able to complete the VAPPP form and was therefore excluded. The final group who completed the 6-month program consisted of 15 subjects.

VAPPP results

The VAPPP and its four domain scores plus the ALS and PRS scores are presented in Figure 1. Lower scores imply improved communication for voice activities and performance; the mean total VAPPP score for all 24 patients was 148.74 ± 7.09, and for patients who received BT injection was 139.68 ± 67.15. All scores showed statistically significant differences from preinjection to 1, 3, and 6 months postinjection periods except for the job and social domains as shown in Table 1. There was an increase in the job domain and in the emotional domain at 6 months compared with the preinjection scores as seen in Figure 1.

No significant differences were found between the preinjection and 6 months postinjection, and also between 1 month and 6 months postinjection for total VAPPP scores. The differences between preinjection and 1 month postinjection scores were significant except for the VAPPP total score. The scores were significantly different in the 3-month postinjection stage from the other time points for all of VAPPP scores (Table 1, Table 2).

Perceptual results

McNemar test analyzed the perceptual voice quality changes based on GRBAS from pre-to postinjection time points. The scores of each GRBAS parameters were divided into two groups. Scores of 0 and 1 were grouped as normal and 2 and 3 as abnormal for all parameters at different time points. We compared two different time points regarding two different situations: normal and abnormal. The descriptive results showed that at the 3-month postinjection time, most of the participants were grouped as “normal” (Table 3). We compared each of the two time points for both normal and abnormal scores. These results are presented in Table 4. As can be seen from preinjection to 1-month postinjection, roughness (R) and strain (S) improved significantly: that was the same for preinjection to the 3-month and 6-month postinjection time points. All parameters were degraded from 3 to 6 months postinjection, but the changes were significant only for overall grade (G).

DISCUSSION

The purpose of this study was to evaluate the perceptual voice changes and QOL in ADSD patients over a 6-month period following a single BT injection. The GRBAS and VAPPP scores demonstrated that the major effect of the BT was seen at the 3-month follow-up period. However, scores indicated improvement at the 6-month period compared with the preinjection scores. The data suggest that BT treatment of ADSD has both a primary and secondary effect on QOL and voice quality.

The results indicated that total VAPPP, daily communication, and emotional scores plus ALS and PRS improved after BT injection. Social communication did not improve significantly. Among all VAPPP scores, only the job score in 1-month postinjection was equal to preinjection. In a study done by Meyer et al 53% of patients claimed that spasmodic dysphonia reduced their productivity and imposed more negative effects on their work-related activities than on their personal activities.77 Patients with ADSD frequently experience negative emotions due to poor voice quality. The improvement in the emotional domain continued over time. The strongest results were obtained 3 months after injection for all VAPPP scores in comparison with 1 and 6 months’ time points. All VAPPP scores showed improvement from 3 months (mean = 77.15; SD = 50) to 6 months postinjection (mean = 114.11; SD = 61.01) but still is lower than preinjection score (mean = 138.80; SD = 69.41); Geneid et al stated that based on their experiences, the clinical effects of BT injection exceed the expected pharmacological effect of about three months in some instances.17 Davidson and Ludlow also believed that based on electromyography (EMG) signals, the reinnervation related to BT injection continues during 12 months postinjection.28 The results derived from the current study are in line with other studies that tried to evaluate the QOL in patients with ADSD after BT injection.

Most of the studies used the VHI to assess the effects of BT injection on patients with ADSD like Benninger et al,10 Wingate et al,26 and Hartman et al.25 Here, the scores improved significantly 4 to 8 weeks postinjection. They did not follow the patients beyond 4 or 8 weeks. One report that continued to follow patients 6 months after BT injection was done by Kim et al using VHI to track the changes. They did not report VHI changes at specific time points but rather stated that patients’ scores improved significantly after treatment.25 Rojas et al investigated the VHI score changes following BT injection. Their results indicated that 30 days (1 month) after injection, overall VHI decreased significantly, but after an average of 137 days (about 5 months), the scores increased but still remained lower than preinjection scores.30 Hogikyan et al showed that Voice-Related Quality of Life overall and domain scores improved significantly 6 weeks after first and second injections. Their results showed that the pre to post changes after the first injection were greater than ones for the second injection. They did not report any data from weeks 6 to 21 at which time patients received the second injection. However, in contrast to their results, our patients’ scores were still better at follow-up than the preinjection scores.40 Silverman et al indicated that patients achieved the best scores at 3 weeks compared with scores at 7 and 12 weeks postinjection.23 In the present study, the best scores were achieved at 3 months.
FIGURE 1. Box plots to show median, minimum, and maximum scores of total VAPPP and its domain.
(about 12 weeks) postinjection. At 1-month postinjection time point, only VAPPP total score showed a significant difference from the preinjection score and the other domains’ scores did not significantly improve.

Three experienced speech-language pathologists used the GRBAS scale to evaluate the voice samples obtained at each recording period. Although the subjects’ voices were not in the normal range at any time point, the results showed that GRBAS parameters improved over the postinjection periods. Voice quality scores were best at 1 and 3 months postinjection, when Roughness (R) and Strain (S) decreased significantly. From pre- to 1-month postinjection, there was a nonsignificant improvement seen for Grade. When comparing pre- with 6 months postinjection, the severity of all parameters was at a lower level, but the difference was significant only for Roughness and Strain. To compare the results of the current study with other similar studies, we could refer to Silverman et al, who reported that their patients achieved their best voice quality 12 weeks after BT injection.23 In our study, the patients’ voices at 1 and 3 months postinjection time were better than the other two time points, while patients’ voice quality after 3 months was at its best status. Hartmann et al used GRB to follow the voice changes after injection and found that only Roughness was reduced significantly 4–8 weeks postinjection. 25 Damrose et al showed that even after repeated BT injection, the patients’ voice quality were still significantly different from a normal group. 19 Our patients received only one BT injection; their voice quality based on GRBAS after 6 months was judged improved in comparison with preinjection time.

The present study differs from previous studies in that for the present study, one injection was tracked for a specific period, a period longer than the expectation for a BT effect. Although more than 15 patients initially began the study, some chose to receive BT before the 6-month follow-up. The present results suggest

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<tr>
<th>TABLE 1. The VAPPP Scores’ Changes From Pre- to Postinjection</th>
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<tr>
<td><strong>VAPPP Domains</strong></td>
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* Values in bold are statistically significant. Abbreviation: df, degree of freedom.

| TABLE 3. GRBAS Descriptive Results From Pre- to Postinjection |
|-------------------------|-----------------|-----------------|-----------------|-----------------|
|                         | Preinjection | 1 Month         | 3 Months        | 6 Months        |
|                         | Grade—N (%)  |                 |                 |                 |
| 0                       | 0             | 0               | 1 (6.7)         | 0               |
| 1                       | 0             | 4 (26.7)        | 10 (66.7)       | 2 (13.3)        |
| 2                       | 5 (33.3)      | 11 (73.3)       | 3 (20)          | 11 (73.3)       |
| 3                       | 10 (66.7)     | 0               | 1 (6.7)         | 2 (13.3)        |
| Roughness—N (%)         |               |                 |                 |                 |
| 0                       | 0             | 1 (6.7)         | 7 (46.7)        | 2 (13.3)        |
| 1                       | 2 (13.3)      | 8 (53.3)        | 6 (40)          | 8 (53.3)        |
| 2                       | 4 (26.7)      | 6 (40)          | 1 (6.7)         | 4 (26.7)        |
| 3                       | 9 (60)        | 0               | 1 (6.7)         | 1 (6.7)         |
| Breathiness—N (%)       |               |                 |                 |                 |
| 0                       | 9 (60)        | 5 (33.3)        | 12 (80)         | 12 (80)         |
| 1                       | 4 (26.7)      | 8 (53.3)        | 2 (13.3)        | 3 (20)          |
| 2                       | 0             | 2 (13.3)        | 1 (6.7)         | 0               |
| 3                       | 2 (13.3)      | 0               | 0               | 0               |
| Asthenia—N (%)          |               |                 |                 |                 |
| 0                       | 9 (60)        | 12 (80)         | 13 (86.7)       | 10 (66.7)       |
| 1                       | 6 (40)        | 3 (20)          | 2 (13.3)        | 5 (33.3)        |
| 2                       | 0             | 0               | 0               | 0               |
| 3                       | 0             | 0               | 0               | 0               |
| Strain—N (%)            |               |                 |                 |                 |
| 0                       | 0             | 6 (40)          | 7 (46.7)        | 2 (13.3)        |
| 1                       | 1 (6.7)       | 6 (40)          | 5 (33.3)        | 5 (33.3)        |
| 2                       | 5 (33.3)      | 3 (20)          | 3 (20)          | 4 (26.7)        |
| 3                       | 9 (60)        | 0               | 0               | 4 (26.7)        |

* Values in bold are statistically significant.
that while short-term changes in QOL and voice quality are expected after BT injection, longer term effects can also be seen. Patients and clinicians should be aware of these changes as they counsel patients regarding treatment of ADSD.

CONCLUSION
Positive effects of BT to treat ADSD include changes in QOL and voice quality. These changes can be seen after the expected period of time that the medication is effective.

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