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Adductor Spasmodic Dysphonia: Botulinum Toxin A Injections or Laser Thyroarytenoid Myoneurectomy? A Comparison From the Patient Perspective

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Objectives/Hypothesis: The current gold standard of therapy for adductor spasmodic dysphonia (AdSD) is injection of botulinum toxin A (BTX) in the adductor musculature. A surgical procedure could potentially offer more stable and long-lasting voice quality. In this study, we report the long-term results of endoscopic laser thyroarytenoid (TA) myoneurectomy versus BTX treatment in the same patients with AdSD.

Study Design: Retrospective case series.

Methods: Between July 2013 and September 2016, a total of 22 patients with AdSD were included. Voice outcomes were measured using the Voice Handicap Index and a Likert-scale patient-reported voice questionnaire. Data were obtained for each patient at four time points: preoperatively with and without BTX and twice postoperatively at 3 months (short term) and 12 months (long term).

Results: No statistically significant differences were found between voice outcome after BTX injection and the short- and long-term postoperative voice outcomes for the group as a whole. During postoperative follow-up, 10 of the 22 patients (45%) needed a second procedure after an average of 18 months (interquartile range, 13–22 months) due to recurrence of their original voice problem.

Conclusions: The TA myoneurectomy showed encouraging results, comparable to BTX after follow-up of 12 months for the group as a whole. However, after good results initially, voice deterioration was seen in 45% of the patients who all underwent a second procedure. These preliminary results provide important insights into the value of TA myoneurectomy as a potential definite treatment for a select group of patients with AdSD. Further research might explore long-term results after revision surgery.

Key Words: Adductor spasmodic dysphonia, thyroarytenoid myoneurectomy, botulinum toxin.

Level of Evidence: 4

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INTRODUCTION

Spasmodic dysphonia, which is classified as focal laryngeal dystonia, is characterized by involuntary endolaryngeal constriction during phonation. The vocal folds are normal at rest, but with an action-induced task-specific movement, the muscles contract inappropriately.¹ This contraction results in an interrupted voice pattern with reduced voice quality, leading to functional and communication problems with extensive effects on quality of life.² The etiology is unknown, but the origin of spasmodic

dysphonia is generally considered to be at the level of the central nervous system. One potential cause is an imbalance of sensory and motor signaling originating in the basal ganglia,³ although evidence from functional magnetic resonance imaging suggests a more heterogeneous localization in the brain (e.g., the somatosensory cortex).⁴

There are two major forms of spasmodic dysphonia: adductor and abductor spasmodic dysphonia. This study focuses on the management of adductor spasmodic dysphonia (AdSD), the more common form of spasmodic dysphonia, which is found in approximately 85% of cases.⁵

The current gold standard of therapy is the administration of botulinum toxin A (BTX) injections in the adductor musculature, causing a temporary chemical denervation of the injected adductors resulting in an incomplete glottal closure by a paresis of the vocal folds.⁶ Significant improvement in voice quality can be accomplished with BTX in the outpatient setting. However, there are several drawbacks of BTX injections. One of them is the need to repeat the injections. The duration of improvement of symptoms varies by individual, but on average it lasts 3 to 6 months.⁷ After an injection, an initial period of breathiness usually leads to a decline in voice quality.⁸ Optimal voicing is achieved during only 30% of the injection cycle, as a result of either awaiting the full therapeutic effect or experiencing a

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therapeutic decline.^{2,7} This rollercoaster effect results in an unpredictable voice and is associated with emotional stress with high impact on quality of life.² Other disadvantages are the lack of uniform results among and within patients, the financial burden of repeated injections, and repeated office visits with time off from work and travel expenses.⁷ Therefore, there is a need for alternative treatments that can offer a more stable and long-lasting beneficial effect. Surgical procedures potentially offer a more definite solution. However, the best surgical procedure for more long-lasting results in reducing the endolaryngeal constriction activity is still unclear.

Although several surgical techniques have been described, over the last 10 years the majority of literature reports on two commonly performed surgical procedures: thyroplasty type II (TP II) and endoscopic laser thyroarytenoid (TA) myoneurectomy.⁹ TP II is a procedure that relieves the symptoms of AdSD by decreasing the excessive closure of the glottis by dividing and separating the thyroid cartilage in the midline and fixing it with a silicone shim or titanium bridge to slightly widen the distance between the vocal fold at the level of the anterior commissure.^{5,10–12} This is in contrast to a TA myoneurectomy procedure, which targets the end organ of AdSD by removing the thyroarytenoid muscle, terminal nerves, and neuromuscular junction. By resecting most of the TA muscle, an attempt is made to prevent muscle regeneration, potentially resulting in a long-lasting effect.⁵ Nomoto et al. compared the outcomes of TP II with TA myoneurectomy.⁹ Voice quality improved in both procedures, but significant differences in severity outcomes favoring TA myoneurectomy were found in strangulation, interruption, tremor, and grade.⁹ Another advantage of TA myoneurectomy is the relative simplicity of the standard endoscopic laser procedure, which does not require a cervical incision. Recent studies suggest that the long-term outcomes of TA myoneurectomy are encouraging.^{13–16} For these reasons, we prefer TA myoneurectomy as the primary surgical procedure for AdSD in our institution.

To the best of our knowledge, a comparison between the gold standard BTX therapy and surgery has never been made. However, this comparison is essential to determine if surgery can provide more reliable voice quality and whether it outweighs the benefits of BTX treatments. Therefore, the first aim of this study was to evaluate the short- and long-term voice outcomes as measured by patient report after TA myoneurectomy. The second aim was to compare those results with the voice outcomes with BTX treatment in the same patient with AdSD.

MATERIALS AND METHODS

Patient Characteristics

Between July 2013 and September 2016, a total of 22 patients with AdSD underwent a TA myoneurectomy by the same surgeon (A.P.M.L.). All patients were available for long-term postoperative follow-up defined as 12 months or longer. Preoperatively, every patient had received at least 2 years of BTX treatment and showed voice improvement after injections.

Selection criteria for surgery were as stated by Tsuji et al.: 1) AdSD diagnosis made by a team of experienced

otorhinolaryngologists and speech therapists, 2) previous improvement of voice quality after BTX injection into the thyroarytenoid muscle, 3) patient's decision opting for surgery to obtain definitive treatment, and 4) patient's informed consent for surgery.¹⁶ None of the patients had a vocal tremor in addition to their dysphonic breaks. Demographic data, including gender, age, and history of previous treatments, were obtained from all patients. This study was approved by the local medical ethics committee.

Surgical Technique

The concept of a TA myoneurectomy is to remove a triangular piece of the TA, including the nerve fibers of the recurrent laryngeal nerve terminating at the TA, while preserving the vocal ligament and its covering, as described by Tsuji et al.¹⁶

Voice Evaluation

Voice outcome was assessed using the validated Voice Handicap Index (VHI) and a nonvalidated patient-reported questionnaire on voice-related topics. The VHI, developed by Jacobson and Grywalski and validated for the Dutch language by Verdonck-de Leeuw et al.,¹⁷ consists of 30 items designed to assess how patients perceive their voice from three aspects: functionally, physically, and psychologically.^{9,18} Each response is scored from 0 (no complaints) to 4 (maximal complaints), with a final score ranging from 0 to 120.¹⁸ Differences in scores of 10 points are considered clinically relevant for individuals in clinical practice, and differences in scores of 15 points are considered relevant in study designs.^{17,19,20} The median value for the VHI score in the general population is 6.²¹

The nonvalidated voice-related questionnaire was a self-assessment Likert scale (SALS) developed in our center. The SALS consists of 10 items (three domains, with four items on voice, three items on communication, and three items on swallowing). In the domains voice and communication, each response is scored from 0 (maximal complaints) to 10 (no complaints). The swallowing domain is scored conversely. An English translation is available online (see Supporting Figure 1 in the online version of this article).

For each patient, voice outcome measurements (VHI + SALS) were performed at four separate time points. The first was obtained prior to surgery, when the effect of previous BTX injections had faded away and the voice was at its baseline quality without BTX. The second voice outcome measurement was obtained prior to surgery, at the time of the best voice achieved after a BTX injection as perceived by the patient. Because all patients had multiple BTX injections in the past and were familiar with their effects, they knew how to judge when the effect of the BTX injection was at its peak or when the beneficial effect of the injection had worn off and their voice quality was at the baseline quality. They were asked to report to the clinic for the two preoperative voice measurements at these times. The third and fourth sets of voice outcome data were obtained at 3 and 12 months after surgery.

Statistical Analysis

SPSS for Mac version 24 (IBM, Armonk, NY) was used to analyze the collected data. Descriptive statistics were calculated for each variable. Statistical analyses were performed using the Wilcoxon signed rank test for paired variables to compare the pre- and postoperative voice quality outcomes. To investigate the responders versus the nonresponders to find any correlation, the χ^2 and Fisher exact test were used to compare the nominal data (gender, comorbidity). The independent-samples *t* test was used for the number of years of previous BTX use, and the Mann-Whitney test was used to compare the voice-quality outcomes.

TABLE I.
Demographic and Clinical Data.

	Frequency (%)	Median	Interquartile Range
Gender			
Female	14 (63.6%)		
Male	8 (36.4%)		
Age, yr		50	44.3–62.3
Preoperative BTX treatment, yr		5.5	3–13.5
Postoperative follow-up, mo		30	26.8–36.3
Multifocal dystonia			
Absent	18 (81.8%)		
Present	4 (18.2%)		

BTX = botulinum toxin A.

The Bonferroni correction was used to correct for multiple testing. To estimate the risk of type II errors, we executed a post hoc two-sided power analysis in R Studio for Mac version 1.1.442 (RStudio, Inc., Boston, MA). Considering the number of included patients, this study would have 90% power to pick up a mean difference of ≥ 0.95 , ≥ 1.65 , or ≥ 5.29 between pre- and postmeasurements for 22, 10, or four included patients, respectively.

RESULTS

A total of 22 patients were included for analysis. Every patient had at least 1 year of follow-up after surgery. Demographic data are summarized in Table I. Ages ranged from 25 to 75 years, with a median age of 50 years. The majority of patients in this study were female (64%). Preoperatively, each patient had received multiple years of BTX treatments, with a median of 5.5 years. Four patients had a multifocal form of dystonia (one of the tongue, one of the hand, and two of the arms). The median follow-up was 30 months, with an interquartile range of 27 to 36 months.

The mean voice outcomes of the VHI and SALS are summarized in Table II. The results of the SALS swallowing

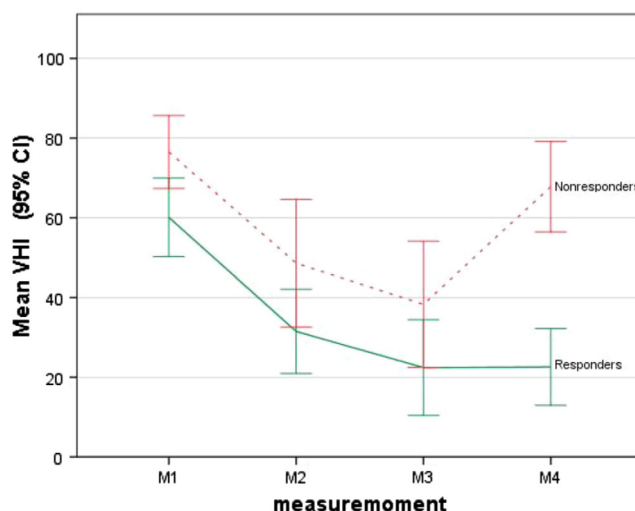


Fig. 1. Mean VHI score for responders versus nonresponders. CI = confidence interval; VHI = Voice Handicap Index. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

domain are not included in the table because none of the patients had swallowing problems pre- or postoperatively.

The results show that the preoperative VHI and SALS outcomes improved significantly with BTX injections (M1-M2, Table II). Comparing the gold standard of BTX treatment with postoperative voice outcomes (VHI and SALS) at 3 months, neither statistically significant differences nor clinically relevant differences (VHI difference score of 9.63) were found (M2-M3, Table II). Twelve months postoperatively, no statistically significant or clinically relevant differences (the VHI difference score was 3.87 points) were found compared to the voice outcome with BTX for the group as a whole (M2-M4, Table II).

Looking at the voice outcomes 12 months postoperatively, the overall voice outcome tended to be slightly deteriorated compared to the voice outcome 3 months

TABLE II.
Mean Pre- and Postoperative Outcomes VHI and Self-Assessment Likert Scale on Voice-Related Topics.

	M1, Mean (SD)*	M2, Mean (SD) [†]	P1, M1-M2	M3, Mean (SD) [‡]	P2, M2-M3	M4, Mean (SD) [§]	P3, M2-M4
Voice quality	3.95 (1.46)	7.68 (1.56)	.000	7.64 (1.43)	.752	6.48 (2.04)	.041
Voice function	2.91 (1.97)	7.09 (1.93)	.000	7.73 (1.91)	.179	5.68 (2.77)	.101
Voice volume	4.68 (1.78)	7.27 (1.80)	.000	7.82 (1.62)	.292	7.27 (2.10)	.895
Voice influence	2.18 (1.89)	4.95 (3.47)	.004	6.64 (3.40)	.107	5.91 (3.58)	.364
Communication with friends	5.73 (2.41)	8.86 (1.52)	.000	8.82 (1.44)	.972	7.68 (2.34)	.064
Communication with strangers	4.73 (2.19)	8.50 (1.77)	.000	8.68 (1.49)	.610	7.86 (2.30)	.285
Communication in reading	2.14 (1.83)	6.45 (2.46)	.000	7.00 (2.66)	.095	5.50 (3.70)	.372
VHI	67.55 (16.32)	39.27 (20.87)	.000	29.64 (21.50)	.040	43.14 (27.57)	.639

The assessment of voice outcome (VHI + SALS) significantly improved preoperatively with BTX compared to the preoperative voice quality without BTX (P1 M1-M2). Three months following the operation, there were no statistically significant differences in voice outcomes compared to the preoperative voice with BTX (P2 M2-M3). Twelve months following the operation, none of the voice outcome scores differed significantly from the preoperative measurement with BTX (P3 M2-M4).

*M1 = preoperative measurement of voice without BTX.

[†]M2 = preoperative measurement of voice with BTX.

[‡]M3 = 3-month postoperative measurement of voice.

[§]M4 = 12-month postoperative measurement of voice.

^{||}Statistically significant difference ($P < .006$; $\alpha = .05$, with Bonferroni correction).

BTX = botulinum toxin A; SALS = self-assessment Likert scale; SD = standard deviation; VHI = Voice Handicap Index.

postoperatively, although no statistically or clinically relevant differences for the group as a whole in mean VHI scores for study design were found (the VHI difference score was 13.5 points). This downward trend could be explained by discriminating between patients who eventually underwent a second procedure (nonresponders) and those who did not (responders), with the two groups having a mean VHI score of 68 points and 23 points, respectively ($P = .000$) (Fig. 1, Table III) at M4 (12 months postoperatively). This discrepancy between responders and nonresponders in mean VHI score was also found at the earlier measurements (Table III). The nonresponders seemed to have a higher VHI score at M1 (Fig. 1, Table III). This difference was statistically significant and clinically relevant, as the VHI difference score was 16 points (Table III). Additionally, the mean difference scores of the VHI at M2 (preoperative measurement with BTX) and M3 (3 months postoperatively) in the responders versus nonresponders were both clinically relevant (17 points at M2 and 16 points at M3) in favor of the responders, although not statistically significant (Table III).

During follow-up of more than 12 months, 10 of the 22 (45%) patients turned out to be nonresponders. They all underwent a second procedure because their voice deteriorated due to recurrence of their dystonic voice. Median time between the first and second procedure was 18 months, with an interquartile range of 13 to 22 months.

The voice outcomes of all 10 reoperated patients 3 months after the second procedure seemed comparable to their voice results with BTX treatment, with no statistically significant differences (M2-M5, Table IV). At present, only four patients have completed the 12-month follow-up measures after their second procedure (M6). In those four patients, although the group was too small to run statistics tests, voice deterioration was seen 12 months after their second surgery (Table IV). When their 12-month postoperative voice outcomes were compared to their voice outcomes 3 months after resurgery, a clinically relevant deterioration of voice outcome with a VHI difference score of 26.2 was found. In those reoperated patients, although not statistically significant, a clinically relevant difference was found when comparing M1 (baseline voice quality

TABLE III.

Differences in VHI Between Responders and Nonresponders.

Measure Moment*	Responders, Mean (SD)	Nonresponders, Mean (SD)	<i>P</i>
M1	60.08 (15.51)	76.50 (12.80)	.009 [†]
M2	31.50 (16.64)	48.60 (22.37)	.041
M3	22.42 (18.90)	38.30 (22.10)	.038
M4	22.58 (15.81)	67.80 (15.89)	.000 [†]

The data show the different median VHI scores between responders who did not need a second intervention and nonresponders who eventually underwent a second procedure.

*M1 = preoperative measurement of voice without BTX. M2 = preoperative measurement of voice with BTX. M3 = 3-month postoperative measurement of voice. M4 = 12-month postoperative measurement of voice.

[†]Statistically significant difference ($P < .0125$; $\alpha = .05$, with Bonferroni correction).

BTX = botulinum toxin A; SD = standard deviation; VHI = Voice Handicap Index.

TABLE IV.
Mean VHI and Self-Assessment Likert Scale on Voice-Related Topics Outcomes After Reoperation.

	M5, Mean (SD), N = 10*	<i>P</i> , M2-M5 [†]	M6, Mean (SD), N = 4*
Voice quality	7.50 (1.27)	.722	8.50 (5.07)
Voice function	7.60 (1.84)	.337	4.50 (1.92)
Voice volume	7.00 (2.40)	.512	6.25 (2.99)
Voice influence	7.20 (1.93)	.074	5.00 (.82)
Communication with friends	8.70 (1.49)	.713	6.25 (2.06)
Communication with strangers	8.60 (1.43)	.496	6.00 (1.83)
Communication in reading	6.60 (1.96)	.497	4.25 (.96)
VHI	31.30 (16.30)	.059	57.50 (12.12)

There were no statistically significant differences in voice quality after the second surgery compared to their preoperative voice with BTX.

*Statistically significant difference ($P < .006$; $\alpha = .05$, with Bonferroni correction).

[†]M2 = preoperative measurement of voice with BTX, measured within the same reoperated patient. M5 = 3-month postoperation measurement of voice (group consisted of 10 nonresponders). M6 = 12-month post-reoperation measurement of voice (group consisted of four nonresponders).

BTX = botulinum toxin A; SD = standard deviation.

without BTX) with M6, with a mean VHI difference score of 76.50 points at M1 versus 57.50 points at M6.

No statistically significant prognostic factors could preoperatively be identified for the nonresponders (gender, age, number of preoperative BTX treatment years or presence of multifocal dystonia, or preoperative SALS scores) (Table V). However, as described in Table III, there was a clinically relevant VHI-difference score at M1 and M2 between the responders versus nonresponders in favor of the responders, although at M2 it was not statistically significant.

Other than the surgical removal of granuloma tissue in three patients, no complications or side effects were found. Moreover, on the standard 12-month postoperatively performed videolaryngostroboscopy, no interference due to postoperative impairment of the mucosal wave was seen.

TABLE V.

Potential Preoperative Predictors for Nonresponders.

Gender	NS
Age	NS
Preoperative BTX treatment	NS
Comorbidity	NS
Preoperative SALS scores (with and without BTX)	NS

No preoperative prognostic factors could be identified for the non-responder group. Neither gender, age, number of preoperative BTX treatment years, presence of multifocal dystonia (comorbidity), or preoperative voice quality measured with a SALS with and without BTX could identify the nonresponder group preoperatively.

BTX = botulinum toxin A; NS = not significant; SALS = self-assessment Likert scale.

DISCUSSION

The current gold standard of therapy for AdSD is the administration of BTX injections in the adductor musculature. Although considerable improvement in voice is accomplished after a BTX injection, the rollercoaster effect, in which optimal voicing is achieved only during 30% of the cycle of repeated injections, has a high impact on quality of life.² The present study was designed to determine if a TA myoneurectomy can provide a more reliable voice quality and how these results compare to the voice outcome after BTX treatment in the same patient. Because the rollercoaster effect leads to a great deal of social and emotional stress, we were focused on the voice outcome from the patient perspective.

The first aim of this study was to assess the short- and long-term voice outcomes after TA myoneurectomy. The short-term effect was defined as 3 months and the long-term effect as 12 months, on the assumption that a steady state would be reached by then.

Our group level results are in line with those published in previous studies, which found a beneficial effect of TA myoneurectomy 1 year after the procedure.^{9,13,16} However, during further follow-up (after 18 months on average), 10 of the 22 patients (45%) eventually needed a second procedure because of recurrence of their dystonic voice problem. When comparing the voice outcomes of the nonresponders group with the voice outcomes of the patients who did not need a second surgery (responders), a significant difference in voice outcomes is revealed. Twelve months after the first surgery, the nonresponders showed a significant voice deterioration compared to the responders. This finding suggests that a stable long-term voice outcome after TA myoneurectomy could only be accomplished in 12 of the 22 patients (55%). We do not know why the symptoms of AdSD reoccurred in the nonresponders (45% of the patients). One might hypothesize that the reoccurrence means that there was not enough muscle and/or nerve resected during the first operation, which would mean that the relapse of AdSD was caused by reinnervation of remnant muscle. Another explanation could be the central activation of other intrinsic laryngeal adductor muscles, such as the lateral cricoarytenoid muscle, due to the underlying dystonia. A third cause for recurrence of the symptoms could possibly be the degree of fibrosis mimicking the TA anatomically. This effect potentially leads to excessive closure by dystonic activity in the remaining adductor muscles. Preoperative predicting factors for the nonresponders could not be identified. However, the preoperative VHI scores seemed to be higher in the nonresponder group, in particular the VHI scores with BTX. A potential predictor for postoperative response could be the preoperative response to BTX treatment on voice quality. Given the small group size, it is not possible to go beyond speculating about the potential predictors for the nonresponder group.

Three months after their second surgery, the same good short-term voice outcome was achieved in all 10 reoperated patients. However, the voice outcomes 12 months after reoperation showed a downward trend. In the small group of four patients who completed the 12-month measure,

outcomes did not appear to show much long-term benefit. We compared the baseline VHI scores of those four reoperated patients with their VHI scores 12 months after their second surgery and could not find statistically significant differences. There appeared to be a clinically relevant difference in favor of the postoperative VHI scores. However, looking at the downward trend, we expected the VHI scores to decrease more over time in the nonresponders. This suggests that there is not much patient-reported long-term effect over and above baseline measures in the nonresponders. Further long-term results (i.e., 3–5 years after the second surgery) are being collected and will be reported in a future publication.

The second aim of our study was to evaluate whether a TA myoneurectomy outweighs the benefits of BTX treatments. As stated in the systematic review by Van Esch et al., no clinical trial has been conducted to compare the effect of BTX injections with surgery among AdSD patients.²² They concluded no preference for a particular surgical or long-term treatment could be advised.²² Our study is the first to compare the effect of TA myoneurectomy with the current gold standard of therapy, BTX injection. Our results showed no statistically significant differences between the patient-reported voice outcomes measured 3 or 12 months after TA myoneurectomy and the best voice outcomes after BTX treatment. Although the results were positive for the group as a whole, the 10 nonresponders out of 22 patients required a second surgery, and long-term results for this group of patients remain unknown. Therefore, it is not possible to draw conclusions for the reoperated patients. However, our results suggest that a stable long-term voice outcome can be accomplished after TA myoneurectomy, equal to the results after BTX treatment in some of the patients (the responder group). Taking into account that the duration of the beneficial effect of BTX is temporary and part of a rollercoaster cycle, the effect of surgery could be more favorable in the end.

Although not the aim of the study, when retrospectively asked during further follow-up, all responder patients in our cohort would describe their quality of voice with BTX at its peak effect as a little better than their voice quality after surgery. This statement was in contrast to our prospectively collected results, showing no significant differences in postoperative voice outcome with BTX. A possible explanation for this discrepancy could be the bias caused by the patient-reported nature of our results and the retrospective character of the question.

Despite this difference, all patients preferred TA myoneurectomy as a treatment because, as they all stated, the advantage of having a more stable and reliable voice causes essential improvements in social confidence by taking away the rollercoaster effect of BTX treatments. Moreover, none of the patients in our study worsened or had any significant complications after TA myoneurectomy.

However, a significant limitation of our study, besides the potential bias due to the subjective character of our outcome measures, was that patients were not randomly assigned but all voluntarily opted for surgery. This self-selection into treatment could potentially lead to a highly biased study population. For example, only 64% of the patients in our study were female, whereas 80% of AdSD

patients are female.²³ Therefore, it is unknown whether our results could be generalized to the broader AdSD population. The small study population was another methodological limitation in this study.

CONCLUSION

The current standard of therapy for AdSD, consisting of BTX injections, has some serious disadvantages, including the need for repeated injections, which creates a roller coaster effect. A TA myoneurectomy could potentially offer a more definite solution, as was shown in previous studies. This is the first study designed to compare the long-term (12 months) voice outcome after TA myoneurectomy with the voice outcome after BTX. A stable, long-term, self-reported voice outcome, equal to the results after BTX treatment, was accomplished after TA myoneurectomy in 55% of the patients. After initially good short-term results, voice deterioration was seen in 45% of the patients during follow-up. The long-term results after a second procedure are still unknown. None of the patients worsened after surgery, and no significant complications occurred during this study. These preliminary results provide important insights into the value of TA myoneurectomy as a potential definite treatment for a select group of patients with AdSD. Further research might explore the long-term results after reintervention and whether these results could be generalized to the broader AdSD population.

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