Treatment for spasmodic dysphonia: limitations of current approaches

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Abstract

Purpose of review—Although botulinum toxin injection is the gold standard for treatment of spasmodic dysphonia, surgical approaches aimed at providing long-term symptom control have been advancing over recent years.

Recent findings—When surgical approaches provide greater long-term benefits to symptom control, they also increase the initial period of side effects of breathiness and swallowing difficulties. However, recent analyses of quality-of-life questionnaires in patients undergoing regular injections of botulinum toxin demonstrate that a large proportion of patients have limited relief for relatively short periods due to early breathiness and loss-of-benefit before reinjection.

Summary—Most medical and surgical approaches to the treatment of spasmodic dysphonia have been aimed at denervation of the laryngeal muscles to block symptom expression in the voice, and have both adverse effects as well as treatment benefits. Research is needed to identify the central neuropathophysiology responsible for the laryngeal muscle spasms in order target treatment towards the central neurological abnormality responsible for producing symptoms.

Keywords

botulinum toxin injection; denervation; myectomy; reinnervation; thyroplasty

Introduction: the spasmodic dysphonias

Spasmodic dysphonia is a primary task specific focal dystonia affecting the laryngeal muscles during speech. Adductor spasmodic dysphonia (ADSD) affects close to 90% of spasmodic dysphonia patients is characterized by voice breaks during vowels during speech due to intermittent hyperadduction of the vocal folds [1]. Abductor spasmodic dysphonia (ABSD) is relatively rare and involves intermittent voiceless voice breaks due to prolonged voiceless consonants before initiation of the following vowels [2]. Approximately, one-third of patients with spasmodic dysphonia also have action induced focal vocal tremor [3,4]. This differs from essential voice tremor alone which can affect many of the head and neck muscles, is much less focal and is manifest at rest [5].

Previous treatments for the spasmodic dysphonias

Dedo first introduced treatment for spasmodic dysphonia; a unilateral section of the recurrent laryngeal nerve (RLN) [6]. This temporarily denervated many of the laryngeal muscles on one side of the larynx: the thyroarytenoid, the lateral cricoarytenoid (LCA), and
the posterior cricoarytenoid (PCA). Section was performed on the left side because of the longer recurrent nerve on the left was more susceptible to injury [7]. By leaving the right side intact, the side less likely to be injured, the risk of the patient developing bilateral paralysis was reduced. However, some patients did suffer breathing problems as a result of the surgery [8]. Shortly after the introduction of this surgery, however, it became apparent that symptoms returned in many patients within a few years [9] due to reinnervation of the recurrent nerve [10,11]. The return of symptoms with reinnervation demonstrated that the nerve paralysis was not changing the disorder but rather only interfering with the symptoms being apparent during speech.

Surgical approaches for treatment of spasmodic dysphonia have been aimed at preventing the symptoms from being manifest in the voice via partial-muscle denervation or total-muscle denervation. These include myoectomies [12–15], unilateral RLN avulsion [16,17] and bilateral denervation with reinnervation of the thyroarytenoid [18,19]. Myoectomies excise muscles of the larynx; either the thyroarytenoid, LCA, or the PCA muscle [12]. These procedures can be performed through a thyroid cartilage window or by endoscopic means [15,18]. Voice breaks can be reduced, although vocal harshness may result and lasting benefit has been unpredictable.

Laryngoplasties involve changing the cartilaginous skeleton of the larynx, either through anterior commissure push back to reduce the tension on the folds, which lowers the pitch [20], or medialization of the vocal folds for ABSD [21]. Recently Isshiki et al. [22,23] has proposed the use of type II thyroplasty widening the thyroid cartilage for ADSD, although others have not found benefit to patients with this technique [24].

The denervation/reinnervation procedure is aimed at providing a permanent thyroarytenoid denervation by reinnervating the RLN branch to the thyroarytenoid muscle with a branch from the ansa cervicalis to block reinnervation bilaterally [18]. The surgery is helpful only for patients with adductor spasmodic dysphonia without tremor and not for ABSD or essential voice tremor. Chronic breathiness is more likely in men who may not benefit as much as women. Because of recurrence of symptoms in some women, myectomy of the LCA muscle was added to improve outcome [25].

The only treatment for ADSD demonstrated to be effective by a controlled clinical trial, albeit small, is the bilateral injection of small amounts of botulinum toxin into the adductor muscles (thyroarytenoid primarily) [26]. The toxin initially blocks the release of acetylcholine at endplates in the region of injection in the muscle. Within a few weeks of injection, the nerve endings begin to sprout and innervate new fibers. However, many of these new sprouts do not survive and reinnervation at the original endplates begins around 2 months and symptoms gradually return as reinnervation becomes complete after 4–5 months [27]. Although the bilateral partial thyroarytenoid denervation with botulinum toxin is beneficial in over 90% of ADSD patients [28] some change in the central nervous system disorder may also account for symptom reduction as spasms are reduced in untreated muscles in patients with ADSD [29].

**Diagnosis of spasmodic dysphonia**

Surgical treatment options for spasmodic dysphonia may involve permanent structural changes to the larynx, whereas medical or behavioral therapies are transient. Spasmodic dysphonia is a chronic disorder, whereas functional voice disorders can respond to behavioral or medical therapies. Often functional dysphonia can involve psychological factors [30] and be effectively treated by voice therapy alone [31] whereas surgery is applicable to treating chronic stable disorders. Because voice therapy is noninvasive, a trial of voice therapy is often recommended before botulinum toxin injections are considered.
adding to the expense of management and delaying effective treatment. In turn, surgery is used primarily with ADSD patients who have responded well to botulinum toxin injection [18] desiring a long-term approach to symptom control. Therefore, patients may undergo voice therapy, botulinum toxin, then RLN denervation/reinnervation before being managed successfully. For this reason, accurate methods, for the diagnosis of spasmodic dysphonia was identified, as the highest priority for research in spasmodic dysphonia [32**].

Appropriate treatment is also dependent upon the type of spasmodic dysphonia determined by symptom characteristics. Voice breaks in vowels are characteristic in ADSD [33,34]. One-third of ADSD patients also have tremor and are not benefitted by some surgical techniques [18]. Patients with voice tremor alone often have a variety of muscles affected [35] and botulinum toxin injections are not as beneficial [36–38]. Abductor spasmodic dysphonia is rare with breathy breaks during voiceless consonants [2]. Although breaks in this group may be due to spasms in the PCA, the main abductor muscle [39]; this may not apply in some cases of ABSD [40]. Variation in pathophysiology between patients with ABSD may explain why PCA treatment with botulinum toxin injections have not been as beneficial in ABSD [41].

Recent treatment advances 2007–2008

Most treatments for spasmodic dysphonia are aimed at either short-term or long-term denervation of either the adductor muscles such as the thyroarytenoid for patients with ADSD or the PCA for patients with ABSD. Recent advances in treatment of spasmodic dysphonia have been aimed at improving the duration of treatment benefit for this chronic disorder either by lengthening the duration of benefits such as reducing voice breaks and speaking effort or by reducing the duration of side effects such as aphonia, breathy voice quality and swallowing difficulties.

Surgical Approaches

In 2005, bipolar radiofrequency-induced thermotherapy was used in three cases to ablate the distal end of the RLN that innervates the thyroarytenoid muscle [42]. In 2008, a similar technique was used to produce a bilateral myectomy of the thyroarytenoid muscle in 20 cases who has all previously responded to thyroarytenoid botulinum toxin injections [43*]. The prepost and follow-up examinations were performed by members of the research team in an unblinded fashion, which may have biased the results. Although significant improvements were reported initially, the benefits reduced after 6 months and half of the patients had to resume botulinum toxin injections for symptoms management by 12 months postsurgery. Another study performed a bilateral myectomy of the thyroarytenoid muscle from the anterior commissure to the vocal process under microlaryngoscopy in seven patients [44*]. All suffered from breathiness that lasted between 3 and 6 months. Evaluations were unblinded and reported follow-up for at least 2.5 years and some to 8 years. Four of the seven were symptom free whereas three had less frequent voice symptoms. Another study used CO₂ laser-assisted vaporization for partial thyroarytenoid myectomy along with electrocautery for neurectomy of the thyroarytenoid branch of the RLN in seven ADSD patients [45]. Outcome was change in a Voice Handicap Index from baseline, averaging 23 months postsurgery. One patient needed an additional procedure because of aphonia; another did not complete the follow-up questionnaire. The others reported improvement to the surgical team but no objective measures were made of symptom change. In contrast with partial myectomy with frequent symptom return, the authors reported that myectomy and neurectomy produced a better result in the small number of patients studied [45].

These studies differed in the extent of the myectomy/denervation; the first used much smaller reductions in muscle and produced less benefit with more frequent symptom return
after 6 months, whereas, the full myectomy or myectomy with neurectomy had significant breathy side effects but longer lasting benefits.

A retrospective review was published in 2008 on 41 patients undergoing type II thyroplasty with insertion of a titanium bridge [46**]. Two previous papers reported a similar procedure in an earlier group of patients [22,23]. The purpose is to hold the vocal folds further apart, reducing the interference of the spasmodic hyperadductions in the voice. Examiners rated randomized recordings of a prolonged/a/made 12 months or more after surgery on hyperfunction, tremor and hard-voice onsets. As the authors acknowledge, the duration of follow-up was too short, as reoccurrence can appear 3–5 years after surgery. Further, the use of a single prolonged vowel is a significant shortcoming as ADSD symptoms occur during connected speech and are much less frequent on prolonged vowels [47,48].

Surgical approaches have been used most in Japan where the national health system does not cover the costs of botulinum toxin injections, leaving patients to pay for injections. In other countries, botulinum toxin injections are used primarily and surgery is reserved for patients who have responded to botulinum toxin injections and desire a more long-lasting solution. Surgical outcomes have not been systematically investigated or compared with management by botulinum toxin injections over the long term. The follow-up time is crucial because of the high risk of symptom return within 5 years.

**Botulinum toxin**

Treatment of spasmodic dysphonia with botulinum toxin was the subject of several evidence-based reviews in the last year. Both reports used the Therapeutics and Technology Assessment Subcommittee procedures of the American Academy of Neurology [49]. One review [50*] concluded that botulinum toxin injection is an effective treatment for spasmodic dysphonia. The other review, using the same schema [49], concluded that botulinum toxin injection is probably effective for the treatment of ADSD but that there is insufficient evidence regarding the use of botulinum toxin injection for ABSD. The resulting recommendation was that botulinum toxin injection should be considered as a treatment option for ADSD [51**].

There continues to be a lack of evidence regarding botulinum toxin injections for ABSD. In the past, a randomized crossover trial compared electromyographic (EMG) guided versus endoscopic injection techniques into the PCA in ABSD and found no significant treatment effect for either group on blinded measures of symptom frequency [41] whereas an uncontrolled case series of patient reports found some benefit [39]. In 2008, an uncontrolled case series using dosages of 2.5 U administered bilaterally in the PCA [52*] in 14 ABSD patients, reported patient ratings on the Voice related Quality of Life Scale [53] (V-RQOL). They found a large Cohen d effect size for patient ratings of 1.28 with a confidence interval of 0.47–2.1. A controlled clinical trial is needed on treatment of ABSD using both patient ratings as well as blinded quantitative measures of symptom severity in speech.

Many ADSD patients develop compensatory supraglottic hyperadduction, which mitigates the effects of thyroarytenoid bilateral botulinum toxin injections into the thyroarytenoid. Such patients appear similar to muscular tension dysphonia with hyperadduction postures [54] either in the vocal folds, the ventricular folds or, in the most severe cases, involving a sphincteric closure above the vocal folds [55]. After EMG-guided injection in the supraglottic region [56**] four cases were reported to have reduced hyperadduction squeeze on an unblinded rating scale. A more controlled study would be needed to determine if this might be an effective treatment for ADSD patients with supraglottic squeeze.
Botulinum toxin dosages vary widely between physicians and between ADSD patients treated by the same physician. Laryngologists performing botulinum toxin injections for patients with ADSD use dosages between 0.25 and 2.5 mouse units (U) bilaterally with an average of around 0.8 U as a maintenance dose. Some patients seem very sensitive and require ‘microinjections’ of 0.1–0.2 U bilaterally. In such cases the dilution is greater (6–8 ml instead of 4 ml of isotonic saline per 100 U). Recent botulinum toxin studies in ADSD have addressed dosage. One report suggested that the use of EMG improves the accuracy of botulinum toxin injections, that the fidelity of the EMG signal may predict injection benefit [57•], and that lower doses were more beneficial because of fewer side effects [57•]. A report of a portable EMG device allowing the physician to hear the auditory signal during needle placement was introduced to avoid the expense of commercial EMG machines unnecessary for injecting botulinum toxin into the laryngeal muscles [58•].

Recent studies have examined whether different botulinum toxin dosages are used over time within patients through retrospective analyses. One study examined 55 patients treated over 12.5 years [59••] and examined whether dosage reduced with continued injection over time. The mean bilateral dosage titrated within six injections to 2.37 ± 1.6 U and then significantly reduced by the 13th injection to 2.03 ± 1.16 U with no reduction in duration of symptom remission (16.74 ± 7.02 weeks) or the intervals between injections (20.62 ± 8.66 weeks) [59••]. Reduction in dosage over time could be explained by the long-term effects of botulinum toxin found to last upto 36 months in spasmodic dysphonia patients treated with large dosages [60]. Another retrospective analysis in 13 patients and found that it took between one and five injections to reach the appropriate dosage with consistent results [61•]. They concluded that the optimal treatment of ADSD usually remains consistent over time, that an initial bilateral dose of 1.5 U or less improved response consistency and that a starting bilateral dose of 2.5 U was often greater than required.

Basic studies have indicated that botulinum toxin can be transported in a retrograde fashion into motor neurons [62,63]. In 2007, it was demonstrated that botulinum toxin was transcytosed to afferent synapses in the contralateral hemisphere in mice and rats [64••]. Taken together these studies suggest that central synaptic neurotransmission may be partially blocked by botulinum toxin reducing the role of sensory input at the cortex and that descending corticobulbar excitation to the motor neuron pools in the brainstem may be reduced after peripheral injection of botulinum toxin [64••]. The central effects may account for why spasmodic activity reduces with botulinum toxin treatment in noninjected muscles [29]. Another retrospective analysis of the effects of treatment on voice ratings before and after treatment in 42 patients with spasmodic dysphonia [65] found that the benefits from injections were significantly reduced in patients in their seventies and attributed this to the reduction in motor units with aging perhaps affecting the response to botulinum toxin in spasmodic dysphonia patients.

Although botulinum toxin injection reduces voice breaks in speech, a prospective study published in 2008 showed that the patients’ quality-of-life was not consistently benefited by botulinum toxin injections [66]. The authors administered the voice-related quality-of-life instrument (V-RQOL) [53,67] to patients over injection cycles and found that the early breathiness and the later decline in voice function before the next injection, had significant detriments in patients’ quality-of-life. The patients’ functioning was not improved for a large proportion of the cycle from one injection to the next [66].

These are limitations of treatments aimed at controlling the symptoms in the voice and not addressing the neurological bases of the disorder [32••]. In 2008, a study using diffusion tensor imaging evaluated white matter integrity in a group of patients with ADSD and combined with neuropathology in one case with ADSD found reduced white matter in the
genu of the internal capsule on the right side and mineral deposits in the basal ganglia and cerebellum [68]. Further research is needed to identify the neurological central control abnormality so that treatment could focus on the source of symptom generation in the brain.

**Conclusion**

Treatment for spasmodic dysphonia has been aimed at denervation or adjustment of the larynx to prevent the uncontrolled spasms in the laryngeal muscles from interfering with voice production. As a result there is a risk–benefit ratio in that the denervation must be adequate to reduce the detection of symptoms whereas at the same time not producing aphony, breathiness and swallowing difficulties. In the future, treatment might be more satisfactory for persons with this disorder if the central neurological abnormality could be targeted.

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**References**

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).


•• This was the report of a panel of experts that reviewed the state of knowledge on spasmodic dysphonia and made recommendations for future approaches to developing a consensus for diagnosis of spasmodic dysphonia, for determining risk factors for the disorder and for developing and
evaluating new treatments for the disorder. Considerable attention was given to the need to conduct systematic and quantitative studies of the outcome of surgical treatments for the disorder.


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46••. Sanuki T, Ishihiki N. Outcomes of type II thyroplasty for adductor spasmodic dysphonia: analysis of revision and unsatisfactory cases. Acta Otolaryngol. Dec.2008 :1–7. [Epub ahead of print]. [PubMed: 19117162] [•• of outstanding interestA third retrospective study of a series of 41 cases by Ishihiki on the use of Type II thyroplasty in adductor spasmodic dysphonia. Unfortunately the follow-up period was too short, only one year, and symptoms were only rated in prolonged vowels, which are less likely to show symptoms in adductor spasmodic dysphonia. In addition, voice breaks, the symptoms specific to this disorder were not measured. Others have not been able to replicate benefits with this procedure]


51. Simpson DM, Blitzer A, Brashear A, et al. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008; 70:1699–1706. [PubMed: 18458230] [•• of outstanding interest] A large multidisciplinary panel reviewed the evidence regarding treatment with botulinum toxin in movement disorders including spasmodic dysphonia. These authors only concluded that botulinum toxin injections for adductor spasmodic dysphonia are probably effective and that no evidence is available on abductor spasmodic dysphonia. This panel concluded that botulinum toxin should be considered as a treatment option for adductor spasmodic dysphonia


56. Young N, Blitzer A. Management of supraglottic squeeze in adductor spasmodic dysphonia: a new technique. Laryngoscope. 2007; 117:2082–2084. [PubMed: 17828053] [•• of outstanding interest] A new approach to treatment of patients with adductor spasmodic dysphonia who also have constant hyperadductive squeeze that is not benefited by voice therapy. Only four cases were included with some benefit based on unblinded assessment by the treating physicians. Such patients are difficult to treat and a controlled study comparing the addition of this procedure to the usual approach is needed with blinded assessment


Another retrospective series on dosage for bilateral thyroarytenoid injections in patients with adductor spasmodic dysphonia. The authors suggest that a starting dosage of 1.5 Units is often adequate and a 2.5 Units dosage is unnecessary.


64. Antonucci F, Rossi C, Gianfranceschi L, et al. Long-distance retrograde effects of botulinum neurotoxin A. J Neurosci. 2008; 28:3689–3696. [PubMed: 18385327] An important basic study in mice and rats showing central changes due retrograde transport of botulinum toxin producing reductions in sensory inputs in the hemisphere contralateral to injection. They also showed reduced motor neuron excitation by descending corticobulbar inputs to the facial nucleus in the brainstem. These findings may explain why there may be a reduction in spasms in noninjected muscles in dystonia and that the benefits of this treatment may include central changes.


