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BOTULINUM TOXIN FOR ABDUCTOR TYPE SPASMODIC DYSPHONIA : A SYSTEMATIC REVIEW

By

Keyona Sutton

A thesis submitted to the faculty of the University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College.

Oxford, MS

May 2023

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DEDICATION :

I would like to dedicate this to my late father, who I know would be so proud of the perseverance I have exhibited throughout this journey.

ACKNOWLEDGEMENTS:

My profound appreciation goes to Dr. Toshikazu Ikuta for the guidance, support, and instruction provided to me during this process. Thank you for taking the time to work with me and the endless encouragement.

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ABSTRACT:

A systematic review was conducted to show that BTX (Botulinum Toxin) is the most effective treatment for Abductor Spasmodic Dysphonia (ABSD). There were a total of 117 records screened for inclusion in this review. After the initial screening, there were seven successive rounds of screening for eligibility. This process produced a total of three eligible records that met the following conditions: patients presented with spastic abduction, electromyography BTX type A injection into the posterior cricoarytenoid muscle, and measurement of results with acoustic dimensions. After surveying all eligible studies, it was concluded that BTX is an effective treatment for ABSD. Every included study reported all patients with improvement after treatment, however, there was a considerable number of patients who experienced adverse effects. After the initial evaluation of BTX treatment, some patients required additional injections of BTX and/or surgery to maintain results. The use of this review should be used to catapult investigation into long term treatments for ABSD as well as the elimination of adverse effects.

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LIST OF ABBREVIATIONS :

ABSD	Abductor Type Spasmodic Dysphonia
ADSD	Adductor Type Spasmodic Dysphonia
BTX	Botulinum Toxin
PCA	Posterior Cricoarytenoid
SD	Spasmodic Dysphonia
TA	Thyroarytenoid
BAT	Botulinum Antitoxin

INTRODUCTION:

Spasmodic Dysphonia (SD) is a voice disorder that disrupts the function of the laryngeal muscles involved in phonation (Shipp et al.). The condition causes involuntary contraction of the intrinsic laryngeal muscles during sound production, which results in poor voice quality (Watts et al.). SD is an idiopathic condition that occurs more frequently in women than men (Schweinfurth et al.). It mainly affects adults ranging from age 30-50, but can still occur in younger and older patients (Ludlow et al.).

SD directly affects the muscles of the larynx, also known as the voice box. Laryngeal muscles are categorized into two groups, the internal muscles and the external muscles (Andaloro et al.). External muscles primarily work together in swallowing, in contrast to the internal muscles that are distinctly involved in phonation (Saran et al.). Internal muscles, which include posterior cricoarytenoid (PCA), thyroarytenoid (TA), cricothyroid, lateral cricoarytenoid, and interarytenoids are responsible for the abduction and adduction of the vocal cords (Saran et al.). The TA muscles, in particular, make the body of vocal cords and are responsible for forming the glottal region (Yin and Zhang). The adduction of the TA muscles closes the glottis, and the abduction of the TA muscles opens the glottis. (Andaloro et al.). The cricothyroid muscles stretch and stabilize the vocal cords, producing faster vibrations (Andaloro et al.). The lateral cricoarytenoid muscles are the main adductors; they pull on external laryngeal muscles to close the glottal opening (Andaloro et al.). The posterior cricoarytenoid muscle is the only muscle involved in vocal cord abduction (Yin and Zhang). This muscle also tugs on extrinsic muscles but to create a glottal opening (Andaloro et al.). Interarytenoids are other muscles that also assist in the adduction of the vocal cords.

SD occurs when the muscles used adduction and abduction start to exhibit spastic behavior that results in poor voice quality (Ludlow et al.). The onset symptoms, which include hoarseness and breathiness, appear gradually, but eventually they progress into a chronic debilitating voice disorder (Blitzer et al.). SD exists in three forms, which include adductor, abductor, and mixed (Rontal et al.). ADSD is characterized by the hyperadduction of the vocal folds, which causes them to slam together and stiffen (Pototschnig et al.). This specific condition causes a person's speech to sound strained because the vocal folds do not have enough slack to vibrate (Hoffman et al.). In contrast, people diagnosed with ABSD experience a weak, breathy voice because the vocal folds are too far apart (Pototschnig et al.). Patients with a mixture of these two conditions are diagnosed with mixed SD (Hoffman et al.)

SD is theorized to be caused by abnormalities in the basal ganglia, but some researchers have suggested that mutations in certain genes are linked to the development of the disorder (Pototschnig et al.). It is a completely idiopathic condition with no current way to predict the possibility of acquiring it. SD currently does not have a specific diagnostic test however, the clinical detection of speech impairments can confirm a diagnosis of SD (Schweinfurth et al.). Speech pathologists can listen and recognize patterns unique to the condition (Hoffman et al.). In more complicated cases, laryngoscopy and neurological evaluations are used to make a diagnosis (Schweinfurth et al.). Neurological evaluations highlight any connection between the nervous system and development of movement disorders (Hoffman et al.). Contrary to other diagnostic methods, laryngoscopy allows direct visualization of the vocal folds. (Hoffman et al.).

Botulinum toxin (BTX) is often used as a treatment for SD (Ludlow et al.). In fact, it is the accepted treatment for symptoms associated with ADSD (Woodson et al.) It is a neurotoxin produced by Clostridium Botulinum, a naturally occurring bacterium. (Nigam and Nigam). BTX

type A, specifically, is used for the treatment of muscle disorders and cosmetic procedures. It prevents proper acetylcholine transfer, thus inhibiting muscle contraction (Nigam and Nigam). BTX type A is composed of protein complexes with 100 kDa heavy chains and 50 kDa light chains, linked by disulfide bonds (Nassif et al.). The heavy chain of BTX recognizes receptors on the presynaptic membrane then rearranges to facilitate the passage of the light chain to the cytosol of the presynaptic cell (Nassif et al.). Once inside, the light chain inhibits vesicle formation, thus preventing acetylcholine transfer (Nassif et al.). The inactivation of the muscle fibers by BTX is reversible, so the effects are temporary (Lagueny and Burbaud). It is typical in therapeutic and cosmetic cases to need follow up doses to maintain results (Schweinfurth et al.). One study suggests that the temporary effects of BTX are due to gradual reactivation of the muscle fibers (Lagueny and Burbaud). It is also proven that the effects of BTX diminish with recurring treatments, because antibodies are produced against the toxin (Nassif et al.). Despite the impermanence of BTX, its ability to prevent the contraction of local muscles makes it a considerable choice for non-systemic conditions. Although BTX is the preferred treatment for SD, it can be used in tandem with vocal therapy for enhanced results (Schweinfurth et al.).

SD cannot be prevented, nor has any treatment been discovered to alleviate the recurring/adverse symptoms. BTX is the most effective treatment for ADSD, which encompasses 80-90 % of the cases of SD, while ABSD only accounts for 10-20% (Hoffman et al.). There is not nearly as much research on the treatment of abductor type as adductor type. It is important for researchers to do more research into the effects of BTX on ABSD patients to ensure that it is the best treatment for the condition. The lack of studies performed could indicate the existence of a better treatment for ABSD. Additional research will improve management of the condition which in turn, positively impacts diagnosed patients and health care workers.

METHODS:

This process began by formulating a question and exploring databases of scientific literature for relevant evidence. After producing a well defined research question, the parameters for exclusion and inclusion are defined. The studies were initially identified for inclusion using a filtered search in the PubMed Database. The search was sensitive to literature that included the phrases ((posterior cricoarytenoid) OR (abductor)) AND ((botox) OR (botulinum)).
Inclusion criteria were the basis of selection for studies to be included in this report. Studies that satisfied all of the inclusion criteria were eligible to be included. These include studies published after 1990 reporting the use of BTX A as a primary therapy, testing human subjects, including patients with diagnosed ABSD, documenting administration by injection in the PCA muscle, and measuring results using acoustic measures. Excluded were studies in which no experiments were performed. The study design, focus of research, and findings were documented for the eligible studies included in this report.

RESULTS:

The first search yielded 117 records but 2 duplicate records were removed before the initial screening. After the completion of the initial screening, 55 records were excluded because they included research of conditions other than the ABSD. The remaining 60 records were screened for eligibility, eliminating 12 studies where the incorrect treatment process was used. Next, 5 studies were excluded because they included studies where BTX was administered into the incorrect injection site. This review only includes studies in which patients received injections into the posterior cricoarytenoid muscle. Another reason for exclusion was the use of non-human subjects, which eliminated 3 more studies. The next group of studies, 23, was excluded because they included studies completely unrelated to this review. Following this, 12 more studies were excluded because they included the use of additional drugs along with the BTX injection. Finally, 2 more records were excluded because there was no experimental design defined. This final screen resulted in 3 eligible studies to be included in the report. Data from the eligible studies were extracted and compared.

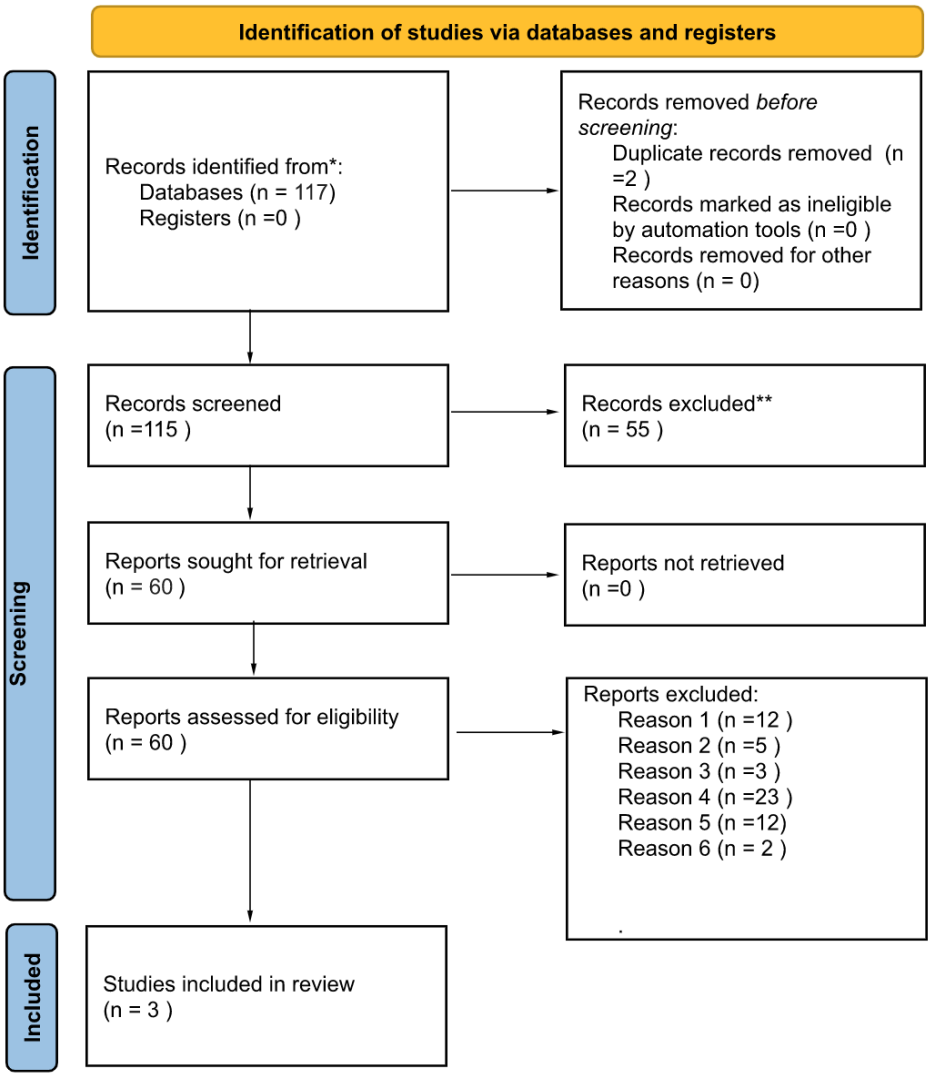

Figure 1: Flow diagram for identification of included studies

Included Reports	Number of Participants	Mean Age	Female/Male Ratio
Report 1 (Rontal et al.)	6	43.5	3:3
Report 2 (Blitzer et al.)	32	39.8	11:21
Report 3 (Woodson et al.)	17	N/A	12:5

Table 1: Demographics of participants in included studies

Included Reports	Improvement with no adverse effects	Improvement after adverse effects	No improvement
Report 1 (Rontal et al.)	0	5	1
Report 2 (Blitzer et al.)	28	4	0
Report 3 (Woodson et al.)	14	3	0

Table 2: Overall results of included studies

DISCUSSION:

The systematic review supports the efficacy of BTX to treat ABSD. In all studies, BTX was shown to be effective across the spectrum to severity. In Report 1, researchers were able to effectively treat five of six patients diagnosed with SD. All participants in the study reported a reduction in abductor spasms, reduction in effortful speech, and reduction in speech fatigue after the initial injection. It is important to note that not all of the spasms resolved themselves within the same time frame. Two participants reported voice improvements three days after the injection. Two participants reported voice improvements after one week post injection. The remaining two participants reported improvement two months after injection. All participants experienced symptom relief immediately after injection but only five participants experienced steady voice improvement after varying periods of mild voice breathiness. The one outlier participant continued to experience breathiness even after five injection attempts. The disadvantage of the procedure used in this study is that the injection methods could have been manipulated to ensure effective diffusion of the toxin. The location of the target PCA muscle could indicate the reason BTX injections do not treat the breathiness associated with ABSD. Since the PCA muscle is located behind other laryngeal musculature, it is difficult to isolate (Eller et al.) . The study is consistent with this finding and includes the supposition of toxin diffusion into other laryngeal muscles, producing the breathiness that persisted in the outlier participant. The results demonstrate the positive effects of BTX injections in the PCA muscle to treat SD.

The participants in Report 2 were grouped differently depending on the associated symptoms to better interpret the results. Of the 32 participants with SD, 16 reported having only focal spasms. The remaining participants reported other symptoms influencing the severity of SD: 8 participants with tremor, 5 participants with cranial/axial dystonic involvement, and 3 participants with a mixture of both symptoms in addition to the focal spasms. The greatest improvement of 42.3 % was reported for the group with only focal spasms. The worst improvement was seen in the group with combined symptoms, reporting 30%. Report 2 measured pre-treatment and post-treatment severity, aphonia, tremor, and breathy voice quality, all of which showed improvement. The results were scaled from 7 being the most severe and 1 being 1 normal. The average severity of the condition went from 5.0 to 3.0. The average aphonia went from 3.2 to 1.8, the average breathy voice quality went from 4.5 to 1.8, and the average tremor dropped only from 2.2 to 2.0. Although these results show overall improvement, it is important to note the adverse experiences. Two of the participants did experience wheezing during extraneous activities and dysphagia after injection, but those symptoms resided within one week. Researchers hypothesized that these effects were due some of the toxin leaking into other nearby muscles. The results in the report were normally sufficient to conclude that BTX is an effective treatment of ABSD. Just as report 1, the results of report 2 also highlight the difficulty of only targeting the PCA muscle.

Report 3 differed from the other reports by altering the injection technique. In this report, researchers determined the laterality of spastic activity, distinguishing a dominant side from a non dominant side. All participants needing subsequent injections received them in the dominant side only. Participants who did not show dominance were arbitrarily assigned a dominant side; Report 3 also determined the dosage amount of BTX for each participant as the study progressed.

All participants started with 5 units of BTX in the dominant side and 1.25 units in the non dominant side. Researchers only reported observing change after 10 units of BTX were administered, and subsequent injections were given to participants by units of five. The maximum amount of toxin administered to one participant was 25 units. 20 patients were chosen to participate, but only 17 completed treatment all the way to the end of the trial. 14 of the 17 participants had a significant decrease in symptoms, 12 of which received only 10 units of toxin. Of the remaining, 3 participants received 20 units, 1 received 15 units and 1 received 25 units. Some participants did experience breathiness after treatment, but researchers hypothesized that the breathiness occurred from incorrectly assigning the dominant side. The results of this report also support the use of BTX as therapy for patients with ABSD.

In all three reports, researchers recorded adverse effects among some of the participants. The first two reports mentioned that breathiness occurs in multiple participants, and was determined to be due to improper diffusion of toxin. It is hypothesized that BTX diffused away from the original injection site, affecting other muscles. All 6 participants from report 1, 4 participants from report 2, and 3 participants from report 3 experienced adverse effects. Whereas report 1 hypothesized that the adverse effects were due to diffusion of BTX only, report 2 attributed the adverse effects to improper diffusion and severity of the condition. The 4 adversely affected participants of report 2 had more severe symptoms, including tremor and axial/cranial dystonic involvement. After breathiness subsided in most participants, there was 1 participant from report 1 who did not experience any period of no breathiness. Comparing the results of these two reports can indicate a more severe case of ABSD in the singular participant with no improvement. These findings suggest that the BTX injection techniques should be altered to accommodate varying severity of ABSD. The results of Report 3 also support this assertion, by

administering units of BTX in intervals. Participants from report 3 who received 15, 20, or 25 units of BTX had a less impressive outcome compared to participants who received only 10 units. This highlights the importance of tailoring the injection technique to each individual diagnosed with ABSD.

Patients treated with BTX are considered to be at immediate risk due to complications of toxin exposure. BTX injections have caused serious adverse effects including dysphagia, dysphonia, dysarthria, respiratory arrest and muscle weakness in therapeutic and cosmetic cases (Witmanowski and Błochowiak). These side-effects are hallmark symptoms of botulism, which is a naturally occurring illness that attacks the nerves resulting in paralysis, and in more severe cases, respiratory arrest and death (Sobel). Iatrogenic botulism, specifically, is when illness is caused by intentional infections, such as cosmetic procedures (Sobel). While cosmetic doses are typically too small to cause infection, higher doses, used to treat muscle disorders, have caused some mild cases of botulism (Sobel). From the years 2014 to 2017 the FDA reported 264 out 13,078 botulism cases being caused by overuse of BTX. (Berntsen et al.) A botulinum antitoxin (BAT) can be used to treat iatrogenic botulism, but can only target circulating toxins, meaning it cannot reverse any pre-existing damage to nerves (Berntsen et al.). Other than BAT, there are no other treatment guidelines for treating iatrogenic botulism (Berntsen et al.). Although the use of BTX could cause potential harm to patients, the incidence of iatrogenic botulism cases are extremely low. In fact, no death or respiratory arrest has been reported with properly administered doses of BTX (Berntsen et al.).

The most common adverse effects seen across these studies is breathiness after injection. Of the 65 total patients, 13 of them, 20 %, experienced adverse effects including breathiness after injection. The breathiness is caused by initial weakness of the vocal musculature (Yershov and Partridge) Breathiness is normally resolved within the first two weeks after injection (Lundy et al.). The results of this review were consistent, showing that only one participant out of all three studies did not show any consistent improvement. In some cases, not found in this review, there is evidence that BTX injections cause other problems stemming from breathiness, such as dysphagia and aspiration (Lundy et al.). One particular study found 8 of 352 patients who needed intubation after treating ADSD with BTX (Yershov and Partridge). Breathiness is a unifying side-effect of ADSD and ABSD, so the risk of respiratory problems is applicable for patients with ABSD. There must be more research into the long term effects of BTX for ABSD patients, and its potential to cause extreme respiratory problems. Researchers should study how the frequency of BTX injection changes its effects over time to make sure BTX maintains its effectiveness. When considering the use of BTX to treat ABSD it is important to think about the potential risk of an accidental overdose or extreme respiratory problems arising as a delayed compilation. The small risk of these events is not enough to outweigh the immense benefit of using BTX to improve the overall voice quality of ABSD patients.

CONCLUSION:

Results from all three reports consistently classify BTX as an effective treatment for the low-incidence condition ABSD. Each report was unique in its attempts to optimize the administration of toxins. This uniqueness was able to compensate for the variability of the condition, for example examining the effects of differing severity and dosage amounts. Although BTX was proven to be an effective treatment of ABSD, it may not be the most effective treatment. In all three reports there were participants who still experienced breathiness, proving that the injections did not completely alleviate all the associated symptoms. More research is needed to ensure BTX should be the accepted treatment for ABSD.

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