Liquid-type Botulinum Toxin Type A in Adductor Spasmodic Dysphonia: A Prospective Pilot Study

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Summary: Objectives. Botulinum toxin (BTX) has been widely used to treat adductor spasmodic dysphonia (ADSD). Most commercially available forms of BTX require reconstitution before use, which may increase the risk of contamination and requires careful titration. Recently, a liquid-type BTX type A (BTX-A) has been developed, which should simplify the procedure and enhance its efficacy. Herein, we present a prospective pilot study to investigate the efficacy and safety of liquid-type BTX-A in the treatment of ADSD.

Methods. Twenty-six consecutive liquid-type BTX-A injections were performed in 12 patients with ADSD. We included as a control group 34 consecutive patients with ADSD who had previously undergone 52 vocal fold injection procedures with freeze-dried–type BTX-A.

Results. All patients in both groups had improvement of symptoms related to ADSD and period of normal voice. Most patients experienced breathiness, and the onset time, the peak response time, and the duration of breathiness were similar in both groups. The duration of effect (days) was 96.96 ± 18.91 and 77.38 ± 18.97 in the freeze-dried–type and the liquid-type groups, and the duration of benefit (days) was 80.02 ± 18.24 and 62.69 ± 19.73 in the freeze-dried–type and the liquid-type groups. To compare the efficacy between the freeze-dried–type and the liquid-type BTX-A, the sessions of the unilateral vocal fold injection were included and were categorized as group A (1 ~ 2 units BTX-A) and group B (2 ~ 3 units BTX-A), according to the dose per vocal fold. There was no significant difference of effect time between freeze-dried–type and liquid-type BTX-A groups. No adverse events related to BTX or vocal fold injection were reported.

Conclusions. Liquid-type BTX-A is safe and effective for the treatment of spasmodic dysphonia. With the advantages of simple preparation, storage, and reuse and animal protein-free constituents, liquid-type BTX-A may be a good option in the treatment of spasmodic dysphonia.

Key Words: Botulinum toxin–Spasmodic dysphonia–Vocal fold injection–Liquid-type–Focal dystonia.

INTRODUCTION

Spasmodic dysphonia (SD) is a focal dystonia characterized by action-induced or task-specific spasm of the vocal folds.[1,2] The estimated prevalence of SD is 5.9 per 100,000.[3] Generally, two types of SD are recognized: adductor spasmodic dysphonia (ADSD) and abductor spasmodic dysphonia.[4] Of these, ADSD is the most common, and it affects nearly 90% of patients with SD. ADSD is characterized by voice breaks during vowel sounds owing to intermittent hyper-adduction of the vocal folds. Abductor spasmodic dysphonia is relatively rare and involves intermittent voice breaks due to prolongation of voiceless consonants before initiation of the vowels.

Many surgical approaches to SD have been introduced since Dedo first proposed unilateral section of the recurrent laryngeal nerve as a treatment,[5] including myectomy of intrinsic laryngeal muscles,[6,7] unilateral recurrent laryngeal nerve avulsion,[8] denervation with reinnervation of thyroarytenoid,[9] and type II thyroplasty.[10] However, these surgical treatments for SD have failed to provide strong evidence, or their benefits have been unpredictable.[2] To date, the only treatment that has been proven effective for ADSD, in a small controlled clinical trial, is the bilateral injection of small amounts of botulinum toxin (BTX) into the adductor muscles, primarily the thyroarytenoid muscle.[11] Since the prominent work of Blitzer et al,[12] the standard of care for SD has been laryngeal botulinum toxin injection.[13]

There are seven distinct types of botulinum toxin, but only two types, A and B, are currently available for clinical use. BTX type A (BTX-A) was developed by Allergan, and since its introduction, it has been the most widely used form of BTX-A in various medical fields. All currently available brands of BTX-A for clinical use are freeze-dried and require reconstitution before injection. However, reconstitution is sometimes inconvenient and requires careful dilution for the preparation of exact concentrations while avoiding contamination. Recently, a liquid-type BTX-A has been developed, which should simplify the procedure and enhance its efficacy. Liquid-type BTX-A has been approved in Korea for treatment of glabellar frown lines,[14] but there are no reports regarding the efficacy and safety of liquid-type BTX-A in the treatment of SD. Herein, we present a prospective pilot study to investigate the efficacy and safety of liquid-type BTX-A in the treatment of SD.

MATERIALS AND METHODS

Botulinum toxin

Two types of BTX-A were used in the study. Patients received vocal fold injections with freeze-dried–type BTX-A (Botox,

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100 units/vial; Allergan Inc., Irvine, CA, USA) or liquid-type BTX-A (Innotox, 0.625 mL/vial, 4 units/0.1 mL; Medytox Inc., Cheongju-si, Chungcheongbuk-do, South Korea).

Participants

Twelve consecutive patients with ADSD were prospectively treated with liquid-type BTX-A between January 2015 and December 2015 (treatment group), and a total of 26 vocal fold injection procedures were performed with liquid-type BTX-A in this group. To avoid the effect of previously injected BTX-A, we excluded patients who underwent vocal fold injection before complete recurrence of the unique symptoms of SD. Outcomes in these patients were compared with those of 34 consecutive patients with ADSD who had previously undergone 52 vocal fold injection procedures with freeze-dried–type BTX-A between January 2012 and December 2014 (control group). The study was carried out with a protocol approved by the Institutional Review Board of Pusan National University Hospital.

Vocal fold injection technique

Vocal fold injections were conducted under electromyography (EMG) guidance or under direct visualization *via* fiberoptic laryngoscopy. For EMG-guided injection, patients were seated with the neck extended, and a 26-gauge Teflon-coated injection needle that was connected to a 1-cc syringe preloaded with BTX-A was inserted through the cricothyroid membrane into the thyroarytenoid muscle under EMG guidance. For the fiberoptic laryngoscopy method, patients were seated with the neck extended and a 4% lidocaine spray was applied to the nasal cavity, pharynx, and larynx. The drugs were then injected through the cricothyroid membrane into the middle portion of vocal fold (thyroarytenoid muscle) with a disposable 25-gauge long needle under direct visualization with transnasal flexible fiberoptic laryngoscopy (ENFVT, Olympus Corporation, Tokyo, Japan). All injections were performed by a single experienced laryngologist (W.C.).

Measures of safety and efficacy

Patients were monitored for drug-related adverse events such as allergic reaction, throat pain, localized burning, dyspnea, bleeding, or hematoma in the outpatient clinic. We evaluated the efficacy of the BTX-A injections in the clinic by inquiring about four subjective criteria proposed by Blitzer et al,[1] specifically: (1) *onset of effe*ct (days), that is, "How many days after the treatment did the voice break stop and the breathy voice start?"; (2) *peak effect* (days), that is, "How many days after the treatment did the breathy voice become most pronounced?"; (3) *duration of the breathy period* (days), that is, "How many days after treatment did the breathy voice end?"; and (4) *duration of the treatment effect* (weeks), that is, "How long did the treatment effect last?" The duration of benefit (days) was calculated as the duration of the treatment effect minus the duration of the breathy period.

Statistical analysis

Student *t* test was used to evaluate the differences between the two groups, and *P* values of <0.01 represented statistical significance. All statistical analyses were performed using *R version 3.2.4 Revised* (The R Foundation for Statistical Computing, Vienna, Austria) and *RStudio 0.99.893* (RStudio, Inc., Boston, MA, USA).

RESULTS

Patient characteristics for both groups are summarized in Table 1.

Twenty-six and 52 vocal fold injections were performed in liquid-type and freeze-dried–type BTX-A groups, respectively. More patients in the freeze-dried–type group received bilateral injections (27 of 52, 51.9%) *versus* the liquid-type group (6 of 26, 23.1%). BTX-A was prepared at the mean concentration of 1.78 ± 1.01 unit/0.1 mL in the liquid-type group and 2.39 ± 0.41 unit/0.1 mL in the freeze-dried–type group. Total dose of BTX-A was 2.37 ± 2.21 units in the liquid-type group and 4.06 ± 1.62 units in the freeze-dried–type group (Table 2).

All patients in both groups had improvement of symptoms related to ADSD and period of normal voice. Most patients experienced breathiness, and the onset time, the peak response time, and the duration of breathiness were similar in both groups. The duration of effect (days) was 96.96 ± 18.91 and 77.38 ± 18.97 in the freeze-dried–type and the liquid-type groups, and the duration of benefit (days) was 80.02 ± 18.24 and 62.69 ± 19.73 in the freeze-dried–type and the liquid-type groups. Both of the periods were statistically different between the two groups (Table 2).

One patient in the liquid-type group and three patients in the freeze-dried–type group had aspiration symptoms more than 2 weeks, but no other adverse events related to BTX or vocal fold injection, including allergic reaction, throat pain, local-

TABLE 1.
Demographic and Clinical Information in Freeze-dried–type Group and Liquid-type Group

	Freeze-dried–type BTX-A	Liquid-type BTX-A
Number of patients (N)	34	12
Age, mean (years)	49.0 ± 16.8	36.8 ± 8.0
Sex (M/F)	0.10	0.20
Male	3	2
Female	31	10
Number of vocal fold injection sessions	52	26
Average sessions of vocal fold injection	1.53	2.17