Botulinum toxin injection into the intrinsic laryngeal muscles to treat spasmodic dysphonia: A multicenter, placebo-controlled, randomized, double-blinded, parallel-group comparison/open-label clinical trial

Masamitsu Hyodo1 | Asuka Nagao1 | Kento Asano2 | Masahiko Sakaguchi3
Kenji Mizoguchi4 | Koichi Omori5 | Yasuhiro Tada6 | Hiromitsu Hatakeyama7
Nobuhiko Oridate7 | Kensei Naito8 | Yoshihiro Iwata9 | Hirotaka Shinomiya10
Hirotaka Hara11 | Tetsuji Sanuki12 | Eiji Yumoto13

1Department of Otolaryngology–Head and Neck Surgery, Kochi University, Nankoku, Japan
2Department of Medical Innovation, Osaka University Hospital, Suita, Japan
3Department of Engineering Informatics, Osaka Electro Communication University, Neyagawa, Japan
4Department of Otolaryngology–Head and Neck Surgery, Hokkaido University, Sapporo, Japan
5Department of Otolaryngology–Head and Neck Surgery, Kyoto University, Kyoto, Japan
6Department of Otolaryngology, Fukushima Medical University, Fukushima, Japan
7Department of Otolaryngology, Yokohama City University, Yokohama, Japan
8Academy of Nursing, Fujita Health University, Toyoake, Japan
9Department of Otolaryngology–Head and Neck Surgery, Fujita Health University, Toyoake, Japan
10Department of Otolaryngology–Head and Neck Surgery, Kobe University, Kobe
11Department of Otolaryngology, Kawasaki Medical School, Kurashiki, Japan
12Department of Otolaryngology, Nagoya City University, Nagoya, Japan
13Department of Otolaryngology, Kumamoto University, Kumamoto, Japan

Abstract

Background and purpose: Botulinum toxin (BT) injection into the laryngeal muscles has been a standard treatment for spasmodic dysphonia (SD). However, few high-quality clinical studies have appeared, and BT is used off-label in most countries.

Methods: We performed a multicenter, placebo-controlled, randomized, double-blinded, parallel-group comparison/open-label clinical trial to obtain approval for BT (Botox) therapy in Japan. Twenty-four patients (22 with adductor SD and two with abductor SD) were enrolled. The primary end point was the change in the number of aberrant morae (phonemes) at 4 weeks after drug injection. The secondary end points included the change in the number of aberrant morae, GRBAS scale, Voice Handicap Index (VHI), and visual analog scale (VAS) over the entire study period.

Results: In the adductor SD group, the number of aberrant morae at 4 weeks after injection was reduced by 7.0 ± 2.30 (mean ± SE) in the BT group and 0.2 ± 0.46 in the placebo...
INTRODUCTION

Spasmodic dysphonia (SD) is a rare form of focal dystonia occurring in the absence of phonatory organ paralysis or other structural pathology. SD is characterized by involuntary intermittent spasms of the intrinsic laryngeal muscles [1,2]. Depending on the muscles involved, SD is divided into three types: adductor, abductor, and mixed. In adductor SD (ADSD) patients, spasms of the adductor laryngeal muscle open the vocal folds, rendering the voice intermittently breathy or aphonie. Mixed SD patients exhibit both types of voice disorder. SD is considered focal dystonia when it affects the larynx, and is sometimes associated with segmental, multifocal, or systemic dystonia [2]. Among all cases of SD, 80% to 95%, and 5% to 17% are of the adductor and abductor type, respectively [3–5]. Mixed SD is very rare. SD likely affects females; the female: male ratio ranges from 1.1:1 to 4.1:1 [2,4–7]. The mean age of onset ranges from 31 to 51 years [2,5–7]. Regardless of type, SD patients find conversations difficult, which compromises both work and social function. Currently, there is no cure for SD. Conservative treatments including voice therapy, psychotherapy, and pharmacological therapy are of limited efficacy [2]. The surgical approaches for ADSD aim to prevent vocal fold hyperadduction and include unilateral recurrent laryngeal nerve sectioning [8,9], thyroarytenoid myectomy [10,11], selective adductor denervation–reinnervation surgery [12] and type 2 thyroplasty [13,14]. These procedures reduce the likelihood of strangled voice and voice breaks. However, hoarseness may develop postoperatively, and long-term improvements remain under investigation [15]. No surgical intervention for ABSD is yet available.

Botulinum toxin (BT) injection into the intrinsic laryngeal muscles is generally considered the treatment of choice for SD [16–18]. However, few well-controlled clinical studies have appeared [19]. BT as an SD treatment has been approved in Australia and some Central and South American countries, but not in the United States, Europe, or Asian countries such as Japan. As a result, many patients were unable to benefit from effective SD therapy in Japan [5]. Therefore, we performed a multicenter, placebo-controlled, randomized, double-blinded, parallel-group comparison/open-label clinical trial (the BOtulinum toxin Injection therapy for Spasmodic dySphonia [BOISS], study) with the aim of obtaining approval for BT therapy for SD in Japan. This is the first clinical trial based on Good Clinical Practice (GCP) guidelines to be conducted on BT worldwide.

MATERIALS AND METHODS

This was an investigator-initiated multicenter clinical trial approved by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan. The study involved eight Japanese institutes.

Study objectives and end points

We performed a phase II/III clinical trial to evaluate the effectiveness and safety of botulinum toxin A (Botox; Allergan, Dublin, Ireland) injection in ADSD and ABSD patients. The primary end point was the change value in number of aberrant morae 4 weeks after drug administration. The secondary end points included the change values in the number of aberrant morae, GRBAS objective dysphonic scale, Voice Handicap Index (VHI), and visual analog scale (VAS) dysphonia severity scores over the entire study period.

Participants

The inclusion criteria were (i) age 12 years or older, (ii) an SD voice disorder for ≥6 months, and (iii) moderate-to-severe SD (≥12/25 and ≥5/27 abnormal morae in ADSD and ABSD patients, respectively, when reading the sentences described below). The exclusion criteria were (i) coexisting systemic neuromuscular disease other than dystonia, (ii) vocal fold paralysis or apparent swallowing disorder, (iii) prior surgical treatment for SD, (iv) voice therapy within the last 8 weeks or BT therapy within the last 24 weeks, and/or (v) severe systemic disease.
Study design

For the initial injections in the ADSD patients, a double-blinded and randomized procedure was followed, and up to two reinjections were permitted as an open-label study. The drug and placebo were dissolved in saline, and transcutaneously injected into the thyroarytenoid muscle through the cricothyroid membrane under electromyography (EMG) guidance. The initial dose was 2.5 U, and the first reinjection was 1.0 to 2.5 U depending on the initial response. The first two injections were given unilaterally to ensure the safety against possible adverse events by BT according to the instruction by PMDA, because the first reinjection in the placebo group was the initial administration of BT. The second reinjection was unilaterally or bilaterally 1.0 to 2.5 U. For ABSD patients, each injection was open-label, because ABSD is very rare, and double-blinding was not feasible. The drug or placebo was injected unilaterally into the posterior cricoarytenoid (PCA) muscle using an anterolateral transcervical approach under EMG guidance. The initial dose was 5 U, and the subsequent doses were 2.0 to 5 U. For both SD types, the interval between injections was at least 12 weeks. After each injection, patients were followed up at 2 and 4 weeks, and every 4 weeks thereafter, for the entire 48-week study period. At each visit, the number of aberrant morae, GRBAS scale, VHI, and VAS scores were collected. Also, laryngeal endoscopy was performed, and phonatory function and blood chemistry were evaluated.

Randomization and blinding

The coordinating investigator confirmed that the appearance and packaging of the drug and placebo were identical and gave the materials to the drug assignment director, who was not involved in the data management or statistical analysis. The director created a key code that was broken only after data collection 16 weeks after the initial injections, at which time all data to be analyzed had been collected from all patients. Eligible ADSD participants were randomly assigned to either the BT or placebo group in a 1:1 ratio using a computerized randomization method. The patients and physicians were both blinded until the key code was broken.

The mora

In Japanese, mora refers to a minimum rhythmic sound unit (phonemes) as represented single Japanese vowel or consonant–vowel complex [20]. Japanese words are composed of morae, analogous to syllables in English. Phonatory disorders in SD are represented as aberrant mora production. In line with the report of Kumada et al. [21], the ADSD patients were asked to read the following sentence aloud: "mu/ka/shi/a/ru/to/ko/ro/n/ni/ja/ku/to/i/u/o/to/ko/no/ko/ga/i/ma/shi/ta" (Many years ago, there lived a boy named Jack.), which contains many voiceless consonants easily disturbed in ABSD. The sentence read by the ABSD patients was "ho/n/ya/to/ha/na/ya/wa/to/o/ri/wo/he/da/te/te/ha/n/ta/i/ga/wa/ni/a/ri/masu" (The bookstore and flower shop are across the street.), which contains many voiceless consonants easily disturbed in ABSD. The sentences contain 25 and 27 morae, respectively. Voices were digitally recorded using the ICD-UX543F recorder (Sony, Tokyo, Japan); no personal information was included. The voice data were sent electronically to a central evaluation committee; three phoniatrics experts separately counted the numbers of aberrant morae. Median values were used in analysis.

The GRBAS scale

The GRBAS scale, which is used for auditory/perceptual evaluation of voice quality, was developed by the Japan Society of Logopedics and Phoniatrics [22,23] and is widely used clinically. Grade (G) indicates the severity of hoarseness, roughness (R) is a rasping or rat-tling voice, breathiness (B) is a whispery voice, asthenia (A) is a weak voice, and strain (S) is an effortful or constricted voice. Each element of the GRBAS is scored as follows: 0, normal; 1, slight; 2, medium; or 3, high. Voice disorders in SD are characterized by abnormally high scores of S in ADSD and B and/or A in ABSD. In this study, physicians applied the GRBAS scale by listening to the voices of each patient.

Voice Handicap Index

The VHI is a patient-rated scale developed by Jacobson et al. used to rate the severity of disability caused by poor verbal communication [24]. The VHI includes 30 items divided into functional, emotional, and physical domains, each with 10 items. The following five-point scale is used for each item: 0, never; 1, almost never; 2, sometimes; 3, almost always; and 4, always. Total scores range from 0 to 120; the more severe the subjective voice disorder, the higher the total score. We used the Japanese version of the VHI [25] with minor modifications.

Visual analog scale

Participants subjectively assessed their dysphonia severity using a 100-mm VAS; higher scores indicated that phonation was more affected by SD. The left and right anchor points corresponded to no dysphonia and the worst possible dysphonia, respectively. An assessor recorded all scores.

Safety measures

As safety measures, laboratory tests (hematology and clinical biochemistry) were performed, and vital signs (blood pressure and heart rate) were recorded. A physical examination was also conducted, and adverse events (AEs) were recorded. Any undesirable or unexpected sign, symptom, disease, or accident arising after injection throughout the study period was regarded as an AE.
Statistical analysis

The primary outcome was the change in the number of abnormal morae at 4 weeks after injection according to analysis of covariance, using the baseline data as covariates. Summary statistics are provided for the test and placebo groups. The secondary outcomes included the change in number of aberrant morae, GRBAS scale, VHI, and VAS at each evaluation time point. Group differences in least squares mean values were calculated with two-sided 95% confidence intervals (CIs) and p values. Data from ADSD patients were analyzed using the Wilcoxon sign rank test, and the Wilcoxon rank sum test was used to compare differences between the two groups. For all comparisons, a p value <0.05 was considered to reflect statistical significance.

Ethics statement

The clinical trial was performed in accordance with GCP guidelines and the ethical principles of the Declaration of Helsinki. The study protocol and informed consent forms were reviewed and approved by the institutional review board of Kochi Medical School (ID: 1492501) and of other institutions. Written informed consent was obtained from each patient prior to randomization. The trial was registered with the Center for Clinical Trials of the Japan Medical Association (Registry ID: JMA-IIA00176).

RESULTS

Demographics

Twenty-two ADSD and two ABSD patients were enrolled. A flow diagram of patient enrolment is shown in Figure 1, and demographics are listed in Table 1. Of the ADSD subjects, 11 were assigned to each of the BT and placebo groups (means ± standard deviation age = 38.5 ± 11.2 and 41.6 ± 10.0 years, respectively; no significant difference). Disease duration ranged from 6 months to 30 years and did not differ significantly between the two groups. The number of aberrant morae and GRBAS scale, VHI, and VAS on enrollment did not differ significantly between the groups.

Primary end points

ADSD

Prior to the initial injection, the number of aberrant morae was mean ± standard error 19.2 ± 1.36 and 21.3 ± 1.86 in the BT and placebo groups, respectively. The change value at 4 weeks after injection was −7.0 ± 2.30 and −0.2 ± 0.46, respectively (Figure 2). The least squares mean difference (95% CI) between the two groups of −6.5 (−11.6, −1.4), was statistically significant (p = 0.0148).

ABSD

The change in the number of abnormal morae at 4 weeks after injection was −2 and 1 in the two ABSD subjects. Although there was no improvement in one subject, a slight improvement was observed in the other subject (Figure 3).

Secondary end points

ADSD

In the placebo group, no significant change was apparent between 2 and 12 weeks after BT injection. The change in the number of abnormal morae peaked at −9.9 ± 2.66 at 2 weeks after BT administration (Figure 2), and then gradually decreased up to 12 weeks (−3.5 ± 1.42). The least squares mean differences (95% CI) between the two groups at 2 and 12 weeks after injection was −8.6 (−14.6, 2051)

\[ \text{Adductor type} \]

Enrollment

Assessed for eligibility (n=22)

Randomization

Allocation

BT group (n=11)

Placebo group (n=11)

Double blind

BT administration (n=11)

Placebo administration (n=11)

Open label

1st re-administration (BT) (n=9)

1st re-administration (BT) (n=11)

2nd re-administration (BT) (n=7)

2nd re-administration (BT) (n=10)

Open label

BT administration (n=2)

1st re-administration (BT) (n=2)

2nd re-administration (BT) (n=2)

\[ \text{Abductor type} \]
−2.6) and −3.6 (−6.7, −0.4), respectively. They showed the treatment efficacy lasted significantly for 12 weeks. In both groups, the changes in the number of aberrant morae after the first and second reinjections were similar to the change after the initial injection of BT. Figure 4 shows the change in number of aberrant morae after injection in seven subjects who received three BT injections. The number of aberrant morae tended to decrease with repeat BT injections.

No change in any element of the GRBAS scale was observed except for S. The change in S score after injection peaked at −1.2 ± 0.33 at 2 weeks and was −0.4 ± 0.24 at 12 weeks in the BT group (Table 2). At 2 weeks, the S score exhibited a significant change from baseline in the BT group (Wilcoxon signed rank test, \( p = 0.0156 \)). There was no significant difference in the placebo group (\( p = 0.6250 \)). The Wilcoxon rank sum test revealed a group difference in the change in S score from baseline at 2 weeks (\( p = 0.0394 \)). In both groups, the S after reinjection was similar to that after the initial injection of BT.

The change in VHI score peaked at −24.0 ± 9.63 4 weeks after the initial BT injection, and the improvement persisted for 12 weeks (Table 2). The least squares mean difference (95% CI) between the two groups was −15.7 (−36.4, 5.0) and −9.4 (−28.6, 9.8) at 4 and 12 weeks, respectively. Similarly, the change in VAS score peaked at −20.5 ± 8.74 at 4 weeks in the BT group, and was −15.6 ± 8.68 at 12 weeks. The least squares mean difference (95% CI) between the two groups at 4 and 12 weeks was −14.7 (−34.9, 5.5) and −12.9 (−31.8, 6.0), respectively. The changes in VHI and VAS scores after reinjections were similar to those after the initial injection of BT. Although statistical significance was not seen in this study, VHI and VAS successfully improved by BT injection.

### ABSD

In one ABSD subject, the changes in the number of aberrant morae after reinjections of BT were greater than that after initial injection (Figure 3). The change value of the G score in the GRBAS scale was −1.5 and −1.0 at 2 and 4 weeks postinjection, respectively; the respective B scores were −1.0 and −0.5. BT treatment improved the G and B, but no other GRBAS element scores changed significantly at any evaluation time point. No significant change in the VHI or VAS scores was seen in two subjects.

### Safety evaluation

No clinically significant changes in the laboratory or vital signs data were observed in any subject. In the ADSD patients, the most frequent AE was a voice disorder (77.3%), followed by a swallowing disorder (40.9%), nasopharyngitis (22.7%), fatigue (13.6%), and gastroenteritis (9.1%). The voice and swallowing disorders were characterized by breathy hoarseness and liquid aspiration, respectively, and were observed after the first to the third BT injections. In affected subjects, vocal fold movement on the BT injection side was mildly impaired. The AEs were mild, with the exception of one subject with a moderate voice disorder; no serious AE was reported. The voice and swallowing disorders resolved after 25.8 and 12 weeks.

| Subject demographics                        | Adductor type | Abductor type |
|---------------------------------------------|---------------|---------------|
|                                            | BT            | Placebo       | BT            |
| No.                                         | 11            | 11            | 2             |
| Age, years                                  | 38.5 ± 11.2   | 41.6 ± 10.0   | 28, 29        |
| Female:male                                 | 10:1          | 10:1          | 1:1           |
| Disease duration, years                     | 10.5 ± 10.0   | 5.9 ± 3.4     | 4, 10         |
| No. of aberrant morae                       | 19.2 ± 1.36   | 21.3 ± 1.86   | 7.15          |

Abbreviations: BT, botulinum toxin; VAS, visual analog scale; VHI, Voice Handicap Index.

---

**FIGURE 2** Changes in the number of aberrant morae in ADSD. The number of aberrant morae decreased significantly at 2, 4, and 8 weeks after BT injection. *\( p < 0.05 \)
15.8 days, respectively. One of the ABSD subjects developed a mild voice disorder after the initial injection, but recovered within 4 days. No swallowing disorder was observed.

**DISCUSSION**

Laryngeal injection of BT to treat SD was first performed in 1984 by Blitzer et al [1]. Over the past 30 years, more than 150 articles on this treatment for SD have been published, with most reporting that it was effective [3,4,6,26,27]. Blitzer et al. reported a 91.2% response rate in a large series of 1,300 patients treated over 24 years [18]. Tisch et al. treated 144 patients, of whom 81.9% showed excellent or very good outcomes [6]. BT is generally safe; only mild hoarseness and aspiration have been reported after injection. Thus, the American Academy of Otolaryngology–Head and Neck Surgery recommend BT therapy as the treatment of choice for ADSD (Clinical Practice Guideline: Hoarseness [Dysphonia]) [16]. BT is also effective for treating ABSD, but less so than for ADSD [27–29]. However, most previous studies were not double-blinded, and the quality of the evidence was low. Boutsen et al. [30] analyzed 30 studies; overall, BT led to moderate improvement, but the patient cohorts, measurements, and treatment conditions varied markedly. It was concluded that caution is required when considering whether to use BT to treat ADSD.

An earlier review [27] found only one study on BT therapy for ADSD, by Troung et al. [31] with high methodological quality (double-blinded controlled study). This prospective, randomized, controlled clinical trial included blinded outcome assessment and met the Class I criteria of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The BT group exhibited a significant reduction in voice perturbation and fundamental frequency range. Also, the spectrographic voice characteristics and speech scores improved. Side effects included breathiness (15.3%) and mild bleeding (7.7%). However, voice perturbation and fundamental frequency range are not specific for SD, and subjective parameters were not assessed.

This study was a placebo-controlled, randomized, double-blinded, parallel-group comparison/open-label clinical trial of ADSD patients based on GCP guidelines. This is the first high-quality study based on GCP guidelines of BT therapy for SD. We found significant improvements in objective measures (the number of aberrant morae) at 2 to 12 weeks after injection in ADSD group. At 2 weeks, the S scale decreased significantly in the BT group. The VHI and VAS also exhibited favorable improvements after BT injection. Interestingly, objective parameters (number of aberrant morae and GRBAS scale) showed a peak of improvement at 2 weeks, whereas subjective ones (VHI and VAS) showed a peak at 4 weeks. This can be explained as follows: BT injection leads to breathy hoarseness resulting in unsatisfactory subjective voice

**FIGURE 3** Changes in the number of aberrant morae in ABSD. In one case, the number of aberrant morae decreased after BT injection.

**FIGURE 4** Changes in the number of aberrant morae after repeat BT administrations in ADSD. The number of aberrant morae tended to decrease at 2 and 4 weeks after repeat BT administrations.
improvement at 2 weeks, but the hoarseness gradually disappears within 4 weeks, accompanied by subjective voice improvement. Notably, repeat BT injection tended to increase the therapeutic efficacy. Many ADSD patients show compensatory supraglottic hyperadduction, which mitigates the effects of BT injection [26]. We speculate that repeat BT injection gradually reduces effortful phonation manner, thus enhancing therapeutic efficacy. The treatment effects persisted for about 12 weeks based on the number of aberrant morae and VHI and VAS scores with gradual decrease after 4 weeks, consistent with previous reports of therapeutic effects lasting from 12 to 15 weeks [6,28,31].

Posttreatment AEs included temporary breathy hoarseness and aspiration that generally resolved within 4 weeks. We found that paralytic dysphonia was the most frequent AE, and had a mean duration of 16.2 days, in agreement with Tisch et al.[6]; they stated that patients with posttreatment hoarseness exhibited better responses to treatment. Transient liquid aspiration has also been reported [6,32,33]. In the present study, occurrence rates of the voice and swallowing disorder were higher than in previous reports, possibly because the coordinating investigator conducted detailed interviews after each session of the treatment, and thus uncovered very mild symptoms. No severe or persistent AE was observed.

We enrolled only two ABSD patients, because this condition is rare. Therefore, the ABSD part of the trial was conducted as an exploratory open-label study. Although one of these two patients exhibited no improvement in any voice parameter, the other showed an improvement in the number of aberrant morae; repeat BT injection tended to enhance this effect, suggesting that BT therapy may be efficacious for ABSD patients. Previous studies also supported the utility of BT therapy for ABSD, although the treatment efficacy was lower than that for ADSD [6,29,34]. This is because the PCA muscle lies behind the larynx, and injection is technically difficult. Although a mild voice disorder developed in one patient, no severe AEs were reported. Because no effective surgical intervention for ABSD has yet been established, BT injection is the current treatment of choice.

The major limitation of this study was the small number of subjects, especially ABSD patients, due to the strict inclusion criteria, including no BT therapy within the last 6 months, and abnormal morae cutoffs of ≥12/25 and ≥5/27 in ADSD and ABSD patients, respectively, and rarity of the conditions. Nevertheless, we showed that BT therapy significantly improved ADSD, and has the potential to improve ABSD. We believe that our study provides additional clinical evidence that BT therapy is appropriate for SD.

### CONCLUSIONS

We performed a high-quality clinical trial based on GCP guidelines examining the efficacy and safety of BT injection therapy for SD. In the ADSD patients, BT successfully improved objective and subjective voice parameters. The number of aberrant morae significantly decreased at 4 weeks after treatment, and the improvement persisted for about 12 weeks. The subjective and VHI and VAS scores also improved after treatment. Of the two ABSD patients, one exhibited a decrease in the number in aberrant morae,
suggested that the treatment was effective. The incidence rates of transient breathy hoarseness and aspiration were relatively high. However, the AEs were generally mild and may reflect therapeutic effects. In conclusion, BT injection therapy reduced the severity of voice disorders and can be considered as the treatment of choice for SD.

ACKNOWLEDGMENTS
The authors would like to thank all trial participants and the Center for Clinical Trials of the Japan Medical Association, which supported the study.

CONFLICT OF INTEREST
No author has any competing interest. Allergan supported the clinical trial by providing the investigational drug and placebo. GlaxoSmithKline KK provided pharmacological and safety information on Botox and scientific advice pertaining to the conduct of the study, and applied for BT approval to the PMDA after the trial. However, no author or institution received any financial support from either company, nor were they involved in the data collection, analysis and interpretation, study management, or manuscript preparation.

AUTHOR CONTRIBUTIONS
Masamitsu Hyodo: Conceptualization (lead); data curation (equal); funding acquisition (lead); methodology (lead); project administration (lead); writing–original draft (lead). Asuka Nagao: Data curation (supporting); investigation (supporting); project administration (supporting). Kento Asano: Data curation (equal); funding acquisition (supporting); methodology (supporting); project administration (lead). Masahiko Sakaguchi: Methodology (equal); project administration (supporting); validation (supporting). Kenji Mizoguchi: Data curation (equal); investigation (equal). Koichi Omori: Conceptualization (supporting); data curation (supporting); investigation (equal). Yasuhiro Tada: Investigation (supporting). Hiromitsu Hatakeyama: Investigation (equal). Nobuhiko Oridate: Data curation (equal); investigation (supporting). Kensei Naito: Investigation (supporting). Yoshihiro Iwata: Data curation (equal); investigation (supporting). Hirotaka Shinomiya: Investigation (supporting). Hirotaka Hara: Data curation (equal); investigation (supporting). Tetsuji Sanuki: Data curation (supporting); investigation (equal). Eiji Yumoto: Conceptualization (supporting); data curation (equal); Investigation (supporting); Project administration (equal); writing–review and editing (supporting).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID
Masamitsu Hyodo https://orcid.org/0000-0001-9144-3242

REFERENCES
1. Blitzer A, Brin MF, Fahn S, Lovelace RE. Clinical and laboratory characteristics of laryngeal dystonia: a study of 110 cases. Laryngoscope. 1988;98:636-640.
2. Aronson AE, Bless DM. Spasmodic dysphonia, Clinical Voice Disorders, 4th edn. New York, NY: Thieme Med Publ; 2009:101-133.
3. Blitzer A. Spasmodic dystonia and botulinum toxin: experience from the largest treatment series. Eur J Neurol. 2010;17(Suppl 1):28-30.
4. Patel AB, Bansberg SF, Adler CH, Lott DG, Crujido L. The Mayo Clinic Arizona spasmodic dysphonia experience: a demographic analysis of 718 patients. Ann Otol Rhinol Laryngol. 2015;124:859-863.
5. Hyodo M, Hisa Y, Nishizawa N, et al. The prevalence and clinical features of spasmodic dysphonia: a review of epidemiological surveys conducted in Japan. Auris Nasus Larynx. 2020;48:179-184. https://doi.org/10.1016/j.anl.2020.08.013.
6. Tisch SHD, Brake HM, Law M, et al. Spasmodic dysphonia: clinical features and effects of botulinum toxin therapy in 169 patients – an Australian experience. J Clin Neurosci. 2003;10:434-438.
7. Creighton FX, Hapner E, Klein A, et al. Diagnostic delays in spasmodic dysphonia: a call for clinician education. J Voice. 2015;29:592-594.
8. Dedo HH, Izdebski K. Intermediate results of 306 recurrent laryngeal nerve sections for spasitic dysphonia. Laryngoscope. 1983;93:9-16.
9. Weed DT, Jewett BS, Rainey C, et al. Long-term follow-up of recurrent laryngeal nerve avulsion for the treatment of spastic dysphonia. Ann Otol Rhinol Laryngol. 1996;105:592-601.
10. Koufman JA, Rees CJ, Halum SL, et al. Treatment of adductor-type spasmodic dysphonia by surgical myectomy: a preliminary report. Ann Otol Rhinol Laryngol. 2006;115:97-102.
11. Nakamura K, Muta H, Watanabe Y, et al. Surgical treatment for adductor spasmodic dysphonia – efficacy of bilateral thyroarytenoid myectomy under microlaryngoscopy. Acta Otolaryngol. 2008;128:1348-1353.
12. Berke GS, Blackwell KE, Gerratt BR, et al. Selective laryngeal adductor denervation-reinnervation: a new surgical treatment for adductor spasmodic dysphonia. Ann Otol Rhinol Laryngol. 1999:108:227-231.
13. Isshiki N, Haji T, Yamamoto Y, et al. Thyroplasty for adductor spasmodic dysphonia: further experiences. Laryngoscope. 2001;111(4 Pt 1):615-621.
14. Sanuki T, Yumoto E. Long-term evaluation of type 2 thyroplasty with titanium bridges for adductor spasmodic dysphonia. Otolaryngol Head Neck Surg. 2017;157:80-84.
15. Murry T. Spasmodic dysphonia: let’s look at that again. J Voice. 2014;28:694-699.
16. Stachler RJ, Francis DO, Schwartz SR, et al. Clinical practice guideline: hoarseness (Dysphonia) (Update). Otolaryngol Head Neck Surg. 2018;158(1 suppl):S1-S42.
17. Sulica L. Contemporary management of spasmodic dysphonia. Curr Opin Otolaryngol Head Neck Surg. 2004;12:543-548.
18. Blitzer A. Spasmodic dysphonia and botulinum toxin: experience from the largest treatment series. Eur J Neurol. 2010;17:28-30.
19. Watts CR, Truong DD, Nye C. Evidence for the effectiveness of botulinum toxin for spasmodic dysphonia from high-quality research designs. J Neural Transm. 2008;115:625-630.
20. Warner N, Arai T. Japanese mora-timing: a review. Phonetic. 2001;58:1-25.
21. Kumada M, Kobayashi T, Kosaki H, Niimi S. ’Mora method’ for objective evaluation of severity of spasmodic dysphonia. Jpn J Logop Phoniatr. 1997;38:176-181.
22. Omori K. Diagnosis of voice disorders. JMAJ. 2011;54:248-253.
23. Yamaguchi H, Shrivas stave R, Andrews ML, et al. A comparison of voice quality ratings made by Japanese and American listeners using the GRBAS scale. Folia Phoniatr Logop. 2003;55:147-157.
24. Jacobson BH, Johnson A, Grywalski C, et al. The Voice Handicap Index (VHI): development and validation. *Am J Speech Lang Pathol*. 1997;6:66-70.

25. Taguchi A, Mise K, Nishikubo K, Hyodo M, Shiromoto O. Japanese version of voice handicap index for subjective evaluation of voice disorder. *J Voice*. 2012;26(668):e15-e19.

26. Ludlow CL. Treatment for spasmodic dysphonia: limitations of current approaches. *Curr Opin Otolaryngol Head Neck Surg*. 2009;17:160-165.

27. Watts C, Whurr R, Nye C. Botulinum toxin injections for the treatment of spasmodic dysphonia. *Cochrane Database Syst Rev*. 2004;3:CD004327.

28. Brin MF, Blitzer A, Stewart C. Laryngeal dystonia (spasmodic dysphonia): observations of 901 patients and treatment with botulinum toxin. *Adv Neurol*. 1998;78:237-252.

29. Blitzer A, Brin MF, Stewart C, Aviv JE, Fahn S. Abductor laryngeal dystonia: a series treated with botulinum toxin. *Laryngoscope*. 1992;102:163-167.

30. Boutsen F, Cannito MP, Taylor M, Bender B. Botox treatment in adductor spasmodic dysphonia: a meta-analysis. *J Speech Lang Hear Res*. 2002;45:469-481.

31. Troung D, Rontal M, Rolnick M, Aronson A, Mistura K. Double blind controlled study of botulinum toxin in adductor spasmodic dysphonia. *Laryngoscope*. 1991;101:630-634.

32. Holzer SE, Ludlow CL. The swallowing side effects of botulinum toxin type A injection in spasmodic dysphonia. *Laryngoscope*. 1996;106(1 Pt 1):86-92.

33. Novakovic D, Waters HH, D’Elia JB, Blitzer A. Botulinum toxin treatment of adductor spasmodic dysphonia: longitudinal functional outcomes. *Laryngoscope*. 2011;121:606-612.

34. Woodson G, Hochstetler H, Murry T. Botulinum toxin therapy for abductor spasmodic dysphonia. *J Voice*. 2006;20:137-143.

How to cite this article: Hyodo M, Nagao A, Asano K, et al. Botulinum toxin injection into the intrinsic laryngeal muscles to treat spasmodic dysphonia: A multicenter, placebo-controlled, randomized, double-blinded, parallel-group comparison/open-label clinical trial. *Eur J Neurol*. 2021;28:1548-1556. [https://doi.org/10.1111/ene.14714](https://doi.org/10.1111/ene.14714)

**APPENDIX 1**

Based on the results of this clinical trial, the use of Botox to treat SD was approved by the PMDA of Japan on May 25, 2018. The cost of Botox is covered by the Japanese social medical insurance system.