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Ophthalmic Technology Assessment

Chemodenervation for the Treatment of Facial Dystonia

A Report by the American Academy of Ophthalmology

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Purpose: To review the medical literature on the outcomes and complications of various Food and Drug Administration-approved botulinum toxins for benign essential blepharospasm (BEB) and hemifacial spasm (HFS).

Methods: Literature searches were last conducted in February 2017 in PubMed for articles published in English and in the Cochrane Library database without language limitations; studies published before 2000 were excluded. The combined searches yielded 127 citations. Of these, 13 articles were deemed appropriate for inclusion in this assessment, and the panel methodologist assigned ratings to them according to the level of evidence.

Results: A combined total of 1523 patients (1143 with BEB and 380 with HFS) were included in the 13 studies. Five studies provided level I evidence, 2 studies provided level II evidence, and 6 studies provided level III evidence. Pretarsal injections were more efficacious than preseptal injections (96% vs. 86%, respectively). Pretarsal injections also resulted in a higher response rate on clinical scales ($P < 0.05$) and a longer duration of maximum response for both HFS and BEB. Patients with HFS require lower overall doses of onabotulinumtoxinA than patients with BEB for a similar duration of effect. Adverse events were dose related, and they occurred more frequently in patients who were given more units.

Conclusions: Level I evidence supports the efficacy of Botox (Allergan Corp., Irvine, CA), Meditoxin, and Xeomin (Merz Pharmaceuticals, Frankfurt am Main, Germany) for the treatment of BEB. Meditoxin and Botox have equivalent effectiveness and incidence of adverse events for BEB and HFS. Dysport (Ipsen Biopharmaceuticals, Inc, Paris, France) seems to have efficacy similar to Botox and Meditoxin for BEB and HFS, but any definitive conclusions from the 2 level II studies in this review are limited by differences in the methodologies used. Higher doses of Botox and Dysport result in more adverse events. Repeated treatments using Botox seem to maintain efficacy for treatment of facial dystonias over a follow-up period of at least 10 years, based on level III evidence. *Ophthalmology 2018;■:1–9 © 2018 by the American Academy of Ophthalmology*

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Oculoplastics and Orbit Panel was to analyze the efficacy of various Food and Drug Administration (FDA)-approved botulinum toxin preparations in the treatment of benign essential blepharospasm (BEB) and hemifacial spasm (HFS).

Background

The first clinical use for botulinum toxin was described in 1980 by Scott,[1] who reported on its potential efficacy in the treatment of strabismus. The toxin blocks release of acetylcholine at the neuromuscular junction, resulting in temporary paresis of the muscle. In 1989, the United States FDA approved the use of onabotulinumtoxinA (Botox; Allergan Corp., Irvine, CA) for the treatment of strabismus and blepharospasm associated with dystonia, including BEB and HFS in patients 12 years of age and

https://doi.org/10.1016/j.ophtha.2018.03.013
ISSN 0161-6420/18

older.[2] OnabotulinumtoxinA also is marketed under the names Botox Cosmetic, Vistabel, and Vistabex.

Of the 7 known botulinum neurotoxins (A−G), only 2 (A and B) are approved by the FDA for clinical use in the United States. Since the initial introduction of Botox, 2 additional botulinum toxin A preparations have been approved for use in facial dystonias: abobotulinumtoxinA (Dysport [also called Reloxin and Azzalure]; Ipsen Biopharmaceuticals, Inc., Paris, France) and incobotulinumtoxinA (Xeomin; Merz Pharmaceuticals, Frankfurt am Main, Germany).[3] Although units are not interchangeable between neurotoxins, some consensus in dosing regimens exists. Dysport is similar to Botox, but has a dose ratio of approximately 2−4:1 for the treatment of BEB and HFS.[3−5] The dose ratio of Xeomin (1−1.2:1) is identical or nearly identical to that of Botox.[3] During the manufacturing of Xeomin, complexing proteins are removed to allow for unreconstituted toxin to be stored at room temperature as well as potentially to reduce the development of antibotulinumtoxinA antibodies, which theoretically could result in tachyphylaxis, although this hypothesis remains unproven.[3,6]

Botulinum toxin B preparations are limited to rimabotulinumtoxinB (MyoBloc; NeuroBloc, Solstice Neurosciences, US WorldMeds, Louisville, KY). Myobloc has higher autonomic side effects than Botox does and therefore is used more often for nonmotor abnormalities (e.g., hyperhidrosis, sialorrhea). The dose ratio between Botox and MyoBloc varies between 1 to 24 and 100.

Question for Assessment

The focus of this assessment was to address the following question: What is the efficacy of various FDA-approved botulinum toxin preparations in the treatment of facial dystonias (BEB and HFS)?

Description of Evidence

Literature searches were conducted last on February 28, 2017, in PubMed for articles published in English and in the Cochrane Library database without a language limitation. Because the goal of this assessment was to compare various botulinum toxins for facial dystonia and not simply to report on the efficacy of Botox, publications before 2000 were excluded. The combined searches yielded 127 citations. The following search terms were used along with date, publication, and language filters: *botulinum toxins*, *onabotulinumtoxinA*, *rimabotulinumtoxinB*, *incobotulinumtoxinA*, *botulinum*, *Botox*, *Myobloc*, *Xeomin*, *hemifacial spasm*, *blepharospasm*, and *Meige syndrome*.

Inclusion criteria required that the study population comprised primarily patients with BEB, HFS, or other facial dystonias and that it included at least 25 patients treated with chemodenervation and followed up for at least 6 weeks. Analysis was confined to products approved by the FDA. Of the 127 citations, 13 studies met the inclusion criteria and were abstracted for review. Abstracted data included study design, number of patients, patient demographics, diagnosis (BEB, HFS, or oral facial dystonia [Meige] syndrome), chemodenervation agent(s) used, clinical assessments before and after treatment, and adverse events. The methodologist (E.A.B.) then assigned a rating to each study based on the rating scale developed by the Oxford Centre for Evidence-Based Medicine.[7] A level I rating was assigned to well-designed and well-conducted randomized clinical trials, a level II rating was assigned to well-designed case-control and cohort studies and lower-quality randomized studies, and a level III rating was assigned to case series, case reports, and lower-quality cohort and case-control studies. Five of the 13 studies were rated level I, 2 were rated level II, and 6 were rated level III.

Clinical Rating Scales

Many rating, or assessment, scales initially were used to measure the efficacy of Botox against placebo when treating BEB. Since then, a variety of rating scales have been used to determine the efficacy of botulinum toxin preparations to treat BEB and HFS, as shown in Table 1.[8−11]

As noted in a review by Wabbels et al,[12] BEB rating scales can be divided into 3 categories: clinical, activities of daily living, and global activity. Clinical scales (e.g., Jankovic Rating Scale [JRS]) are used by observer evaluators and activities of daily living scales (e.g., Blepharospasm Disability Index [BSDI]) are used by patients for self-assessment. Global activity scales (e.g., Patient Evaluation of Global Response [PEGR]) measure the overall, rather than disease-specific, effects of treatment, and typically they are limited to secondary-outcome analyses in most studies.

The 2 most widely used grading systems are the JRS[9] and the BSDI.[11−13] Both have limitations in sensitivity when used to assess mild disease. The JRS consists of 2 categories, severity and spasm frequency, and each category is divided into 5 levels (0−4) on a Likert-type scale of ascending symptoms. The BSDI survey measures the impact of BEB and BEB treatment on 5 specific activities of daily living and 1 generalized activity ("doing everyday activities").[13] Each activity is rated according to a 5-point scale, with an option to select "not applicable."

Jankovic et al[13] used the data of 300 patients with BEB who were treated with either Botox or Xeomin to study the validity of the BSDI compared with other rating scales. Patients completed the rating scales at baseline and 21 days after treatment. A high internal consistency was found between the BSDI and the JRS and PEGR scales. In addition, significant improvement in both JRS and BSDI scores for both Botox and Xeomin were noted. The authors stressed that the use of BSDI is important in evaluating treatment efficacy in BEB to demonstrate improvement in quality-of-life metrics. The use of both observer-based evaluations (usually for primary outcomes) and patient self-assessment scales (usually for secondary outcomes) is becoming more prevalent.

Published Results

The published results on the efficacy of various FDA-approved botulinum toxin preparations for the treatment of