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Effectiveness of 0.3% Hyaluronic Acid Eye Drops for Benign Essential Blepharospasm and Hemifacial Spasm with Botulinum Toxin–induced Dry Eye

Anuchit Poonyathalang, MD
Nanida Tiraset, MD
Natthapon Rattanathamsakul, MD

Background: This study evaluates the effectiveness of 0.3% hyaluronic acid (HA) eye drops in patients receiving concurrent botulinum toxin (BoNT) injections for benign essential blepharospasm (BEB) or hemifacial spasm (HFS).
Methods: This randomized controlled cross-over trial study involved 14 patients with BEB and 33 patients with HFS randomized into two groups (early treatment and deferred treatment) for 3 months of treatment with 0.3% HA eye drops. Data collected at baseline, 3 months, and 6 months included Blepharospasm Severity Scale (BSS) score in patients with BEB; Samsung Medical Class Grading Scale score in patients with HFS; and dry eye symptoms, lower eyelid tear meniscus height (TMH), tear breakup time (TBUT), and corneal fluorescein staining in both groups.
Results: After 3 months of 0.3% HA instillation, patients with BEB in both groups showed significant improvement in BSS, TMH, TBUT, and the amelioration of subjective dry eye symptoms and corneal staining ($P < 0.05$). However, discontinuation of 0.3% HA eye drops worsened BSS, TMH, and TBUT. Patients with HFS also experienced significant improvement in Samsung Medical Class score, subjective dry eye symptoms, and objective corneal findings ($P < 0.05$).
Conclusions: Treatment with 0.3% HA eye drops led to significant improvement in spasm severity, and dry eye parameters, after 3 months of instillation in patients with BEB or HFS during concurrent treatment with BoNT injections. The 0.3% HA eye drops were safe and might serve as an add-on treatment for symptom improvement. *(Plast Reconstr Surg Glob Open 2024; 12:e6050; doi: 10.1097/GOX.0000000000006050; Published online 13 August 2024.)*

INTRODUCTION

Benign essential blepharospasm (BEB) and hemifacial spasm (HFS) are rare facial dystonias[1–3] that typically initiate with an abnormal, increased frequency of involuntary, blinking. Although BEB is characterized by bilateral involuntary eyelid closure, HFS is a movement disorder leading to facial muscles contracting involuntarily.[4] If these disorders progress, the frequency of their symptoms increases until they become uncontrollable, visible, and distressing and impair daily activities and quality of life (QoL[5]). Both conditions also cause anxiety, depression, social disability, and socioeconomic probelms.[5–8]

The increased blink rate associated with BEB and HFS can result in abnormal restoration of tear film or tear film instability, causing eye dryness[9]; in fact, dry eye disease (DED) is common in patients with BEB or HFS.[6,10–15] Patients with BEB typically display compromised tear production, distribution, and drainage.[15] Furthermore, blepharospasm contributes to ocular inflammation in patients with DED,[16] with significantly increased levels of several inflammatory cytokines in the tear fluid of patients with BEB and DED.[16] Conversely, DED symptoms may trigger blinking to compensate for tear film instability or deficiency.[10] The medial portion of the orbicularis oculi muscle in the lower eyelid may also act as a lacrimal

From the Department of Ophthalmology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

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pump to drain tears into the canaliculi[17] and contribute to eye dryness.

DED is a multifactorial disease of the ocular surface whose etiology includes tear film instability[18] and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities.[19] Ocular symptoms of DED include discomfort, pain, dryness, and foreign body sensation,[20] all of which diminish QoL.[20] Mild DED causes foreign body sensations and increases tearing, whereas severe, untreated DED can cause corneal ulcerations. Like BEB and HFS, DED prevalence increases with age.[2,21–25]

The local injection of botulinum neurotoxin (BoNT) type A (BoNT-A)[1,26] remains the gold standard for treating both BEB and HFS and has been found to be both safe and highly effective.[27] Notably, periorbital BoNT-A injections (eg, into the medial orbicularis oculi[28,29]) was found to decrease DED symptoms[15] or improve DED in patients with BEB.[10,11,15,30] However, there is conflicting evidence[31] that BoNT-A may either not improve DED[10] or may weaken the orbicularis oculi muscle. Consequently, lagophthalmos[32] may occur such that incomplete eyelid closure leads to DED. Importantly, BoNT-A muscle paralysis is temporary[33,34] and requires serial repeated injections for total symptomatic control, suggesting that the patient may experience repeated episodes of DED.

DED treatments include hypotonic or isotonic buffered artificial tears comprising electrolytes, surface-active agents, and assorted viscosity-enhancing surface lubricants that are intended to replace or augment the natural tear film.[35,36] Artificial tears aid in the relief of DED symptoms by replenishing deficient tear volume,[16] increasing tear stabilization, reducing tear hyperosmolarity, providing a smoother corneal surface, and diluting tear inflammatory cytokines.[35] Currently, hyaluronic acid (HA) is routinely used as an effective lubricating component in tear supplement products to treat DED. HA effectively binds to water, resists dehydration, stabilizes tear film, protects against corneal epithelial damage, stimulates epithelial migration, and demonstrates excellent biocompatibility.[36,37] Commercially available forms of HA artificial eye drops include concentrations of 0.1%, 0.18%, and 0.3%, with one experimental animal model of dry eye showing higher effectiveness with 0.3% HA artificial tears than with 0.1% or 0.18% HA artificial tears.[36]

To our knowledge, there remains a lack of information concerning the efficacy of 0.3% HA in patients with BEB or HFS. Additionally, the potential for post-BoNT-A DED and its consequences requires increased awareness by physicians treating HFS and BEB, whether or not preexisting DED is present. We thus sought to investigate the effectiveness of 0.3% HA eye drops in improving spasm severity and clinical dry eye parameters, in patients with BEB or HFS and concurrent treatment with BoNT-A injections.

METHODS

Study Design

This randomized controlled cross-over open-label study was conducted between April 2020 and July 2021 in the Ophthalmology Clinic of Ramathibodi Hospital, a quaternary care hospital in Bangkok, Thailand.

Takeaways

Question: In patients receiving botulinum toxin (BoNT) for blepharospasm (BEB) and hemifacial spasm (HFS), does 0.3% hyaluronic acid (HA) effectively treat spasm severity and BoNT-induced dry eye symptoms?

Findings: Three months of 0.3% HA eye drops significantly improved dry eye symptoms and test results in patients with BEB and HFS, although this had to be continued to prevent symptom worsening.

Meaning: Clinicians treating BEB or HFS with BoNT-A should offer 0.3% HA eye drops for 3 months post-toxin to improve spasm severity and dry eye symptoms.

Participants

We consecutively recruited all patients with the diagnosis of BEB or HFS who were concurrently treated with BoNT-A injections, regardless of dry eye symptoms. Enrolled participants were 18 years of age or older and provided informed consent to participate in the study.

We excluded patients with any of the following conditions: neurological abnormalities other than craniocervical dystonia, features suggestive of secondary dystonias, history of other active ocular surface disorders or anterior segment diseases, ocular trauma or eyelid/ocular surgery in the preceding 6 months, contact lens wear, and/or concurrent application of any type of artificial tears or other treatments for DED in the preceding 3 months.

Study Protocol

Included patients were randomized into group A (early treatment) or group B (deferred treatment) using a random number method. Neither participants nor investigators were masked to the intervention type.

All patients were scheduled to undergo assessments during three visits: baseline evaluation (month 0), cross-over visit (month 3), and final visit (month 6). Hialid (0.3% purified sodium hyaluronate; Santen Pharmaceutical, Osaka, Japan) was used as a treatment intervention. After allocation, patients in group A were instructed to apply 0.3% HA eye drops to both eyes at 4-hour intervals for 3 months consecutively. In contrast, patients in group B were not allowed to apply any type of artificial tears. In the cross-over visit, patients in group A were instructed to discontinue the eye drops, whereas patients in group B were instructed to begin using 0.3% HA eye drops as described earlier for group A. At the final visit, all patients were re-evaluated. A flow diagram depicting the study protocol is shown in Figure 1. During the study period, all eligible patients were concurrently treated with BoNT-A injections at 3-month intervals.

At each visit, each patient underwent evaluation of BEB or HFS spasm severity, as well as the degree of eye dryness. To minimize measurement variations, all parameters were assessed by the same examiner (N.T.). Adverse events were recorded throughout the study.

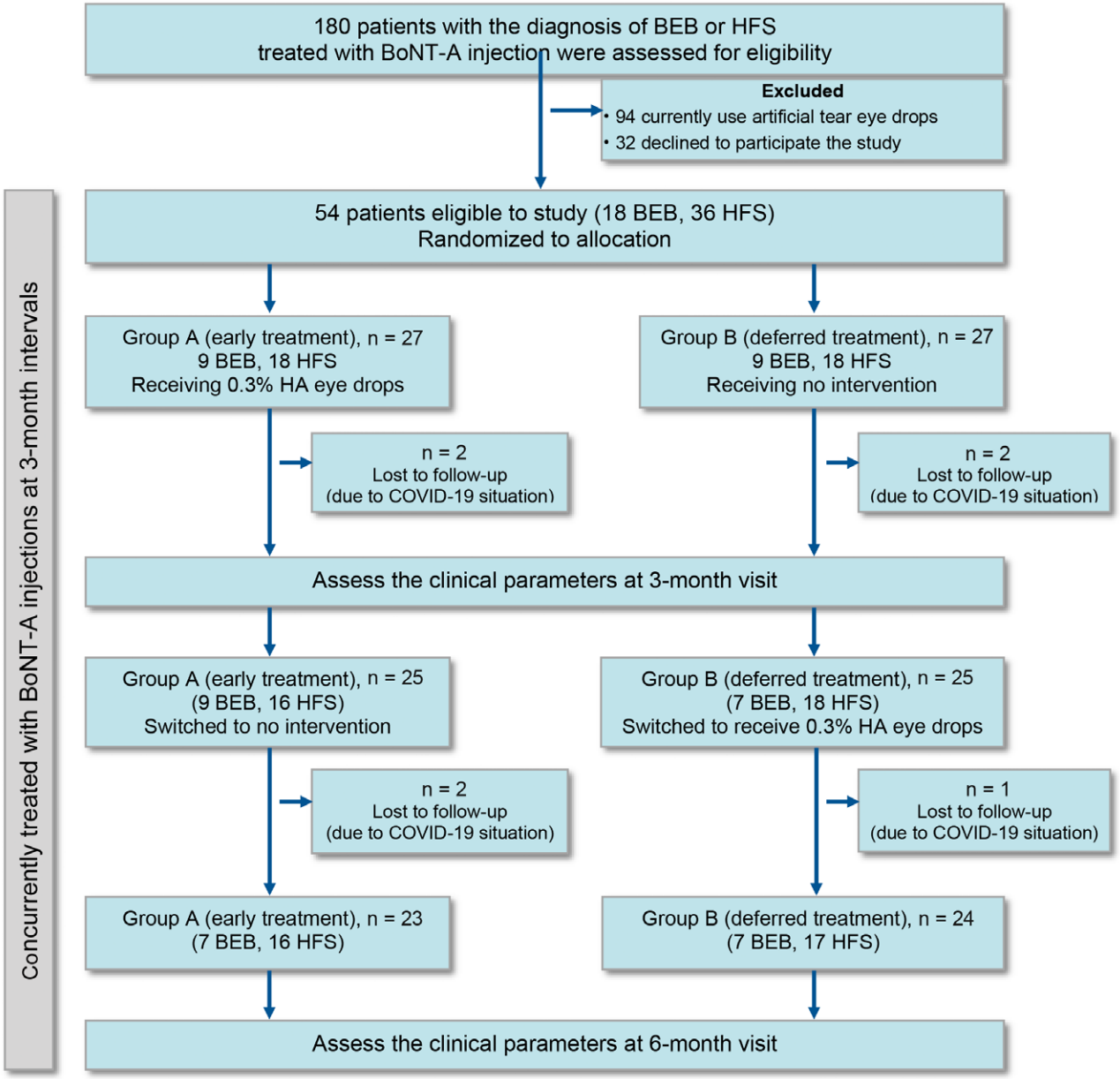

Fig. 1. Flow diagram depicting study protocol.

Blepharospasm Severity Assessment

The Blepharospasm Severity Scale (BSS)[38] was used to evaluate the severity of BEB. This scale is based on objective clinical parameters; it has demonstrated perfect reliability and internal consistency.[38] Spasm severity was video-recorded for 2 minutes, then reviewed by a neuro-ophthalmologist to score the intensity and frequency of spasms, according to parameters shown in Supplemental Digital Contents 1a and 1b, respectively. [**See table, Supplemental Digital Content 1**, which displays (a) parameters of intensity score in BSS, (b) parameters of frequency score in BSS, (c) severity of hemifacial spasm involvement according to Samsung Medical Class (SMC) grading system, (d) frequency of HFS according to SMC grading system, (e) rating of each item in questionnaire regarding subjective symptoms of eye dryness, and (f) baseline characteristics of patients included in the analysis. **http://links.lww.com/PRSGO/D420**.]

HFS Severity Assessment

Spasm severity in HFS was evaluated using the SMC grading scale,[39] as indicated in Supplemental Digital Contents 1c and 1d (**http://links.lww.com/PRSGO/D420**). A disease-specific QoL assessment, the HFS-7 self-rating scale, was used to determine the impact of HFS on daily life.[40] The HFS-7 comprises seven items: having difficulty driving, having difficulty reading, having difficulty watching television or movies, feeling depressed, avoiding eye contact, feeling embarrassed about having the condition, and feeling worried about other's reactions to

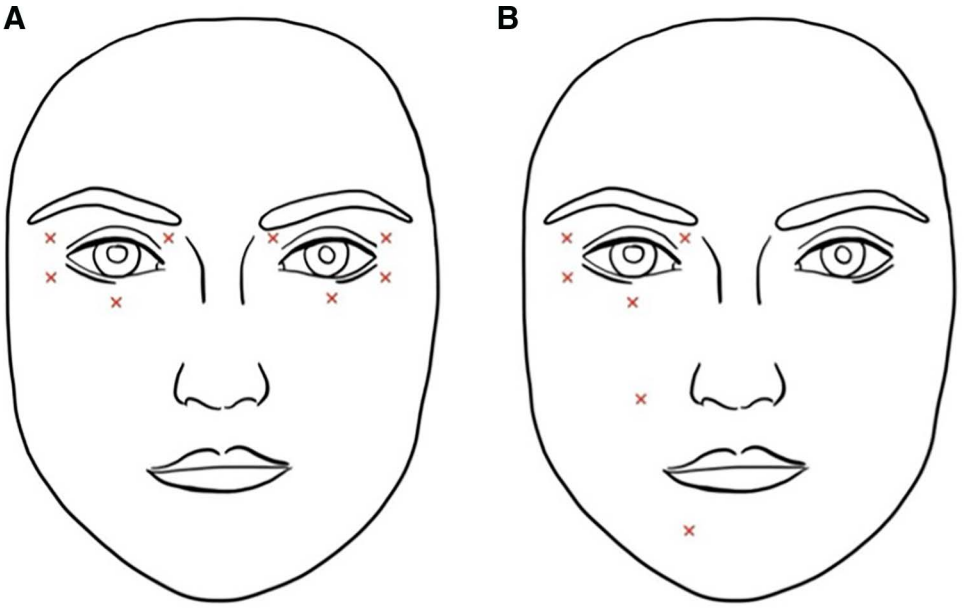

Fig. 2. Schematic illustration showing BoNT-A injection sites. A, Benign essential blepharospasm. B, Hemifacial spasm.

oneself. Patients were asked to score each item on a five-point scale ranging from 0 (never) to 4 (always).

DED Assessment

At each visit, patients underwent assessment of DED using a questionnaire that focused on subjective symptoms of eye dryness; they also underwent an ocular examination. The short questionnaire was adapted from the Standard Patient Evaluation of Eye Dryness questionnaire[12] and consisted of six items: eye dryness, grittiness, or scratchiness; eye soreness or burning; watering; eye fatigue; blurred vision; and eyelid spasms causing difficulty when opening eyes. The patients were asked to score each item on a four-point scale ranging from 0 (no problem) to 3 (intolerable or unable to perform daily task) (**Supplemental Digital Content 1e, http://links.lww.com/PRSGO/D420**); the maximum total score was 18 points.

In the ocular examination, slit lamp biomicroscopy was used to evaluate lower eyelid tear meniscus height (TMH), tear breakup time (TBUT), and corneal fluorescein staining. A sterile fluorescein strip was gently touched to the lower eyelid fornix to stain tear film; patients were then instructed to blink several times to distribute the tear film evenly. Under cobalt blue filter light, the time interval (in seconds) from eye opening to the first appearance of a dark spot on the tear film was recorded, whereas patients gazed straight ahead without blinking; this interval was measured three times, and the mean value was recorded as the TBUT. Moreover, clinical grading of corneal staining was performed using the Oxford grading scale (grade 0–V).[41] The examiner compared the overall corneal staining appearance in a patient with the appearance in a reference figure.

Assessment of Adverse Treatment Effects

The safety of 0.3% HA was assessed during follow-up visits (at 3 and 6 mo). The ocular adverse effects assessment comprised six items: eye irritation, eye burning sensation, eye itching, blurred vision, eye redness, and periocular inflammation. The patients were asked to provide responses to self-rating questions and score each reaction on a 5-point scale ranging from grade 0 (none) to grade 4 (severe reaction).

BoNT-A Injection

BoNT-A (Onabotulinum toxin A, Botox; Allergan, Inc., Irvine, Calif.) was reconstituted from vacuum-dried vials of 100 units by adding 4 or 6 mL of sterile, nonpreserved 0.9% sodium chloride solution to achieve a concentration of 2.5 or 1.67 units per 0.1 mL, respectively. BoNT-A was injected into the bilateral orbicularis oculi muscle in patients with BEB (as shown in Fig. 2A); it was injected into ipsilateral facial nerve-innervated muscles of the upper and lower face in HFS patients (as shown in Fig. 2B). The dosage of BoNT-A in each visit depended on the patient's condition and the physician's clinical judgment.

Ethical Approval

This study protocol followed the tenets of the Declaration of Helsinki and was approved by the institutional review board of the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok. The study protocol has been reviewed and approved retrospectively by the Thai Clinical Trials Registry. The identification number is TCTR20220423002. The study purpose and protocol, as well as the treatment risks and benefits, were clearly explained to each eligible individual. All participants provided informed consent before inclusion in the study and their privacy was protected throughout the analysis.

Statistical Analysis

Participants who completed the study protocol were included in the final analysis. Statistical analyses were

Table 1. Baseline Characteristics of Patients Included in the Analysis

Variables	Total (n = 47)	BEB (n = 14)	HFS (n = 33)
Age, y*	62.8 ± 9.5	69.6 ± 3.8	59.9 ± 9.7
Female sex, n (%)	30 (63.8)	10 (71.4)	20 (60.6)
Affected side, n (%)			
Right	32 (68.1)	14 (100)	18 (54.5)
Left	29 (61.7)	14 (100)	15 (45.5)
Subjective dry eye symptom questionnaire, n (%)			
None (score 0)	6 (12.8)	1 (7.1)	5 (15.2)
Mild (score 1–6)	34 (72.3)	11 (78.6)	23 (69.7)
Moderate (score 7–12)	6 (12.8)	2 (14.3)	4 (12.1)
Severe (score 13–18)	1 (2.1)	0 (0.0)	1 (3.0)
Mean subjective dry eye symptom questionnaire score*	4.1 ± 3.1	3.8 ± 2.1	4.3 ± 3.5
Concentration of BoNT-A use, units/mL			
16.67 (100 units/6 mL)	43 (91.5)	14 (100)	29 (87.9)
25 (100 units/6 mL)	4 (8.5)	0 (0.0)	4 (12.1)
Mean dose of BoNT-A injection per visit, units*	14.4 ± 5.0	14.7 ± 2.5	14.3 ± 5.8

* Data shown as mean ± SD.

performed using PASW software for Windows, version 18.0 (SPSS, Inc., Chicago, Ill.). Categorical variables were reported as n (%); continuous variables were reported as mean ± SD for normally distributed data or as median (interquartile range) for nonnormally distributed data. Paired *t* tests were used to assess changes in parameters with normal distributions, whereas the Wilcoxon signed rank test was used to assess changes in parameters with nonnormal distributions. All *P* values were two-tailed, and a *P* value of less than 0.05 was considered statistically significant.

RESULTS

Demographic Data

In total, 54 patients receiving BoNT-A treatment (18 BEB and 36 HFS) were eligible for inclusion in the study. Of these, 47 patients (14 BEB and 33 HFS) completed all visits and provided information for analysis (Table 1). The mean ages at recruitment were 69.6 ± 1.0 years in the BEB group and 59.9 ± 1.7 years in the HFS group. More than 60% of the patients were women. Most patients (87.0%) exhibited one or more dry eye symptoms with varying degrees of severity (mainly mild). The mean dose of BoNT-A per visit was 14.4 ± 5.0 units; this did not differ between diseases. After randomization, group A (early treatment) comprised seven patients with BEB and 16 patients with HFS, whereas group B (deferred treatment) comprised seven patients with BEB and 17 patients with HFS. Baseline characteristics were similar between groups, as shown in Supplemental Digital Content 1f (**http://links.lww.com/PRSGO/D420**).

Assessments of Patients with BEB

Baseline BSS scores were similar between groups. After 3 months of treatment with 0.3% HA eye drops (between baseline and 3-month visits), patients in group A experienced significant improvements in BSS score ($P = 0.030$), TMH ($P = 0.004$), TBUT ($P = 0.001$), and mean corneal fluorescein staining grade ($P = 0.005$). They also reported a significant improvement in the mean subjective dry eye symptom questionnaire score ($P = 0.010$). The proportion of patients without subjective dry eye symptoms (score 0) increased from 14.3% to 57.1% after intervention. Furthermore, the proportion of patients without corneal fluorescein staining (grade 0) increased from 42.9% to 92.9% (Table 2).

After 3 months of 0.3% HA instillation (between 3- and 6-month visits), patients in group B showed improvements in BSS score ($P = 0.002$), TMH ($P = 0.002$), TBUT ($P = 0.004$), and mean corneal fluorescein staining grade ($P = 0.023$). The proportion of patients without corneal fluorescein staining (grade 0) increased from 42.9% to 85.7%. Although these patients reported a significant improvement in the mean subjective dry eye symptom score ($P = 0.004$), the proportion of patients without subjective dry eye symptoms (score 0) showed a small increase (from 0% to 14.3%).

After discontinuation of 0.3% HA eye drops in group A, the patients exhibited significant worsening of BSS score ($P = 0.022$), as well as TMH and TBUT ($P = 0.010$ and 0.001, respectively). The mean corneal fluorescein staining grade and mean subjective dry eye symptom score also worsened after discontinuation of 0.3% HA ($P = 0.004$ and 0.035, respectively).

Assessments of Patients with HFS

At baseline, patients in both groups had similar SMC and HFS-7 scale scores. After 3 months of treatment with 0.3% HA (between baseline and 3-month visits), patients in group A showed a significant improvement in total SMC score ($P = 0.013$), and the intensity and frequency of spasm subscores ($P = 0.022$ and 0.023, respectively). The mean subjective dry eye symptom scores, TBUT, and mean corneal fluorescein staining grade also demonstrated improvements ($P = 0.007$, 0.010, and 0.020, respectively). The HFS-7 scale score and TMH tended to decrease after therapy, but these differences were not statistically significant ($P = 0.074$ and 0.131, respectively). The proportion of patients with normal corneal staining (grade 0) increased from 56.3% to 93.8% (Table 3).

Table 2. Changes in Spasm Severity and Dry Eye-related Parameters in BEB during the Study Period

	Group A (Early Treatment) n = 7 (14 Eyes)					Group B (Deferred Treatment) n = 7 (14 Eyes)				
Parameters	**Baseline**	**3 mo**	**6 mo**	***P****	***P*†**	**Baseline**	**3 mo**	**6 mo**	***P****	***P*†**
Mean score of BSS‡§	8.0 ± 1.8	6.3 ± 2.0	7.6 ± 1.7	0.030	0.022	7.4 ± 2.0	7.4 ± 1.8	5.9 ± 1.6	1.000	0.002
Subjective dry eye symptom questionnaire, n (%)§										
None (score 0)	1 (14.3)	4 (57.1)	1 (14.3)	0.350	0.350	0 (0.0)	0 (0.0)	1 (14.3)	0.143	1.000
Mild (score 1–6)	5 (71.4)	3 (42.9)	5 (71.4)			6 (85.7)	6 (85.7)	6 (85.7)		
Moderate (score 7–12)	1 (14.3)	0 (0.0)	1 (14.3)			1 (14.3)	1 (14.3)	0 (0.0)		
Severe (score 13–18)	0 (0.0)	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)	0 (0.0)		
Mean score of subjective dry eye symptom questionnaire§	3.4 ± 2.4	1.4 ± 2.2	3.9 ± 3.9	0.010	0.035	4.1 ± 1.9	4.9 ± 2.0	1.6 ± 1.0	0.253	0.004
TMH, mm¶	0.17 ± 0.09	0.27 ± 0.05	0.19 ± 0.09	0.004	0.010	0.23 ± 0.10	0.22 ± 0.08	0.31 ± 0.04	0.655	0.002
TBUT, s¶	2.86 ± 1.72	4.06 ± 1.49	2.37 ± 1.59	0.001	0.001	3.08 ± 1.14	3.08 ± 1.24	4.33 ± 1.27	0.510	0.004
Corneal fluorescein staining grade, n (%)¶										
Grade 0	6 (42.9)	13 (92.9)	5 (35.7)	NA	NA	8 (57.1)	6 (42.9)	12 (85.7)	NA	NA
Grade I	7 (50.0)	1 (7.1)	7 (50.0)			4 (28.6)	6 (42.9)	2 (14.3)		
Grade II	1 (7.1)	0 (0.0)	2 (14.3)			2 (14.3)	2 (14.3)	0 (0.0)		
Grade III	0 (0.0)	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)	0 (0.0)		
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)	0 (0.0)		
Grade V	0 (0.0)	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)	0 (0.0)		
Mean grade of corneal fluorescein staining¶	0.64 ± 0.63	0.07 ± 0.27	0.79 ± 0.70	0.005	0.004	0.57 ± 0.76	0.71 ± 0.73	0.14 ± 0.36	0.157	0.023

*Parameters compared between baseline visit and visit at 3 months.
†Parameters compared between visit at 3 months and visit at 6 months.
‡Data shown as mean ± SD.
§Calculated according to the number of patients.
¶Calculated according to the number of eyes measured.
NA, not available.

After 3 months of treatment with 0.3% HA (between 3- and 6-month visits), patients in group B showed improvements in SMC total score ($P = 0.024$), involvement of spasm subscore ($P = 0.027$), and frequency of spasm subscore ($P = 0.030$), as well as TMH ($P = 0.012$), TBUT ($P = 0.001$), and mean corneal fluorescein staining grade ($P = 0.007$). Additionally, they showed an improvement in subjective dry eye symptoms ($P = 0.073$). The proportion of patients without subjective dry eye symptoms (score 0) increased from 17.6% to 52.9%, whereas the proportion of patients without corneal fluorescein staining (grade 0) increased from 47.1% to 94.1%. Nonetheless, the HFS-7 scale score failed to show improvement after intervention ($P = 0.423$).

After discontinuation of 0.3% HA eye drops in group A, patients showed significant worsening of TBUT ($P = 0.004$) and mean subjective dry eye symptom score ($P = 0.043$). The SMC score, HFS-7 scale score, TMH, and corneal fluorescein staining grade tended to worsen after discontinuation of HA, but these differences were not statistically significant ($P > 0.005$).

Safety and Adverse Effects of 0.3% HA

No serious adverse events occurred during the study. All patients could tolerate 0.3% HA well and completed the 3-month period of eye drop instillation. No periocular inflammation was reported; a few patients reported a mild burning sensation (6.4%) and eye redness (2.1%) (Table 4). Higher numbers of patients reported eye irritation (10.6%), eye itching (17.0%), and transient blurred vision (19.1%). However, most reported adverse events were mild (grade 1).

All study outcomes are summarized in the graphical representation in Figure 3.

DISCUSSION

To our knowledge, this is the first study to evaluate the effects of artificial tears on spasm severity in patients with BEB or HFS and suggests artificial tear substitution as a potential primary treatment option for post-BoNT-A DED in these individuals. Consistent with previous reports, our patients with BEB and HFS also exhibited a high prevalence of DED; overall, 87.2% of our patients had some degree of dry eye. We demonstrated that 0.3% HA eye drops could ameliorate subjective and objective dry eye parameters while reducing spasm severity in these patients. However, these effects may be temporary and can be reversed after discontinuation of treatment.

Sodium hyaluronate, the sodium salt of HA, is an anionic glycosaminoglycan is present in connective tissue, joints, vitreous humor, and aqueous humor. It functions as a tissue lubricant, and its high viscosity provides mechanical protection to tissues. The instillation of 0.3% HA eye drops helped to reduce the BSS score in patients with BEB and the SMC score in patients with HFS. It also improved many clinical dry eye parameters, including TMH and TBUT. The reversible and transient effect of 0.3% HA on BEB or HFS spasm severity and clinical parameters after its discontinuation is likely due to physiological tear drainage

Table 3. Changes in Spasm Severity, HFS-related QoL Score, and Dry Eye-related Parameters in HFS during the Study Period

	Group A (Early Treatment) n = 16 (32 Eyes)					Group B (Deferred Treatment) n = 17 (34 Eyes)				
Parameters	**Baseline**	**3 mo**	**6 mo**	***P****	***P*†**	**Baseline**	**3 mo**	**6 mo**	***P****	***P*†**
SMC grade‡										
Involvement score	2.1 ± 1.2	1.1 ± 1.3	1.6 ± 1.3	0.022	0.131	1.9 ± 0.9	2.2 ± 1.1	1.5 ± 0.8	0.218	0.027
Frequency score	1.9 ± 1.2	1.0 ± 1.2	1.5 ± 1.1	0.023	0.066	1.7 ± 0.8	2.1 ± 1.0	1.6 ± 0.8	0.088	0.030
Total score	3.9 ± 2.2	2.1 ± 2.4	3.1 ± 2.2	0.013	0.076	3.6 ± 1.7	4.3 ± 2.0	3.1 ± 1.5	0.131	0.024
HFS-7 rating scale‡										
Difficulty driving	1.3 ± 2.3	0.6 ± 1.7	1.8 ± 2.9	0.068	0.080	2.1 ± 2.8	1.4 ± 2.7	1.3 ± 2.9	0.281	0.854
Difficulty reading	3.1 ± 2.7	2.5 ± 3.2	2.1 ± 3.1	0.384	0.481	3.4 ± 2.5	3.1 ± 3.5	3.0 ± 2.9	0.721	0.811
Difficulty watching television/movies	1.1 ± 1.8	0.4 ± 1.3	0.0 ± 0.0	0.141	0.180	2.4 ± 2.9	2.4 ± 3.2	1.3 ± 2.3	0.798	0.105
Feeling depressed	1.3 ± 2.2	0.8 ± 2.1	2.2 ± 3.0	0.323	0.063	1.9 ± 3.3	1.7 ± 2.9	2.2 ± 3.5	0.865	0.500
Avoiding eye contact	2.4 ± 2.9	1.8 ± 2.9	1.3 ± 2.5	0.396	0.581	2.2 ± 3.0	2.9 ± 3.9	2.6 ± 3.6	0.269	0.340
Feeling embarrassed about having this condition	2.7 ± 3.3	1.7 ± 2.8	1.9 ± 2.9	0.149	0.833	3.1 ± 4.0	2.6 ± 3.7	2.4 ± 3.6	0.571	0.611
Feeling worried about other's reaction to oneself	2.7 ± 3.2	1.8 ± 2.6	1.8 ± 3.0	0.181	1.000	2.8 ± 3.4	2.9 ± 3.9	2.6 ± 3.6	0.905	0.343
Total score	14.5 ± 12.9	9.6 ± 13.9	11.1 ± 13.3	0.074	0.386	17.9 ± 15.0	17.0 ± 18.2	15.5 ± 18.0	0.609	0.423
Subjective dry eye symptom questionnaire, n (%)§										
None (score 0)	3 (18.8)	4 (25.0)	5 (31.3)	0.848	0.091	2 (11.8)	3 (17.6)	9 (52.9)	0.126	0.073
Mild (score 1–6)	11 (68.8)	12 (75.0)	10 (62.5)			12 (70.6)	10 (58.8)	8 (47.1)		
Moderate (score 7–12)	1 (6.3)	0 (0.0)	1 (6.3)			3 (17.6)	3 (17.6)	0 (0.0)		
Severe (score 13–18)	1 (6.3)	0 (0.0)	0 (0.0)			0 (0.0)	1 (5.9)	0 (0.0)		
Mean score of subjective dry eye symptom questionnaire§	3.8 ± 3.9	1.3 ± 0.9	2.4 ± 2.6	0.007	0.043	4.8 ± 3.1	4.4 ± 3.7	1.2 ± 1.4	0.888	0.004
TMH, mm¶										
Affected side	0.21 ± 0.14	0.28 ± 0.07	0.27 ± 0.11	0.131	0.730	0.23 ± 0.12	0.21 ± 0.07	0.27 ± 0.08	0.317	0.012
Unaffected side	0.19 ± 0.10	0.28 ± 0.05	0.27 ± 0.11	0.011	0.595	0.21 ± 0.12	0.23 ± 0.11	0.28 ± 0.08	0.405	0.059
TBUT, s¶										
Affected side	3.26 ± 1.56	5.24 ± 2.74	3.60 ± 1.80	0.010	0.010	3.22 ± 1.89	2.77 ± 1.36	4.87 ± 2.34	0.162	0.001
Unaffected side	3.48 ± 1.66	5.55 ± 2.58	4.43 ± 1.93	0.002	0.002	3.34 ± 1.80	3.60 ± 1.52	5.31 ± 2.21	0.170	0.003
Corneal fluorescein staining grade, n (%)¶										
Affected side										
Grade 0	9 (56.3)	15 (93.8)	11 (68.8)	NA	NA	9 (52.9)	8 (47.1)	16 (94.1)	NA	NA
Grade I	6 (37.5)	1 (6.3)	5 (31.3)			7 (41.2)	8 (47.1)	1 (5.9)		
Grade II	1 (6.3)	0 (0.0)	0 (0.0)			1 (5.9)	1 (5.9)	0 (0.0)		
Grade III	0 (0.0)	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)	0 (0.0)		
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)	0 (0.0)		
Grade V	0 (0.0)	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)	0 (0.0)		
Unaffected side										
Grade I	15 (93.8)	16 (100.0)	11 (68.8)	NA	NA	11 (64.7)	12 (70.6)	16 (94.1)	NA	NA
Grade II	1 (6.3)	0 (0.0)	5 (31.3)			5 (29.4)	4 (23.5)	1 (5.9)		
Grade III	0 (0.0)	0 (0.0)	0 (0.0)			1 (5.9)	1 (5.9)	0 (0.0)		
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)	0 (0.0)		
Grade V	0 (0.0)	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)	0 (0.0)		
Mean grade of corneal fluorescein staining¶										
Affected side	0.50 ± 0.63	0.06 ± 0.25	0.31 ± 0.48	0.020	0.102	0.53 ± 0.62	0.59 ± 0.62	0.06 ± 0.24	0.705	0.007
Unaffected side	0.06 ± 0.25	0.00 ± 0.00	0.31 ± 0.48	0.317	0.025	0.41 ± 0.62	0.35 ± 0.61	0.06 ± 0.24	0.564	0.059

*Parameters compared between baseline visit and visit at 3 months.
†Parameters compared between visit at 3 months and visit at 6 months.
‡Data shown as mean ± SD.
§Calculated according to the number of patients.
¶Calculated according to the number of eyes measured.
NA, not available.

Table 4. Safety Outcomes of 0.3% HA Eye Drops (n = 47)

	No. Patients Experiencing Adverse Effect (n, %)				
Adverse Effects	**Grade 0 (None)**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4 (Severe)**
Eye irritation	42 (89.4)	4 (8.5)	0 (0.0)	1 (2.1)	0 (0.0)
Eye burning sensation	44 (93.6)	2 (4.3)	1 (2.1)	0 (0.0)	0 (0.0)
Eye itching	39 (83.0)	8 (17.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blurred vision	38 (80.9)	9 (19.1)	0 (0.0)	0 (0.0)	0 (0.0)
Eye redness	46 (97.9)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Periocular inflammation	47 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

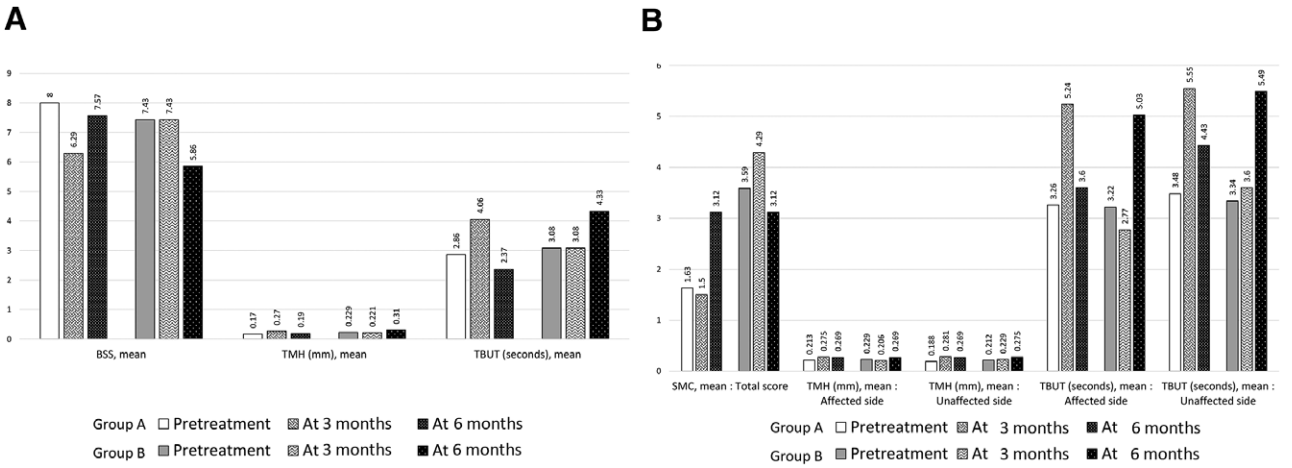

Fig. 3. Graphical representation of study outcomes. Group A applied 0.3% HA eye drops consecutively for 3 months from visit 1. Group B was not allowed to apply any artificial tears. At visit 2 at 3 months, group A discontinued the eye drops, whereas group B initiated application of 0.3% HA eye drops. A, Comparison of statistically significant clinical parameters of patients with BEB at initial phase and cross-over phase. Group A showed statistically significant improvements after treatment with 0.3% HA in BSS ($P = 0.023$), in TMH ($P = 0.004$) and TBUT ($P = 0.001$) at 3 months (initial phase) and statistically significant aggravation after discontinuing 0.3% HA in BSS ($P = 0.041$), TMH ($P = 0.010$), and TBUT ($P = 0.010$) at 6 months (cross-over phase). Group B showed no statistically significant change at 3 months (initial phase) and statistically significant improvements after treatment with 0.3% HA in BSS ($P = 0.016$), TMH ($P = 0.002$), and TBUT ($P = 0.004$) at 6 months (cross-over phase). B, Comparison of statistically significant clinical parameters of patients with HFS at initial phase and cross-over phase. Group A showed statistically significant improvement after treatment with 0.3% HA in SMC total score ($P = 0.013$), TMH on unaffected side ($P = 0.011$), and TBUT on both affected ($P = 0.010$) and unaffected sides ($P = 0.002$) at 3 months (initial phase) and statistically significant aggravation after discontinued 0.3% HA in TMH on both affected ($P = 0.004$) and unaffected sides ($P = 0.009$) at 6 months (cross-over phase). Group B showed no statistically significant change at 3 months (initial phase) and statistically significant improvement after treatment with 0.3% HA in SMC total score ($P = 0.024$), TMH on affected side ($P = 0.012$), and TBUT on both affected ($P = 0.001$) and unaffected sides ($P = 0.004$) at 6 months (cross-over phase).

problems, or to the inability of eye drops alone to correct all DED etiologies.

The cornerstone of BEB and HFS[4] treatment is the injection of BoNT into affected muscles such as the orbicularis oculi, to inhibit acetylcholine release from neuromuscular junctions. Patients may receive between 1.25 and 2.5 units of BoNT, with activity occurring within 3 days, peaking between 1 and 4 weeks, and persisting for up to 4 months. As such, BoNT treatment must be repeated for sustained relief of BEB spasms. However, a definitive impact of BoNT on the ocular surface remains to be established.[31] BoNT-A injection has often been reported to effectively relieve blepharospasm, decrease Ocular Surface Disease Index scores,[16] and increase TBUT in patients with BEB and DED[13,16,42] or HFS.[42] Yet, others have reported that although BoNT-A injections effectively relieved blepharospasm,[10] they significantly decreased Schirmer test values and were ineffective at treating DED.[42] Thus, other treatment modalities may be needed to alleviate dry eye symptoms in patients with BEB or HFS.

A study of the characteristics of tear abnormalities associated with BEB demonstrated tear film instability, shorter TBUT, ocular surface epithelial damage, and decreased wettability.[43] Consistent with the findings in previous reports, we observed short TBUT and a mild degree of ocular surface epithelial damage in patients with BEB or HFS. Unsurprisingly, DED affects tear parameters of both eyes in patients with BEB. In contrast, HFS is expected to be a unilateral disease that does not affect the contralateral eye; however, we found that both TMH and TBUT were reduced bilaterally in patients with HFS. This finding is in agreement with the results reported by Jariyakosol et al.[44] The underlying mechanism may involve activation of compensatory supranuclear control to the contralateral orbicularis muscle, which alters bilateral tear film stability.[42]

We note that almost all objective clinical parameters improved after treatment with 0.3% HA eye drops; however, subjective parameters (ie, subjective dry eye symptom questionnaire results and HFS-7 scale score) did not significantly improve. These results suggest that a more reliable rating scale for the quantitative assessment of disease-specific dry eye symptoms, is needed. Moreover, given that we administered BoNT-A at low doses and with standard injection frequencies, we do not recommend mitigating DED risks in these patients by reducing either treatment parameter. Instead, and given the detrimental effects of DED on patients' QoL,[45] aesthetic physicians planning to administer BoNT for facial spasms should be aware of the DED risks, and proactively ensure that DED assessments are conducted before and after BoNT-A treatment. Treating physicians should also be aware of the difficulty of distinguishing true DED from BEB and accurate diagnosis of DED in patients with BEB because both conditions often occur together.[13,43]

Patients found to have pre-BoNT DED should be prioritized for 0.3% HA eye drops or other DED treatments. As we and others have shown, such treatments relieve existing DED symptoms and prevent DED worsening. Additionally, because treating DED with HA drops also has positive, knock-on benefits for alleviating facial spasms, physicians may wish to proactively provide HA eye drops, which are generally inexpensive, as soon as possible. The cost effectiveness or benefits of dry eye treatments to the patient has already been demonstrated, but in Asia, where this study was conducted, these costs are higher and may continue to increase over time.[46] Once HA is stopped, DED symptoms can recur. Thus, it may be essential for patients to persist with the drops for substantially longer posttreatment or follow-up periods, or until the BoNT-A toxin effect wears off.

An important strength of our study was its randomized controlled cross-over design, which avoided the occurrence of measurement bias. Moreover, clinical parameters concerning the severity of abnormal facial muscle spasms and the severity of DED were assessed. Both aspects demonstrated the benefit of 0.3% HA artificial tears, and taken together, our results support the use of 0.3% HA eye drops as adjunctive therapy during standard treatment for BEB or HFS (eg, BoNT-A injection).

This study had several limitations. First, patients and investigators were not blinded to the intervention; thus, the placebo effect might have influenced the results. Second, the sample size from recruitment was smaller than expected because of the COVID-19 situation; this may have affected the statistical power, thereby limiting our ability to detect significant differences. A larger sample size or multicenter study is needed to confirm our findings. Finally, we used the adapted version of the subjective dry eye symptoms questionnaire to shorten the time for data collection; thus, we could not directly compare our findings to the results from Ocular Surface Disease Index or Dry Eye Questionnaire analyses in previous studies.

CONCLUSIONS

During concurrent treatment with BoNT-A injection, 3 months of treatment with 0.3% HA eye drops was safe and improved spasm severity and clinical dry eye parameters in patients with BEB or HFS, although these effects declined after discontinuation. Thus, aesthetic physicians planning BoNT treatment for BEB or HFS should consider add-on treatments with 0.3% HA eye drops for symptom improvement in those who develop DED.

Anuchit Poonyathalang, MD
Department of Ophthalmology
Faculty of Medicine, Ramathibodi Hospital
Mahidol University
Bangkok, Thailand
E-mail: au.tumn@yahoo.com

DISCLOSURES

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