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Tear film lipid layer thickness and blink dynamics in patients with blepharospasm

Ji-Sun Paik[1], Min Jeong Kwon[1], Ga Hee Nam[1], Kyungdo Han[2], Woong-Joo Whang[1], Ho Sik Hwang[1], Suk-Woo Yang[3], Hyun-Seung Kim[3], Kyung Sun Na[1*†] and Won-Kyung Cho[4*†]

Abstract

Background This study investigates the effect of botulinum toxin A on lipid layer thickness (LLT) and blink dynamics in patients with benign essential blepharospasm (BEB) compared to dry eye disease (DED) patients.

Methods We reviewed the medical records of patients with dry eye disease (DED) and BEB treated with botulinum toxin A (BoT A) injections. Data on demographics, lipid layer thickness (LLT), meiboscore, and blink dynamics measured using a LipiView II interferometer before and 2 months after BoT A were collected.

Results Each 28 eyes from 28 patients with BEB and age- and sex-matched patients with DED were included. When comparing blink dynamics, complete blink rate was significantly higher in the pre-injection BEB group compared to the DED group (5.25 ± 4.32 times/20 s vs. 2.43 ± 2.82 times/20 s, $p = 0.0055$). In tear film lipid profiles analyzed in BEB patients at pre-injection and 2-month follow-up after injection, average LLT significantly increased after injection (72.4 ± 22.7 nm to 83.0 ± 22.2 nm, $p = 0.0215$). Diabetes and young age were associated factors influencing the LLT increase. Significant increase in LLT was observed post-injection, with specific demographic factors, including diabetes and age, associated with this improvement. Additionally, blink dynamics showed a decrease in complete blink rate post-injection.

Conclusions These findings suggest that BoT-A may alleviate BEB symptoms, but ophthalmologists should carefully interpret LLT and blink patterns in BEB patients due to potential overestimations of blink efficacy by the interferometer.

Keywords Blepharospasm, Blink dynamics, Botulinum toxin A, LipiView, Lipid layer thickness

Background

Benign essential blepharospasm (BEB) is a type of cranial dystonia characterized by sustained involuntary spasms of the bilateral orbicularis oculi, corrugator, and procerus muscles, resulting in partial or complete eyelid closure [1, 2]. Most patients with BEB primarily complain of dry eye symptoms and eyelid opening difficulties due to overactive eyelid contraction [3]. Despite the exact pathophysiology not being established, the treatment of choice has been established, including neurotoxin injections into the facial muscles. Botulinum neurotoxin injection causes temporary facial muscle paralysis and can relieve eyelid-opening difficulties [2]. In a recent study, botulinum toxin injections were associated with an improvement in dry

†Kyung Sun Na and Won-Kyung Cho contributed equally to this work.

*Correspondence:
Kyung Sun Na
drna@catholic.ac.kr
Won-Kyung Cho
vivicho@naver.com
[1] Department of Ophthalmology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[2] Department of Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea
[3] Department of Ophthalmology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[4] Department of Ophthalmology, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

eye parameters in patients with blepharospasm through reduced lacrimal duct outflow and improved lubrication [4, 5]. Periocular botulinum toxin injections have also been used for treating intractable dry eye disease [6]. If botulinum toxin injections improve eyelid blinking in BEB patients, this may improve ocular surface health theoretically.

Dry eye disease (DED) is classified into a wide spectrum, with a predominant etiology within the aqueous-deficient and evaporative continuum [7]. It has minimal correlation between symptoms and signs, making early diagnosis difficult [8]. While DED is typically related to insufficient tear production or rapid evaporation, BEB affects blink patterns through involuntary spasms, which can create unique challenges in interpreting tear film measurements.

A LipiView II interferometer (Tear Science Inc. Morrisville, NC, USA) enables quantitative analysis of lipid layer thickness (LLT) in tears and morphological analysis of the meibomian glands (MGs), which is the main tissue involved in lipid secretion [9, 10]. Additionally, it can be utilized for quantitative and qualitative analyses, such as the number and completeness of eyelid blinking over a certain period [11]. The LipiView II interferometer allows for detailed LLT and blink dynamics assessment, making it useful for differentiating tear film stability variations in BEB and DED patients.

It is widely accepted that BoT-A injections improve dry eye symptoms in blepharospasm patients by reducing lacrimal outflow and enhancing lubrication, yet there remains limited understanding of how BoT-A injections impact tear film and blink dynamics in BEB patients. In this study, we compared the structure (infrared meibography) and function (LLT) of MGs and the blinking pattern before and after botulinum neurotoxin A injection using the LipiView II interferometer. Furthermore, we analyzed the factors influencing the changes before and after botulinum neurotoxin A injection. This study aims to address this gap by providing quantitative data on LLT and blink changes post-treatment.

Materials and methods

Patients and clinical evaluation

This retrospective, cross-sectional study was approved by the Institutional Review Board (IRB) of Yeouido St. Mary's Hospital, The Catholic University of Korea (SC22RISI0088), and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. We reviewed the medical records of patients with BEB who received botulinum toxin A injections between January 2017 and March 2022 at Yeouido St. Mary's Hospital, Seoul, Republic of Korea. Patients over 19 years old who underwent the LipiView II interferometer test, which measures lipid layer thickness, analyzes blink dynamics, and images of the meibomian gland structure during visits: 1) before (pre-injection) and 2) 2 months after botulinum toxin A (Botox 100 IU, Allergan, Inc., Irvine, CA, USA) injection (post-injection) in the outpatient clinic. Twenty-eight patients who effectively responded to botulinum toxin A were included, and their demographic data and clinical profiles, including age, sex, comorbidities of diabetes mellitus (DM), and/or hypertension (HBP), were collected. Exclusion criteria aimed to minimize variables that could independently affect LLT or blink dynamics, such as topical steroid use or systemic conditions impacting ocular health. These criteria were as follows: age > 80 years, active eye infection, a history of chemical or thermal injury to the ocular surface, previous operation on the eyelid or conjunctiva, hormonal imbalance (especially sex hormones such as postmenopausal hormone therapy or polycystic ovary syndrome), rheumatic conditions (e.g., Sjogren's syndrome), neurological conditions (e.g., Parkinson's ds), dermatological diseases (e.g., atopy, rosacea, Stevens-Johnson syndrome, psoriasis), history of hematopoietic stem cell transplantation, use of topical antiglaucoma medications, and use of oral antihistamines, antidepressants, retinoids, or omega-3 fatty acid supplements. To characterize BEB disease entities in comparison with other relatively well-known ocular surface diseases, we recruited 28 age- and sex-matched newly diagnosed patients with DED as controls to provide a baseline comparison for LLT and blink parameters, given the relevance of tear film instability in both DED and BEB. All participants underwent the same LipiView II test. Patients with DED along with secondary dystonia or other systemic and ocular conditions that could affect blink dynamics were excluded. The demographic data of patients with DED were also collected. We compared the pre- and post-injection changes in lipid profiles and blink dynamics. Demographic factors that significantly influenced the post-injection lipid profile and blink dynamics were also evaluated.

Lipid profiles and blink dynamics

Lipid layer profiles of the tear film were detected using a LipiView II interferometer. The right or left eye was randomly selected according to the Bernoulli distribution. Minimum (min), maximum (max) and average (avg) lipid layer thickness (LLT) were collected. For LLT values exceeding 100 nm, they were considered to be 100 nm since the machine reads the LLT as 100 nm. Meibomian gland (MG) loss was also evaluated. The MG loss grades ranged from 0 (0%) to 4 (> 75%), with 1 grade increase corresponding to 25% gland loss.

The LipiView II recorded blink dynamics over 20-s (s) intervals, classifying blinks as complete if the upper and lower lids fully met, and partial if incomplete closure was observed. Total blink (times/20 s), complete blink (times/20 s) and partial blink (times/20 s) were recorded. Partial blink ratio (%) was also calculated [12].

Statistical analyses

We performed the Shapiro–Wilk test to determine whether our samples fit a normal distribution and concluded that parametric statistical methods could be applied to our analyses. The two-sample t-test for continuous variables and chi-square test of Fisher's exact test for categorical variables were utilized for statistical analyses between the pre-injection BEB group and DED group for their characteristics. Statistical tests, including t-tests and regression analyses, were applied to assess the significance of differences between and within groups. Given the number of comparisons, a Bonferroni correction was considered to minimize Type I error risk. A paired t-test was conducted for comparing between the pre-injection and post-injection BEB groups, and Pearson analysis was used for correlation. The results are expressed as mean ± standard deviation (SD). Pearson correlation analysis and two-sample t-tests were used for identifying variables associated with changes in the pre- and post-injection BEB status. Multiple linear regression was used to identify the demographic factors affecting the post-injection results. A general linear model was used to determine the presence of interactions between the factors. All statistical analyses were performed using SAS® for Windows (version 9.3, Cary, NC, USA) and considered as statistically significant with $p < 0.05$.

Results

A total 28 eyes from 28 patients with BEB (8 of male and 20 of female) who met the inclusion and exclusion criteria were enrolled in this study (Table 1). No significant differences were found in most demographic data and parameters associated with ocular conditions between the pre-injection BEB group and age- and sex-matched DED groups. However, complete blink rate was significantly higher in the pre-injection BEB group compared with the DED group (5.25 ± 4.32 times/20 s vs. 2.43 ± 2.82 times/20 s, $p = 0.0055$), indicating enhanced spontaneous blinking in blepharospasm and demonstrating that the two groups are well matched for comparison.

In tear film lipid profiles analysed in patients with BEB at pre-injection and 2-month follow-up after injection, the average LLT significantly increased after injection (72.4 ± 22.7 nm to 83.0 ± 22.2 nm, $p = 0.0215$) (Table 2). Among the blink indices, both total blink rate and complete blink rate decreased after injection, although the change was significant only for complete blink rate, which showed a mean difference of -1.57 blinks per 20 s (5.25 ± 4.32 times/20 s to 3.68 ± 3.24 times/20 s; 95% CI, -2.4 to -0.8; $p = 0.0307$). The partial blink rate increased after injection; however, the change was not statistically

Table 1 Demographics of the patients. BEB Group data collected are pre-injection data of botulinum toxin

	BEB Group	DES Group	*p* Value
N (eyes)	28	28	
Age (mean ± SD, years)	62.2 ± 12.4	64.6 ± 11.7	0.4537*
Male Gender (%)	8 (28.6)	6 (21.4)	0.5371†
with DM (%)	3 (10.7)	3 (10.7)	1.0†
with HBP (%)	10 (35.7)	13 (46.4)	0.4151†
LLT min (mean ± SD, nm)	56.4 ± 27.2	67.2 ± 25.1	0.1280*
LLT max (mean ± SD, nm)	83.4 ± 18.1	83.7 ± 22.2	0.9529*
LLT avg (mean ± SD, nm)	72.4 ± 22.7	76.2 ± 25.4	0.5591*
MG loss (mean ± SD, number)	1.93 ± 1.05	1.70 ± 0.95	0.4103*
BCVA	0.72 ± 0.29	0.66 ± 0.29	0.4966*
IOP (mean ± SD, mmHg)	14.6 ± 2.9	15.3 ± 2.9	0.4034*
Total blink (mean ± SD, times/20 s)	7.71 ± 3.44	5.46 ± 4.87	0.0510*
Comp blink (mean ± SD, times/20 s)	5.25 ± 4.32	2.43 ± 2.82	0.0055*
Partial blink (mean ± SD, times/20 s)	2.68 ± 2.76	3.04 ± 3.82	0.6899*
Partial blink ratio (mean ± SD, %)	39.5 ± 38.2	50.3 ± 40.4	0.3055†

BEB Benign essential blepharospasm, *DES* Dry eye syndrome, *SD* Standard deviation, *LLT* Lipid layer thickness, *min* minimum, *Max* Maximum, *avg* Average, *MG* Meibomian gland, *BCVA* Best-corrected visual acuity, *IOP* Intraocular pressure, *Comp* Complete

* t-test, †chi-square test were used for statistical analyses

Table 2 Changes between pre- and post-botulinum toxin injections within BEB Group

	Pre injection	Post injection	*P* value
LLT min (mean ± SD, nm)	56.4 ± 27.2	65.9 ± 25.0	0.0678
LLT max (mean ± SD, nm)	83.4 ± 18.1	90.9 ± 18.1	0.0551
LLT avg (mean ± SD, nm)	72.4 ± 22.7	83.0 ± 22.2	0.0215*
MG loss (mean ± SD, number)	1.93 ± 1.05	2.04 ± 0.96	0.1845
BCVA (mean ± SD)	0.72 ± 0.29	0.85 ± 0.19	0.3023
IOP (mean ± SD, mmHg)	14.6 ± 2.9	14.0 ± 3.10	0.3085
Total blink (mean ± SD, times/20 s)	7.71 ± 3.44	7.14 ± 3.93	0.5019
Comp blink (mean ± SD, times/20 s)	5.25 ± 4.32	3.68 ± 3.24	0.0307*
Partial blink (mean ± SD, times/20 s)	2.68 ± 2.76	3.46 ± 3.20	0.2865
Partial blink ratio (mean ± SD, %)	39.5 ± 38.2	48.7 ± 36.5	0.1666

Paired t-test was used for statistical analyses

Statistically significant $p < 0.05$ was marked with *

SD Standard deviation, *LLT* Lipid layer thickness, *min* Minimum, *max* Maximum, *avg* Average, *MG* Meibomian gland, *BCVA* Best-corrected visual acuity, *IOP* Intraocular pressure, *Comp* Complete

significant. The reduction in complete blink rate following BoT-A injection may indicate partial relief from blepharospasm symptoms, though the clinical implications of increased partial blinks warrant further investigation.

We performed a Pearson correlation analysis and a two-sample t-test to further analyze the potential variables associated with the changes between the pre- and post-injection results in the BEB group (Table 3). The presence of diabetes and age showed statistically significant correlations with the degree of change in LLT after botulinum toxin injections. The change in average LLT was significantly greater in patients with diabetes ($p=0.0003$). The higher prevalence of diabetes in BEB patients may partially explain LLT differences, given its known effects on tear film quality. Additionally, a significant negative correlation was identified between age and the amount of change in the average LLT (r = -0.46, $p=0.0149$). In other words, when botulinum toxin was injected into patients with BEB, LLT increased more significantly in patients with diabetes and in younger patients. Meanwhile, sex, age, and the presence of hypertension had no significant effects on blink dynamics.

Discussion

The lipid layer of tears plays a crucial role in preventing tears from evaporating and in providing a smooth ocular surface [9]. Lipid meibum is secreted from the meibomian glands during blinking, and it is thought that the lipid layer spreads by interacting with the aqueous sub-phase of the tear film during the dynamic process of closing and opening the eyes [10]. Incomplete blinking is associated with decreased tear breakup time (TBUT), increased ocular surface disease index (OSDI), and increased meibomian gland dropout, potentially due to its contribution to meibomian gland obstruction and subsequent loss of tear film homeostasis [11]. In the current study, we found that the rate of incomplete blinking was higher in the age- and sex-matched non-BEB-DED group than BEB group. It should be noted that the blink pattern measured by the interferometer may not provide accurate information for patients with BEB. Generally, it is meaningful to observe changes in incomplete blink rates before and after treatment in patients with DED; however, this may not be meaningful in patients with BEB. Therefore, dry eye symptoms should be treated differently in patients with BEB. Furthermore, clinicians should note that DED in patients with BEB may present with different characteristics and etiologies from other causes of DED and should proactively treat DED aside from botulinum toxin injection.

Normal eye blinking comprises four stages: downstroke, turning point, upstroke, and interblinking [13]. During a complete blink cycle, the upper and lower lids contact each other, whereas during an incomplete blink cycle, the upper lid does not fully contact the lower lid [13]. For patients with BEB, involuntary eyelid closure may manifest as twitches and spasms of the eyelids, making it highly likely that the interferometer will not be able to distinguish between normal and abnormal complete blinking [1]. A previous study investigated blink profiles and indices using tear interferometry in patients with BEB before and after botulinum neurotoxin administration [12]. They divided the groups into responders and non-responders to botulinum neurotoxin injections. The normalized total blink rate was observed in the responder group, while other indices, such as the partial blink ratio and eyelid blink time, did not vary in either group. They suggested that the etiology of BEB may not only be dystonia of orbicularis oculi contraction but also decreased function of the eyelid levator muscles in the non-responder group. We only included the responder group, leading to different results such that the incomplete blink rate increased in the responder group. As very few studies have objectively evaluated blinking kinematics before and after botulinum neurotoxin injections, it is crucial to verify this with more patients in the future.

Increased incomplete blinking leads to inadequate lipid distribution [14–16]. The general understanding is that LLT is significantly negatively correlated with the incomplete blinking rate [17]. Our study revealed an increase in LLT in patients with BEB after BoT injection despite an increase in the incomplete blink rate, which is supported by a previous study [18]. Increasing LLT after BoT injection may be misunderstood as an improvement of normal

Table 3 Factors which affect the changes between pre- and post-botulinum toxin injections shown as *p* value

	Sex	DM	HTN	Age
LLT min	0.2320	0.0090*	0.5138	-0.38 (0.0441)
LLT max	0.1518	< 0.0001*	0.2304	-0.43 (0.0236)
LLT avg	0.2249	0.0003*	0.3929	-0.46 (0.0149)
MG loss	0.0283*	0.1850	0.3891	0.15 (0.4541)
BCVA	0.7442		0.1051	0.50 (0.2049)
IOP	0.6047	0.8760	0.5610	-0.31 (0.1128)
Total blink	0.2903	0.5655	0.3256	-0.12 (0.5444)
Comp blink	0.6205	0.6578	0.8924	0.01 (0.9740)
Partial blink	0.3933	0.3187	0.4280	-0.19 (0.3294)
Partial blink ratio	0.7925	0.2071	0.5896	-0.27 (0.1569)

Pearson correlation analysis and two-sample t-test were used for statistical analyses

Statistically significant $p < 0.05$ was marked with *

DM Diabetes mellitus, *HTN* Hypertension, *LLT* Lipid layer thickness, *min* Minimum, *max* Maximum, *avg* Average, *MG* Meibomian gland, *BCVA* Best-corrected visual acuity, *IOP* Intraocular pressure, *Comp* Complete

blink; hence, cautions need to be taken when interpreting the blink pattern among patients with BEB. Increased LLT post-BoT-A injection may indicate improved tear film stability, but the rise in incomplete blinking suggests that full functional restoration of blinking is not achieved. Ocular surface changes and blink patterns should be examined using a slit lamp; however, the usefulness of tear interferometry may be limited, especially in patients with BEB.

Dry eye symptoms are often reported in patients with blepharospasm. Blepharospasm can cause DED since periodic blinking of the eyelids is crucial for the maintenance and renewal of the precorneal tear film. Conversely, DED may worsen blepharospasm since the blinking rate increases to compensate for the tear film instability or deficiency. Recent studies have interpreted the synergistic pathological mechanism of the association between DED and blepharospasm; however, no main outcomes have been achieved. There are several conflicting opinions on the effect of neurotoxin injection used as treatment for DED in patients with BEB. Previous studies confirmed the efficacy of botulinum toxin A injections in improving dry eye symptoms [4, 5]. Botulinum toxin A has also been suggested as a dry eye therapy due to its ability in reducing lacrimal drainage after treatment [6]. Paralysis of the orbicularis oculi muscles affects the canaliculi and decreases pump function during blinking. However, another study reported that botulinum toxin A injections only slightly increased tear break up time (TBUT) and did not improve dry eye symptoms (Schirmer's test, impression cytology, and Rose Bengal staining) [19]. This is consistent with the findings of Dutton and Buckley, who reported that subjective dry eye symptoms were the most common side effects of long-term botulinum toxin therapy for blepharospasm [20]. Moreover, decreased tear production has been reported in patients with BEB even prior to treatment [18]. This finding did not correlate with hyperosmolarity, and this association is well-accepted in DED. Our study also revealed that changes in ocular surface parameters were not typical in patients with BEB between pre- and post-injection of botulinum toxin compared to patients with DED. Similar studies on BoT-A effects in DED have reported mixed results in terms of tear stability improvement; however, our findings align with reports of BoT-A's role in reducing blink-related tear film disruption.

A limitation of this study is the lack of DED parameters, including tear breakup time, ocular surface staining, Schirmer's test, and subjective symptom score. Recently, it has been shown that LLT may be influenced by mucous-aqueous volume and that tear secretion may change after BoT injection. A previous study reported that reduced tear secretion appears to be present in patients with BEB patients even prior to treatment. Additionally, eye drops, including artificial tears, may affect the results of LLT. It should also be noted technological limitations that LipiView II may overestimate blink completeness due to the involuntary spasms in BEB, which could skew results and necessitates cautious interpretation of blink metrics in these patients. Another limitation is that, as a retrospective study with a relatively small sample size, these findings may not be generalizable; future studies with larger cohorts and controlled prospective designs are recommended. However, our study was the first to compare blink patterns, meibomian gland morphology and function, including LLT in both patients with BEB and DED. Our results suggest that BoT injection is effective not only for orbicularis oculi muscle contracture but also for improving tear stability. Restoring a normal blink pattern after BoT injection may be a key factor in improving tear dynamics in patients with BEB. For clinicians, these findings suggest that while BoT-A can improve LLT, it is essential to evaluate tear film metrics alongside patient-reported outcomes to gauge symptomatic improvement.

In conclusion, this study demonstrated a significant increase in LLT in BEB patients following BoT-A injection, while the complete blink rate decreased and partial blink rate increased, though the latter change was not statistically significant. Although BoT-A injections show potential in stabilizing LLT in BEB patients, careful interpretation of blink dynamics is necessary to avoid overestimating symptomatic relief. Future studies should explore a broader range of tear film parameters and examine longitudinal outcomes to provide a more comprehensive understanding of BoT-A's effects on tear film health in BEB.

Ten Demographic Data Interpretation (Lines 85–90): While demographics are listed, discuss potential implications of diabetes and age on LLT. Include: "The higher prevalence of diabetes in BEB patients may partially explain LLT differences, given its known effects on tear film quality."

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Authors' contributions
JSP, KSN and WKC contributed to the conceptualization, design, and drafting of the manuscript. MJK and GHN drafted the manuscript. KDH and GHN analysed and interpreted the data. WJW, HSH, SWY and HSK contributed to the concept and design. All authors have read and approved the final manuscript.

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Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board (IRB) of Yeouido St. Mary's Hospital, The Catholic University of Korea (SC22RISI0088) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The IRB waived the requirement for obtaining informed consent from participants due to the retrospective nature of the chart review in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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