ORIGINAL ARTICLE

Comparison of Two Doses of Botulinum Toxin A for Dry Eye Treatment by Injection into the Medial Lower Eyelid: A Randomized, Comparative Pilot Study

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Objective: To determine the appropriate dose of botulinum toxin type A for the treatment of dry eye disease in terms of effectiveness and complications.

Materials and Methods: Patients with dry eye having a similar degree in both eyes treated with non-preservative artificial tears for at least one month and in whom dry eye symptoms persisted with positive fluorescein corneal staining were enrolled. In each patient, a subcutaneous injection of 3.3 units of botulinum toxin type A was administered in the medial part of the randomly selected lower eyelid, while 2.5 units of the same was administered to the second lower eyelid. Complete subjective and objective evaluations were performed at baseline and 2-, 8-, 12-, and 16-weeks after the intervention.

Results: Eleven patients, with a mean age of 64.63±14.81 years, were included. Dry eye symptoms assessed by the mean of ocular surface disease index (OSDI) score improved significantly after treatment in both the 3.3- and 2.5-units groups. Eight of 11 (72.7%) eyes in both groups had improved OSDI scores. No statistically significant improvements were observed in most objective variables. Comparison of post-treatment OSDI score, Tear film break-up time (TBUT), Schirmer's test, and modified Oxford grading scheme between the 3.3- and 2.5-units groups showed no significant difference at any time point of the study.

Conclusion: Both 3.3- and 2.5-units botulinum toxin injections into the medial lower eyelid improved dry eye symptoms in up to three-quarters of the patients. Botulinum toxin injection into the medial lower eyelid can be used as an adjunctive treatment for dry eye disease by the initial dose of 2.5 units.

Keywords: Botulinum toxin; Dry eye; Ocular surface disease

Received 27 February 2024 | Revised 5 June 2024 | Accepted 7 June 2024

J Med Assoc Thai 2024;107(8):601-6

Website: http://www.jmatonline.com

The prevalence of dry eye disease, with and without symptoms, ranges from 5% to 50%, reaching 75% in some populations. Asian ethnicity is a risk factor. The most severe economic impact of dry eye disease results from the costs related to decreased work productivity[1].

Several medications and methods are available for treating dry eye disease. Tear conservation therapy is a treatment for tear insufficiency[2]. Studies reported that the injection of botulinum toxin type A in the medial part of the lower eyelid decreases the tear volume ejected at each blink and the ability to drain tears, favoring the maintenance of the teardrop, which may benefit patients with dry eye[3-10]. This effect is due to paralysis of the lacrimal part of the orbicularis oculi muscle and Horner's muscle, which is closely related to the components of the lacrimal drainage system and decreases the effect of the lacrimal pump as well as tear drainage[11].

There are few publications about botulinum toxin use for dry eye treatment, all of which demonstrated that botulinum toxin injection into the medial lower eyelid can improve signs and symptoms of dry eye[3-10]. Nevertheless, the concentration of botulinum toxin used varies among studies.

Sahlin et al.[5] reported that a botulinum toxin concentration of 3.75 international units (U) can reduce the mean blink output to 70% of the baseline values and improve eye comfort in six of nine cases.

Bukhari[7] concluded that the 3.3 U/0.1 mL botulinum toxin A injections can be an alternative to

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How to cite this article:

Mekhasingharak N, Sawatdiwithayayong J, Kosaiyaganonth N. Comparison of Two Doses of Botulinum Toxin A for Dry Eye Treatment by Injection into the Medial Lower Eyelid: A Randomized, Comparative Pilot Study. J Med Assoc Thai 2024;107:601-6.

DOI: 10.35755/jmedassocthai.2024.8.14019

punctal plugs in improving the clinical manifestations of dry eye disease and is associated with the development of fewer and milder complications as well as higher levels of patient satisfaction. He also indicated that eight out of 24 patients (33.3%) who received botulinum toxin A reported getting shampoo in their eyes while showering, which implies that one-third of the patients had some degree of lagophthalmos due to botulinum toxin injection[7].

Although a high complication rate was reported in Bukhari's study[7], Serna-Ojeda and Nava-Castaneda[8] reported effective treatment without any adverse events while using 4 U/0.1 mL botulinum toxin injection.

The present study aimed to determine the appropriate dose of botulinum toxin type A for the treatment of dry eye disease in terms of effectiveness and complications.

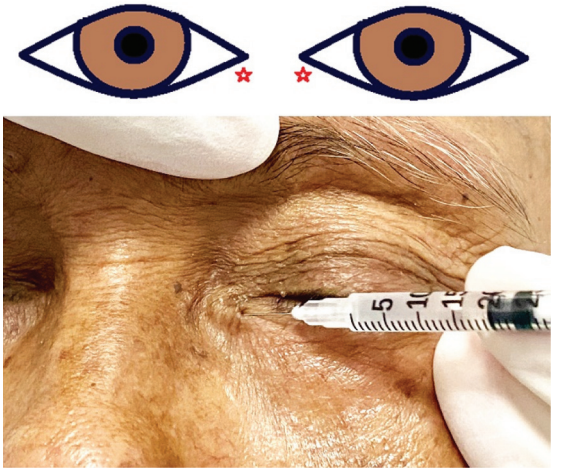

Figure 1. Subcutaneous injection of botulinum toxin type A in the medial part of the lower eyelid, 2 mm inferior to the lid margin, and 5 mm medial to the lower punctum (star).

Materials and Methods

The present study was a prospective, double-blind, randomized, comparative, eye-to-eye interventional study conducted at the Department of Ophthalmology, Naresuan University Hospital, Thailand between January 2020 and April 2021. Inclusion criteria were patients with dry eye older than 20 years who had a similar degree of dry eye in both eyes, received treatment with non-preservative artificial tears for at least one month, and dry eye symptoms persisted with positive corneal fluorescein staining. Patients with dry eye attributable to eyelid abnormalities, nasolacrimal duct obstruction, active corneal infection, or history of botulinum toxin hypersensitivity were excluded. Active inflammatory dry eye cases and severe dry eye cases that required autologous serum were also excluded because retention of proinflammatory tear components could occur and enhance damage to the ocular surface after botulinum toxin injection[12].

Subjective evaluation was achieved using the ocular surface disease index (OSDI) questionnaire to assess the symptoms of dry eye for each eye. Objective evaluation included best-corrected visual acuity (BCVA), margin reflex distance 2 (MRD-2), tear film break-up time (TBUT), Schirmer's test, and a modification of the Oxford grading scheme for corneal and conjunctival staining. A double-blind technique was used. All objective data were assessed by an ophthalmologist (JS) who was blinded to the treatment received.

BCVA was assessed using the Early Treatment of Diabetic Retinopathy Study chart. TBUT was defined as the time required for dry spots to appear on the corneal surface after blinking following fluorescein staining, and the mean value of three measurements was recorded. Schirmer's test was performed without instillation of topical anesthetic, sterile paper strips were inserted into the inferotemporal aspect of the conjunctival sac for five minutes to measure tear production in millimeters (mm). The modified Oxford grading scheme for corneal and conjunctival staining was used after fluorescein staining, to grade according to severity from 0 for absent to 5 for severe[14].

Using the randomization list generated by www.randomization.com, one eyelid was randomly administered a subcutaneous injection of 3.3 units (U) of botulinum toxin type A (Botox; Allergan, Irvine, CA, USA) in the medial part of the lower eyelid, 2 mm inferior to the lid margin, and 5 mm medial to the lower punctum (Figure 1). The other eye underwent a similar procedure with 2.5 U of botulinum toxin type A. Complete subjective and objective evaluations were performed at baseline and 2-, 8-, 12-, and 16-weeks after the intervention.

Statistical analyses were performed using Stata, version 12 (StataCorp LP, College Station, TX, USA). Demographic variables were analyzed using descriptive statistics. To determine the differences in the variables among the eyes, the Mann-Whitney U test, Wilcoxon signed-rank tests, two-sample t-test and paired t-test were used. Statistical significance was set at p-value less than 0.05.

The present study was approved by the Human Research Ethics Committee of the Faculty

Table 1. Baseline and post-treatment dry eye characteristics

Variable	3.3 U (n=11)	2.5 U (n=11)	p-value
OSDI score; median (IQR)			
Baseline	18.18 (10.42 to 47.73)	27.27 (14.58 to 43.18)	0.793†
2 weeks post-treatment	8.33 (4.55 to 15.91)*	8.33 (6.25 to 27.08)*	0.767†
8 weeks post-treatment	6.82 (6.25 to 20.00)*	8.33 (6.82 to 25.00)*	0.175†
12 weeks post-treatment	6.25 (4.55 to 18.18)	7.50 (4.55 to 18.18)*	0.895†
16 weeks post-treatment	7.50 (4.17 to 20.45)*	6.82 (4.17 to 22.50)*	0.948†
TBUT; median (IQR)			
Baseline	5.00 (3.67 to 6.67)	4.33 (3.00 to 6.33)	0.645†
2 weeks post-treatment	3.67 (3.30 to 5.67)	3.67 (3.33 to 6.67)	0.620†
8 weeks post-treatment	5.33 (3.67 to 6.00)	5.33 (4.00 to 6.33)	0.792†
12 weeks post-treatment	3.33 (2.33 to 4.67)*	3.67 (3.67 to 4.33)	0.408†
16 weeks post-treatment	3.00 (2.67 to 3.67)*	4.00 (2.67 to 6.33)	0.177†
Schirmer's test; median (IQR)			
Baseline	7.00 (5.00 to 12.00)	11.00 (4.00 to 13.00)	0.869†
2 weeks post-treatment	8.00 (5.00 to 14.00)	10.00 (4.00 to 15.00)	0.948†
8 weeks post-treatment	8.00 (4.00 to 15.00)	7.00 (3.00 to 11.00)	0.576†
12 weeks post-treatment	5.00 (3.00 to 11.00)	6.00 (3.50 to 7.00)	0.869†
16 weeks post-treatment	5.00 (3.00 to 7.00)*	5.00 (4.00 to 8.00)*	0.528†
Modified Oxford grading scheme; median (IQR)			
Baseline	1.00 (1.00 to 2.00)	2.00 (1.00 to 2.00)	0.715†
2 weeks post-treatment	1.00 (0.00 to 1.00)*	1.00 (0.00 to 1.00)*	0.765†
8 weeks post-treatment	1.00 (1.00 to 2.00)	1.00 (1.00 to 2.00)	0.715†
12 weeks post-treatment	1.00 (1.00 to 2.00)	1.00 (1.00 to 2.00)	0.914†
16 weeks post-treatment	1.00 (0.00 to 2.00)	1.00 (1.00 to 2.00)	0.925†
MRD2; mean±SD			
Baseline	5.18±0.60	5.09±0.70	0.747‡
2 weeks post-treatment	5.27±0.65	5.18±0.75	0.764‡
8 weeks post-treatment	5.27±0.47	5.18±0.40	0.631‡
12 weeks post-treatment	5.18±0.40	5.09±0.54	0.660‡
16 weeks post-treatment	4.82±0.60	4.82±0.60	1.000‡

OSDI=ocular surface disease index; TBUT=tear film break-up time; MRD=marginal reflex distance; IQR=interquartile range; SD=standard deviation
* Significant change from baseline ($p<0.05$) using Wilcoxon signed-rank tests and paired t-test, † Mann-Whitney U test, ‡ Two-sample t-test

of Medicine, Naresuan University (COA No. 138/2019) and under the Thai Clinical Trials Registry (TCTR20221004007). The study was conducted in accordance with the Declaration of Helsinki. Informed consents were obtained from all subjects.

Results

Eleven patients were included, with a mean age of 64.63±14.81 years. After randomization, the eye treated with 3.3 U of botulinum toxin type A was the right eye in five patients (45%), and the left eye in six patients (55%). The baseline OSDI score, MRD-2, TBUT, Schirmer's test, and modified Oxford grading scheme were similar in both groups (Table 1).

The baseline and post-treatment data are presented in Table 1. Eight of 11 eyes (72.7%) in both groups had better OSDI scores. Dry eye symptoms assessed using the OSDI score improved after treatment in both groups (Figure 2), with significant improvements in the median OSDI at 2-, 8-, and 16-weeks post-treatment in the 3.3 U injection group ($p=0.023$, 0.010, and 0.016, respectively) and at all follow-up visits in the 2.5 U group ($p=0.016$, 0.016, 0.013, 0.008, respectively). Although the symptoms improved, no statistical significance was reached for most objective variables. The modified Oxford grading scheme tended to improve after treatment, but statistically significant improvement was observed only at 2-weeks post-treatment in both the 3.3 and 2.5 U groups ($p=0.027$ and 0.009, respectively) (Table 1, Figure 2).

The post-treatment OSDI score, TBUT,

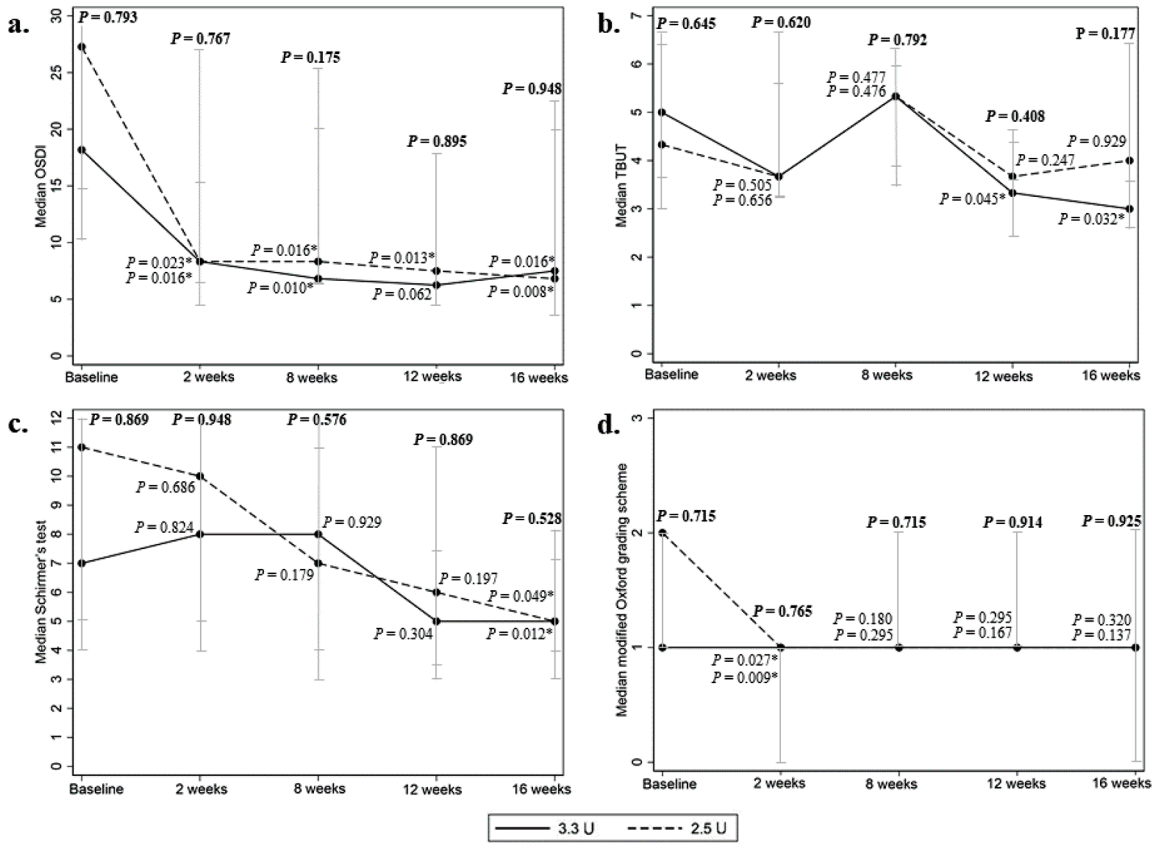

Figure 2. Dry eye characteristic at baseline and post-treatment. (a) median ocular surface disease index (OSDI) score, (b) median tear film break-up time (TBUT), (c) median Schirmer's test without anesthesia value, (d) median modified Oxford grading scheme value.

* Statistically significant improvement after treatment

Schirmer's test, and modified Oxford grading scheme were not significantly different between the 3.3 and 2.5 U injection groups at any time point of the study (Table 1).

All the patients completed the 16 weeks follow-up. The minimal retraction of the lower lid was mentioned as increased MRD-2 in three of 11 eyes in both 3.3 and 2.5 U groups. One patient reported that the lower eyelid had more laxity when treated with 3.3 U botulinum toxin, but no lagophthalmos was found and no other potential adverse event including ectropion, strabismus, cutaneous infection, and hematoma, were reported in the present study.

Discussion

Botulinum toxin injection into the medial part of the lower eyelid is a dry eye treatment method aimed to decrease tear drainage into the lacrimal sac. There are few publications on the use of botulinum toxin in dry eye treatment. The reported effective dose varies from 3.3 to 4 U[3-10]. To the author's knowledge, the present study is the first study to compare different dosages of botulinum toxin injections in an eye-to-eye interventional study.

Bukhari[7] reported an effective dose of 3.3 U/0.1 mL botulinum toxin. This is the lowest dosage for single-point lower eyelid injection that has been documented in literature. He also reported that 33.3% of patients reported getting shampoo in their eyes while showering. Therefore, the present study compared two dosages of botulinum toxin 2.5 and 3.3 U to determine the more cost-effective dosage and the dosage associated with fewer complications.

Although a high complication rate was reported in the study by Bukhari[7], Serna-Ojeda and Nava-Castaneda[8] reported effective treatment without any adverse events while using 4 U/0.1 mL botulinum toxin injection. These results imply that the effectiveness and complication rate depend on the dosage of botulinum toxin and injection technique. Injection at a more central lower eyelid increases the risk of lower lid laxity and lagophthalmos.

Therefore, the injection site of the present study was approximately 5 mm medial to the lower punctum to avoid complications after injection.

The results of the present study demonstrated that the OSDI score improved after treatment in both groups, but no statistical significance was reached for most objective variables. These results differ from those of previous studies that reported improvements in TBUT, Schirmer's test, and the modified Oxford grading scheme[7,8]. This difference may be due to the difference in baseline dry eye severity of the patients enrolled in each study. Schirmer's test has poor discriminability for milder forms of dry eye disease[14,15]. The baseline dry eye severity of patients in the present study were better than those of the patients included in both Bukhari's[7] and Serna-Ojeda and Nava-Castaneda's[8] studies, therefore, the change may not reach a significant value.

Jones et al.[2] reported eyes that received botulinum toxin had better TBUT, Schirmer's test, modified Oxford grading scheme, and some dry eye symptoms when compared with the sham group at three months post-intervention, and these variables were not significantly different at six months[2]. In the present study, at 2-weeks post-treatment, the mean OSDI score, and modified Oxford grading scheme improved significantly and remained steady until the end of follow-up at 16-weeks. This may imply that the effect of botulinum toxin could last longer than 16-weeks. Further studies are needed to follow up the patients until six months post-intervention to determine the longest duration effect and time to repeat injection of botulinum toxin.

Limitations of the present study were expected given the small sample size. The study did not specify the baseline severity of dry eye in the enrolled patients, which may have affected the outcomes and comparisons between the groups. The strength of the study is that it was a prospective, double-blind, randomized, comparative, eye-to-eye interventional study, which helped avoid bias.

Conclusion

Both the 3.3- and 2.5-units botulinum toxin injections into the medial lower eyelid improved dry eye symptoms in up to three-quarters of the patients. Botulinum toxin injection into the medial lower eyelid can be used as an adjunctive treatment for dry eye disease by the initial dose of 2.5 units.

What is already known on this topic?

There are few publications that have demonstrated that botulinum toxin injection into the medial lower eyelid can improve the signs and symptoms of dry eye. Nevertheless, the concentration of botulinum toxin used, its effectiveness, and complications vary among studies.

What does this study add?

To the authors' knowledge, this is the first study to compare different doses of botulinum toxin injections in an eye-to-eye interventional study. The study demonstrated that both 3.3- and 2.5-units botulinum toxin injections improved dry eye symptoms in approximately 75% of the patients. Therefore, botulinum toxin injection into the medial lower eyelid can be used as an adjunctive treatment for dry eye disease by the initial dose of 2.5 units for minimizing complications.

Acknowledgement

The authors would like to thank to the Faculty of Medicine, Naresuan University (Phitsanulok, Thailand) for research funding and to the Department of Ophthalmology, Faculty of Medicine, Naresuan University for provision of facilities.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare no conflict of interest.

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