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Original Research Paper

Ophthalmology

CLINICAL EFFICACY OF BOTULINUM TOXIN A INJECTION IN ORBICULARIS OCULI MUSCLE TO IMPROVE MODERATE TO SEVERE DRY EYE DISEASE.

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ABSTRACT Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles. Typical symptoms of dry eye syndrome are dryness, burning and sandy-gritty eye irritation, and itchy, stinging, or tired eyes. The resultant damage to the eye's surface increases discomfort and sensitivity to bright light. The eyelid motion, tear distribution, and tear drainage are all fundamental and supposed to provide the main mechanism of action for lacrimal drainage. The paralysis of the lacrimal part of the orbicularis oculi muscle for its close relationship with the components of the lacrimal drainage system, the effect of the lacrimal pump decreases and the tear drainage as well and that the injection of botulinum toxin type A in the medial part of the eyelid decreases the amount of 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. The present study was done to determine the effect of Botulinum toxin on the lacrimal drainage function and to assess the possible clinical use of Botulinum toxin in dry eye conditions. This was a prospective, single-blind, interventional study, conducted over a period of 14 months from FEBRUARY 2021- MARCH 2022, in the Department of Ophthalmology, Career Institute of medical sciences in Lucknow. **Results And Observation:** The eyes in the active intervention group showed better results as compared to the placebo group both in subjective and objective parameters. A significant difference was found at any point in the study between the treatment and sham groups. It was observed that Botox has shown significant improvement in the dry eye symptoms. The best improvements in the patient with Botox were observed in the 1st month's follow up and then as effects started to wean off a gradual progression of symptoms was seen. **Conclusion:** Botulinum toxin A injection into the medial part of the eyelids improves the clinical sign and symptoms of dry eye and can be used as a potential treatment option for patients with severe dry eye disease.

KEYWORDS : Botulinum toxin A, Botox, Orbicularis oculi, Dry eye disease, Lacrimal drainage.

INTRODUCTION

According to the international dry eye workshop, Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface (DEWS 2007). It is a chronic ocular pathology and a major global health problem leading to patients experiencing difficulties in daily routine activities thus compromising their quality of life [1].

Botulinum toxin, also called "miracle poison," is a neurotoxin produced by clostridium botulinum, which acts on the motor end plate of neurons, and when injected locally causes muscle paralysis interfering with the release of acetylcholine at neuromuscular junctions. FDA approved Botox® in December 1989 as an orphan drug for the treatment of strabismus, hemifacial spasms, and blepharospasm. The use of botulinum toxin was introduced in ophthalmology for the first time in 1980 [2].

The major forces responsible for the drainage of tears are blinking and gravity. Most humans blink about 12-16 times per minute. Sphincter-like action is exerted by the orbicularis oculi pars lacrimalis muscle that compresses and contracts the lower canaliculus, causing tears to move toward the nasolacrimal duct [3]. The relationship between the lacrimal canaliculus and the lacrimal part of the orbicularis oculi muscle or Horner's muscle is supposed to provide the main mechanism of action for lacrimal drainage [5].

Previously, it was reported that the injection of botulinum toxin type A in the medial part of the eyelid causes a decrease in the horizontal sliding of the lower eyelid when blinking. Therefore, decreasing the amount of 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 [4].

Decreased mean blink-time output in patients with dry eyes after botulinum toxin injections, indicates that the injection of botulinum toxin could reduce the efficacy of lacrimal drainage by paralyzing the orbicularis oculi muscles leading to decreased action of the lacrimal pump and prolonged lubrication of the ocular surface [3]. The current study was conducted to determine the efficacy of Botulinum toxin type A injection in improving dry eye disease.

OBJECTIVE

To determine the efficacy of Botulinum toxin type A injection in improving the dry eye signs and symptoms based on a set of subjective and objective parameters.

MATERIAL AND METHODS

This is a prospective, single-blind, interventional study, conducted over a period of 14 months during February 2021-March 2022 in a total of 80 eyes of 40 patients, in the Department of Ophthalmology at a Tertiary Teaching Hospital in Lucknow, India. Institutional Ethics Committee approval was obtained beforehand. Informed written consent was obtained from all the participating patients. Patients suffering from moderate to severe dry eye in both eyes were included to be part of the study. Patients showing signs and symptoms of mild dry eye in either of the eyes were excluded from the study. Subjective evaluation of the patient was done by a questionnaire assessing symptoms, Dryness, Redness, Watering, and foreign body sensation.

Table 1: Each Symptom Was Graded From 0 To 5 Depending On The Frequency

0	Never
1	Rarely (once a week)

2	Occasionally (several times a week)
3	Frequently (once a day)
4	Usually (several times a day)
5	Continually (every hour of the day)

Table 2: The Vision Quality And Ocular Comfort Level Were Graded From 1 To 5.

1	Very good
2	Good
3	Not bad
4	Bad
5	Very bad

The patients were carefully asked and explained the above-said parameters. The objective evaluation included Tear film breakup time (TBUT). Tear film breakup time (TBUT)was considered as the time required for dry spots to appear on the corneal surface after blinking with fluorescein staining, recording the mean value of three measurements, Schirmer's test (type 2) test was performed with the instillation of topical anaesthetic Whatman paper strips were inserted into the conjunctival sac for 5 min to measure the production of tears in millimeters., Corneal Conjunctival staining (oxford grading scale). The simplified Oxford grading scheme for corneal and conjunctival staining was used after fluorescein staining, according to the severity from 0 (absent) to 5 (severe). The right eye of each patient received a subcutaneous injection of 2.5 IU/ml of botulinum toxin (Botox; Allergan, Irvine, CA, USA) in the medial orbicularis oculi muscle in the lower eyelid. Each vial was of 50 IU in powder form which was reconstituted with 20 ml of .9% sodium chloride and every 2-3 months 5-6 patients were scheduled for the visits and then BOTOX was injected. The left eye of each patient received 1 ml of saline solution as a placebo. After completing the intervention, the subjective and objective evaluations of each patient were performed before treatment and at 1st month, 3rd month, and 6th month after injection.

STATISTICAL ANALYSIS

The data from case record forms were tabulated in a Microsoft Excel spreadsheet. Statistical analysis was done using IBM SPSS 21.0 version (Chicago, inc., USA) Windows software. Data were collected and expressed as numbers and percentages. Categorical data, compared using chi sq. test

OBSERVATION/RESULTS

A total of 80 eyes of 40 patients were included to be part of the study. Botulinum toxin A injection was subjected to all the patients in the study There were dropouts in the study in the 3rd and 6th month follow-up.

1 month after the botulinum toxin A injection, all patients showed a decrease in the horizontal movement of the lower eyelid when blinking. Some patients also had a minimal retraction of the lower lid. It was observed that Botox has shown significant improvement in the dry eye symptoms. There was no evidence of any side effects The eyes in the active intervention group showed better results as compared to the placebo group both in subjective and objective parameters as shown in Table 3.

Table 3: The Subjective And Objective Parameters Showed Insignificant Changes In The Placebo Group As Compared To Active Interventional Group.

	Botulinum toxin A	Placebo
Subjective improvements	70%	30%
Objective improvements	90%	10%

Significant difference was found at any given point in the study between the treatment and placebo groups in both subjective and objective analysis. In 6 months follow up there was little change throughout the study period in the placebo group, while changes were evident in the active treatment group, showing improvement in 1 month, and reaching statistical differences between groups in four of the symptoms at the one-month follow-up measurement, holding a difference by 3 months in three of the three symptoms, and again not showing much of statistical differences between the groups at 6 months as for the subjective parameters, majority of patients in the pre-treatment group frequently experienced dryness in the eyes, within one month of treatment now majority of patients now rarely have experienced dryness in their eyes. However, it was observed that in the 3rd-month follow-up and 6 months follow up patient had occasional dryness as shown in Table 4.1.

Maximum patients in the pre-treatment group frequently had foreign body sensations in their eyes, within one month of treatment now the majority of patients now rarely have experienced foreign body sensations in their eyes. However, it was observed that in the 3rd-month follow-up and 6 months follow up patient has occasional foreign body sensations in their eyes as depicted in Table 4.2.

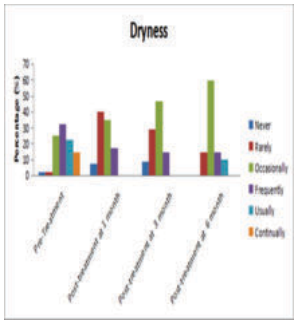


Table 4.1

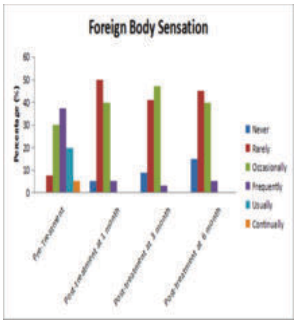
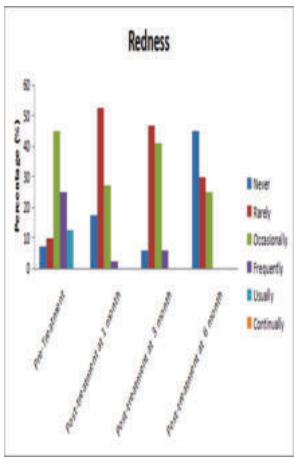


Table 4.2

Table 4.3 demonstrates that the majority of patients in the pre-treatment group occasionally had redness in their eyes, within one month of treatment now the majority of patients now rarely experienced dryness in their eyes which continued till the 6th month's follow-up.

The majority of patients in the pre-treatment group had good/not bad vision quality in their eyes, within one month of treatment now the majority of patients now have very good vision quality which was seen till 3rd month follow up but a shifting trend was observed that in 6th month follow up patients now had a good / not bad vision quality as shown in table 5.1.



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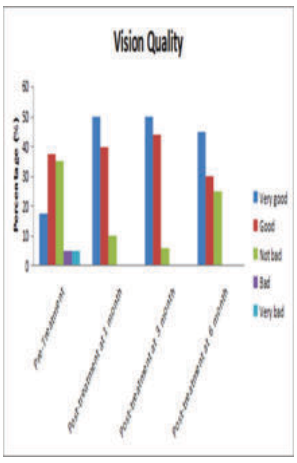

Table 5.1

Table 5.2 gives us a very clear idea that the majority of patients in the pre-treatment group had good ocular comfort, there was no change observed within one month of treatment. In 3rd and 6th-month follow-up patients experienced very good ocular comfort.

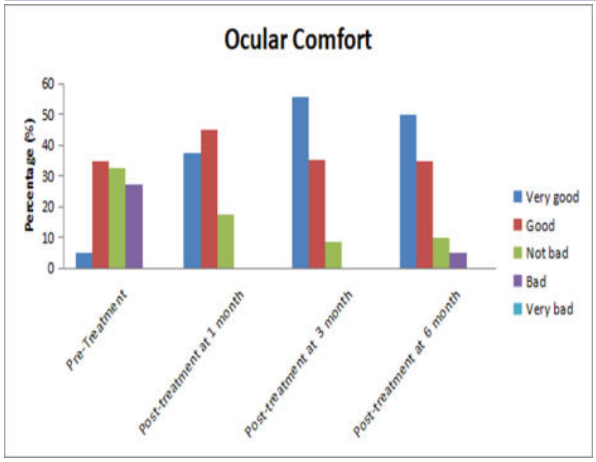

Table 5.2

The objective evaluation was more reliable in assessing dry eye disease. In most of the subjects, TBUT was low before the intervention although significant at 1 month in the active treatment group, reaching statistical significance but not much change in the 3rd month and 6th-month follow-up as most patients continued to have TBUT in the marginal range (table 6.1).

In most of the subjects, Schirmer was in the severe dry eye category before the intervention not much change was observed in the in-3rd month and 6th-month follow-up as the majority of patients continued to have Schirmer's in the moderate to severe dry eye disease as shown in table 6.2.

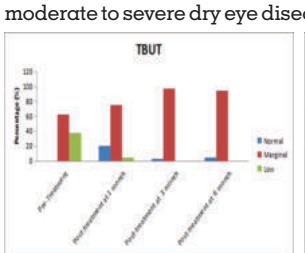

Table 6.1

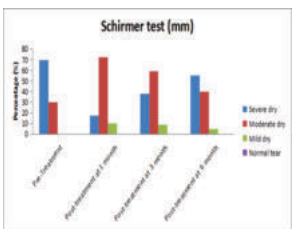

Table 6.2

The corneal and conjunctival staining were significantly lower in the active treatment eye group. In pre-treatment subjects, corneal conjunctival staining had a grade 3 stain and one patient also had a grade 5 staining on the ocular surface the treatment showed improvement as the majority of the patients after 1 month of treatment had grade 1/3 ocular surface stain which in 3rd month and 6th month follow up with little change continued to be a grade 2/3 stain as shown in table 6.3.

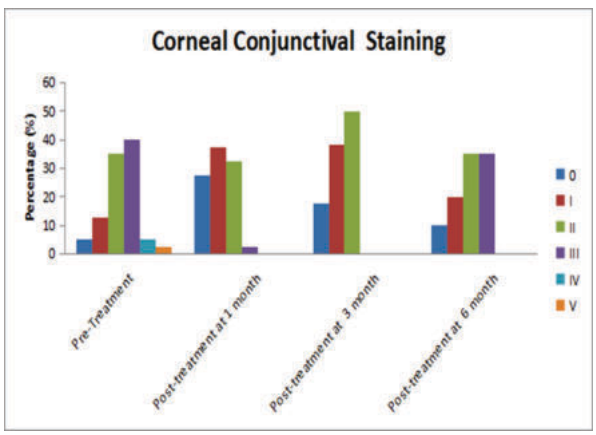

Table 6.3

There were no differences between groups at 6 months in the objective evaluation. The best improvements in the patient with Botox were observed in the 1st month's follow up and then as effects started to wean off a gradual progression of symptoms was seen. There were drop-outs due to loss of follow-up, possibly because of covid.

DISCUSSION

Dry eye is a common yet complex condition due to inadequate tear volume or function, resulting in an unstable tear film and ocular surface disease. Intrinsic and extrinsic factors can cause dysfunction of the lids, lacrimal glands, meibomian glands, ocular surface cells, or neural networks. These problems would ultimately be expressed at the tear film–ocular surface interface. The manifestations of these problems are experienced as symptoms such as grittiness, discomfort, burning sensation, hyperemia, and secondary epiphora in some cases reducing ocular comfort and visual performance[6]. The symptoms range from mild to severe and can occur intermittently or throughout the day. The classification of the dry eye usually applied is that of the 2007 International Dry Eye Workshop (DEWS), with a basic division into aqueous-deficient and evaporative types [1]. Evaluating dry eye needs multiple standard set approaches that include clinical history and symptoms that the patient experiences and that the examiner diagnoses. There is no globally-accepted guideline for dry eye diagnosis and none of the available tests may hold the title of the 'gold standard' [6]. Therefore, in our study, a set of subjective and objective parameters were taken to assess the dry eye sign and symptoms and monitor the progression of the disease after the intervention. Depending on the causes, there are numerous treatments for dry eye syndrome/tear film dysfunction, but the more common treatment modalities include Education and environmental/dietary modifications, Artificial tear substitutes eyelid therapy, serum eye drops, and methods that reduce lacrimal drainages like Punctal plugs and Botulinum toxin A injection. In our study, we investigated the efficacy of the periorbital BTA injection in order to improve dry eye symptoms. The eyelid motion, tear distribution, and tear drainage are all fundamental supposed to provide the main mechanism of action for lacrimal drainage. Kakizaki et al. reported that the common canaliculus expands and the lower parts and canaliculi are compressed, while with the relaxation of the Horner's muscle, the upper part of the lacrimal sac and common canaliculus are compressed and the lower parts and canaliculi expand [7]. Juan Carlos Ojeda stated that mechanism of action of the botulinum toxin on lacrimal drainage could involve a paralysis of the orbicularis oculi muscle acting on the canaliculi with a decreased compression of the canaliculi during blinking, thus decreasing the lacrimal pump function. Sahlin and co-workers (2010) studied for the first time the effect of botulinum toxin injection on the lacrimal drainage in dry eye conditions demonstrating decreased lacrimal drainage and improved eye comfort with reference to Choi EW (2021) 2.5 IU of Botulinum toxin A injection was injected in the lower eye lid [8].

Our study has similar results as Sahlin & Linderoth 2008, which showed significantly lowered the blink output 3 weeks after treatment and the effect lasted for approximately 3 months, when objective values returned to baseline.

In patients with blepharospasm and hemifacial spasm, previous studies with injection of Botulinum toxin A have demonstrated an increase in the TBUT Kim et al. 1995[9]; Horwath-Winter et al. 2003[10], but the results of Schirmer's test vary in some cases showing a decreasing value and an increase in others (Kim et al. 1995; Horwath-Winter et al. 2003), Consistent with the results in our study.

LIMITATIONS

Our study presents some limitations. There was limited number of subjective and objective parameters in our

assessment. Other objective measurements including the fluorescein clearance test, the blink rate was not evaluated in our study. Watering was not taken in account in our study as it itself presents as a symptom in dry eye disease Another limitation is that the study sample is small, so studies with a larger number of patients are needed to establish the definitive clinical utility of this therapeutic approach. In a tertiary care center, it is a relatively expensive modality of treatment for the dry eye over conventional methods of treatments and Subject to availability in selected centers is of great paramount. once injected the effect is non-reversible for months and is a painful procedure endured by the patients.

CONCLUSION

The injection of botulinum toxin A in the medial part of the lower eyelid is an effective and safe procedure in the treatment of dry eye disease. It is a temporary therapeutic approach, as expected for the natural duration of the toxin effect in the muscles. To achieve the long-term effect, it would require multiple serial applications of injection.

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