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Susmita Banerjee
Dr. D.Y. Patil Institute of Optometry & Visual Sciences, Sant Tukaram Nagar, Pimpri, Pune, Maharashtra, India

Corresponding Author:
Susmita Banerjee
Dr. D.Y. Patil Institute of Optometry & Visual Sciences, Sant Tukaram Nagar, Pimpri, Pune, Maharashtra, India

Corneal astigmatism & tear film changes after Botulinum toxin: A injection in patients with benign essential blepharospasm or hemifacial spasm in south Indian population

Susmita Banerjee

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Abstract
Aim: To investigate the influence of BTX-A on corneal parameters & tear film in patients with blepharospasm or hemifacial spasm.
Objectives
1. To compare the difference between Corneal Astigmatism by using corneal topography in Hemifacial Spasm or benign essential Blepharospasm before and after injecting Botox –A.
2. To compare the differences of Tear film break up time values in Hemifacial Spasm or benign essential Blepharospasm before and after injecting Botox –A.
3. To compare the schirmer values in Hemifacial Spasm or benign essential Blepharospasm before and after injecting Botox –A.
4. To compare the difference between OSDI Scoring in Hemifacial Spasm or benign essential Blepharospasm before and after injecting Botox –A.
5. To compare the difference between JRS Severity & Frequency in Hemifacial Spasm or benign essential Blepharospasm before and after injecting Botox –A.

Keywords: astigmatism, Botulinum toxin, blepharospasm, hemifacial spasm

Introduction

Benign Essential Blepharospasm & Hemifacial Spasm are two of the most common eyelid movement disorders, where Benign Essential Blepharospasm is bilateral, which characterized by grumbling facial expression, fluttering of the eyelids, increased frequency of blinking & chronic or sustained involuntary contractions (muscle spasms) & Hemifacial Spasm is the Unilateral, Intermittent clonic or tonic contractions of the facial expression muscles, innervated by epsilateral muscles, which lead to involuntary closure one side facial closure.

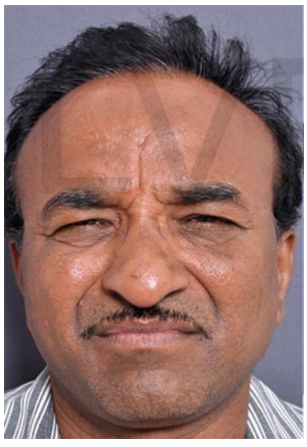


Fig 1: Benign Essential Blepharospasm

Fig 2: Hemifacial Spasm

Various treatment options have been proposed for Blepharospasm & Hemifacial spasm, including oral medications such as a Anticholinergics, Presynaptic monoamine depleting agents, Dopamine agonists, Botulinum Toxin injections & in refractory patients, surgical disruption of the facial nerve fibers (Neurosurgery for Hemifacial spasm), Myectomy surgery for Benign Essential Blepharospasm. These surgery is useful for those who do not adequately respond to Botox injections, cannot afford it, having difficulty getting transportation for the shots or who do not choose to have repeated injections.

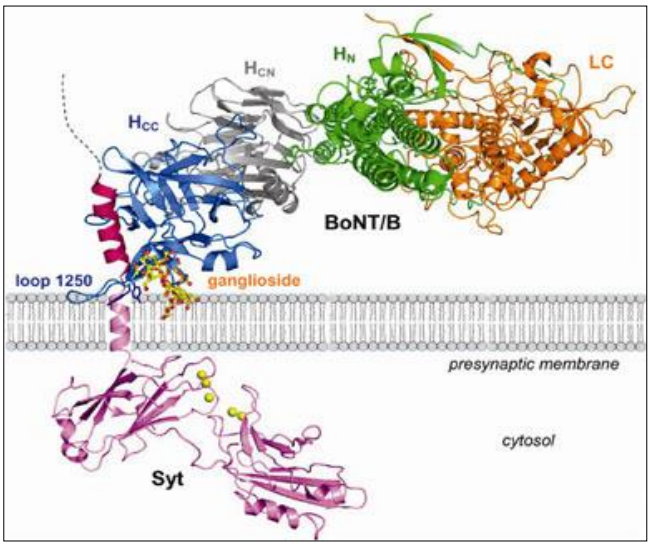


Fig 3: The botulinum toxin is a proteic neurotoxin produced by the "Clostridium botulinum"

Clostridium bacterium

The Clostridium bacterium is an obligate anaerobic (it lives only in absence of Oxygen because it doesn't have a cytochromes system and it is forced to produce ATP using the fermentation of different substrates), GRAM positive, spore-former bacterium. Clostridii are usually found in the upper part of soil and are responsible of human affections only after an accidentally introduction of the bacterium because of a wound or after the ingestion of aliments infected by the toxin.

Toxin

The botulinum toxin is a polypeptide made by 2 chains joined by a disulfide bond; preventing vesicles from anchoring to the membrane to release acetylcholine, in order to interfere with the nerve impulses and causing flaccid paralysis of muscles. There are seven different types of botulinum toxin, designated A through G and produced by seven types of Clostridium botulinum. A, B and E types are the main responsible for human poisoning. Once ingested, the toxin arrives in the intestine without being inactivated by the proteolytic enzymes, it is absorbed and it starts to be spread through the blood. It arrives at the neuromuscular junction and to all the cholinergic pre and post-ganglia nerve endings of the PNS.

Botulism

The toxin itself is rapidly destroyed by heat (for example cooking process), meanwhile the spores that produce the toxin are heat-tolerant and will survive boiling water for an extended period of time. Botulism can result in death due to respiratory failure, caused by the paralysis of the respiratory muscles, so treatment consists of antitoxin administration and artificial ventilation until the neurotoxin are excreted or metabolized. There are two primary botulinum antitoxins available:

- Trivalent (A, B, E), derived from equine sources using whole antibodies.
- Heptavalent (A, B, C, D, E, F, G), derived from equine sources using despeciated IgG antibodies, which have had the Fc portion cleaved off.

The BTX-A is now available in freeze-dried form for injection that are useful to treat spasms and dystonias but also have a cosmetic application; in fact Botox is used to prevent development of wrinkles by paralyzing facial muscles or to temporarily improve the appearance of moderate-to-severe frown lines between the eyebrows. BTX-A Is gold standard treatment for Benign Essential Blepharospasm & Hemifacial Spasm because of its efficiency & safety.

Astigmatism

It is one of the most important causes of ocular fatigue and visual disturbance. It is primarily caused by the optical center not being focused at one point due to the differences of refractive power from each meridian of the anterior, and posterior corneal surfaces and the lens itself. Among them the corneal astigmatism accounts for most of the ocular astigmatism. In fact, the cause of corneal astigmatism remains still unclear. Since Snellen first postulated that eyelids might affect the corneal shape and astigmatism in the 19th century, many other studies have reported reciprocal results. Among them, Gullstrand suggested that if the cornea were not influenced by the external pressure, it would maintain against-the-rule astigmatism and that with-the-rule astigmatism would occur due to the lid tension imposed on the corneal surface. Similarly, we can often see with-the-rule astigmatism in those with high lid pressure like children, whereas against-the-rule astigmatism develops with the reduction of lid pressure in the aged. The evidence that the pressure of eyelids has a direct effect on corneal shape can be found in common clinical situations. In the interpretation of the normal corneal topographies, we have to take some other factors into considerations. First, alteration in the distribution of tear can induce the corneal

topographic changes [9]. It is because the topographic images are taken from the most anterior ocular surface, and the physiologic outermost ocular surface is made up of tear film. Its conformation can change over time after blinking and the tear layer is known to reach its most regular state at 3-10 sec after each blink. We also have to consider diurnal variations of corneal curvature and other systemic factors such as age, gender, and intraocular pressure to evaluate the change of corneal topography [9]. In this study, we tried to investigate the role of eyelids in the development of corneal astigmatism in patients who have involuntary lid spasm, by observing that the induced astigmatism could be released with the removal of the mechanical pressure of the lid using Botulinum toxin-A. In the course of spasm, the tension of superior lid was so strong that we could ignore the effect of other subtle confounding factors.

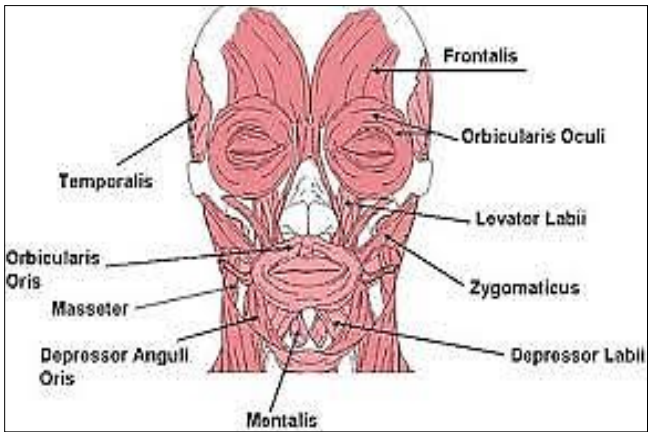
Tear Film

Many of patients with blepharospasm & hemifacial spasm also have dry eye disease, in varying degrees [3]. Park *et al*. (3) reported that the production, distribution & drainage in tears were affected in patients with blepharospasm. In addition, neurotoxin injection improved dry eye symptoms in patients with blepharospasm, & this treatment has been suggested for dry eyes.

Alime Gunes, *et al*. found that Botox –A was affected the tear film in patient with Blepharospasm & Hamifacial spasm but there was no changes in corneal parameters, except corneal astigmatism in these patient after treatment [2].

Material and method

This was a Prospective interventional study of 45 cases of Hemifacial Spasm or Benign essential Blepharospasm before conducted at a tertiary eye care centre LV Prasad eye institute KVC campus, Vijayawada. with the informed consent, we studied 27 patients with hemifacial spasm &18 patients with Benign Essential blepharospasm or involving lids for more than 12 months were visited LV Prasad Eye Institute from November 2016 to April 2017. After noting age and sex, the corneal astigmatism was measured using a (Zeiss ATLAS 9000 Corneal Topography system.) The lid tension was measured subjectively by grasping eyelashes with two fingers and pulling them outward and upward. We excluded from our study the patients in whom the corneal astigmatism could not be measured by this method due to their severe blepharospasm and the patients with other ocular problems that could cause any corneal surface alterations. To evaluate the direct mechanical effects of eyelids, we evaluated the keratometric changes in 2 ways. At first, the topographic changes were measured before and after passively opening the eyelids in all the patients enrolled in our study, paying attention not to dry the cornea. It was taken at 5 to 10 sec after their eyes were passively opened by the speculum. And at the same time, special efforts were made to avoid external forces evoked by hands or speculum exerting on lids and to avoid meibomian secretion running down into the tear layer. In this manner, we could minimize the effects of tear flow, and thus we could evaluate the short-term influence of eyelids on corneal topography. And to evaluate the long term changes of corneal astigmatism after removal of mechanical effects of eyelids, we used 100 IU Botulinum toxin-A (Botox, Allergan). It was stored at -20 ℃ and diluted with 2ml saline solution just before injection. The usual dilution of BTX- A was 5 IU per 0.1 ml was injected into 2.5 IU subcutaneously at each point with 26 guage insulin syringing in all of the patients. The toxin was injected in 5 selected sites: the lateral & medial connections of the Preseptal & orbital parts of the orbicularis oculi muscle, lateral to lateral canthus, the middle of the pretarsal orbicularis oculi muscle of the upper eyelid, & the middle of the lower eyelid.



All the procedures were conducted by the same physician. The follow-up examinations for the relaxation of spasm & resultant changes of corneal astigmatism &Tear Film exchange were performed with their eyes open spontaneously at 1 months after the injection, because the effect of toxin was to reach its maximum by 1 month and disappear by 6 months after injection into musculature [6]. We analyzed the amount and steepest axis of central corneal astigmatism from the Corneal Topographic System values obtained from (Zeiss ATLAS 9000 Corneal Topography system). We defined with-the-rule astigmatism when it steepest meridian lies from 45° to 135° and against the-rule astigmatism from 0° to 45° and 135° to 180°. order to evaluate the changes of astigmatism after treatment, If the vector points of astigmatic change after botulinum toxin injection lay in right side of the map, we could tell that they had the tendency towards against-the-rule astigmatism & accordingly the left side towards with-the-rule astigmatism. The refractive data were measured two times at each visit. The measurements were performed before treatment, & after 1month injection.

According to the pretreatment astigmatic values, we divided the patients into two groups as with-the-rule (group 1), and against-the-rule (group 2), and we compared the mean corneal Astigmatism. The changes in astigmatism were evaluated by vector analysis described by Moon *et al.* [1].

Fig 4: Zeiss ATLAS 9000 Corneal Topography system

Spasm severity & frequency was evaluated by only physician in all of the patients, before &1 month after treatment, using the Jancovik Rating scale [6] The Severity (0-No symptoms, 1-Increased blinking produced by external stimuli, 2-Mild spontaneous blinking, clearly visible, sometimes troublesome with no functional impairment, 3-Moderate spasm clearly visible with moderate impairment, 4-Severe spasm probably with involvement of other facial muscles.), whereas the Frequency (0-No symptoms, 1-Slightly increasing blinking frequency, 2-Flickering of eyes with individual blink duration of less than one second, 3-spasm lasting more than one second & open more than 50%of waking time, 4-Functional blindness caused by prolonged closure of the eys for more than 50% of waking time),

Patient's ophthalmological examinations included the spherical equivalent, Best corrected visual acuity, Intraocular pressure, Tear Break up Time (TBUT), Schirmer test, under topical anesthesia. The Ocular Surface Disease Index (OSDI) questionnaire was used to assess subjective discomfort related to dry eyes. This questionnaire is used to evaluate the symptoms of ocular irritation inked dry eye disease [7].

Evaluation of the Tear Film

The TBUT test was performed with a sterile fluorescein strip placed in the lower eyelid fornix. The patient was instructed to blink 3 times & then look straight ahead, without blinking. The time interval between a complete blink & the first appearance of the dry spot in the precorneal tear film was measured under cobalt blue- filtered light. The mean of 3 consecutive TBUT test measurements was calculated.

The schirmer test was performed using topical anesthesia. Three minutes after 1 drop of proparacaine 0.5% was instilled, the schirmer test strip was placed behind the lower lid, between temporal & middle third of the eyelid. After 5 minutes, strip was removed & the wet portion of the paper was measured; a distance of <5 mm with anesthesia was considered dry eye disease.

All measurement were performed before treatment at 1 month after the injection. To avoid diurnal variation in corneal parameters, all measurements were performed within the same time interval (9:00am-3:30pm) & at a 20 to 25 degree C temperature range & 35% to 45% relative humidity [8].

However as per our knowledge, no studies have been conducted regarding changes in corneal astigmatism & Tear film before & after injecting Botulinum Toxin-A injection in South India. Therefore the aim of the study was to &investigate the influence of BTX-A on corneal parameters & tear film in patients with blepharospasm or hemifacial spasm.

Observation & Results

A total of 90 eyes of 45 patients were enrolled in this study 28 were female &17 were male having 27 Hemifacial Spasm & 18 Benign Essential Blepharospasm & the mean age was 52.55 ±10.32 years. The mean duration of the disease was 10.62 ±1.88 month.

Table 1: The demographic data of patient

Total no of the patients	**45**
Total no of the eyes	90
Age	52.44±10.32
Female	28%
Male	17%
Hemifacial Spasm	27
Benign Essential Spasm	18

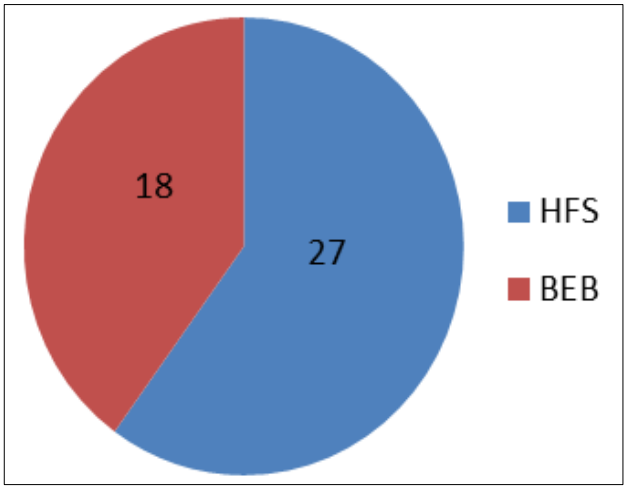


Fig 5: Total No. of Spasm

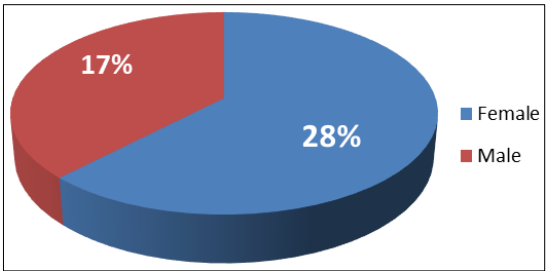


Fig 6: Gender ratio

Corneal measurements taken before Botulinum toxin-A injection revealed that the patients having with-the-rule astigmatism outnumbered those having against-the-rule astigmatism of 54 eyes showed with the- Rule astigmatism (group 1) and 36 eyes against-the-rule astigmatism (group 2).

The long-term influence of eyelids on the corneal astigmatism after injection of Botulinum toxin-A.

The average values of corneal astigmatism measured before botulinum toxin-A injection, and 1 month after injection were (82.70±17.36 D & 55.09±15.56D),in group 1,and (64.10±74.38 D & 32.97±14.39D) in group 2respectively. Regarding the changes of corneal astigmatism, the mean value significantly decreased in all the patients of group 1 group 2 after the injection.

Table 2: Mean corneal astigmatism after injection of BTX-A in patients with Benign Essential Blepharospasm& Hemifacial Spasm (mean±standard deviation)

	Before Injection	1 month After Injection
Group 1(Diopter)	82.70±17.36	55.09±11.56
Group 2(Diopter)	64.10±74.38	32.97±14.39

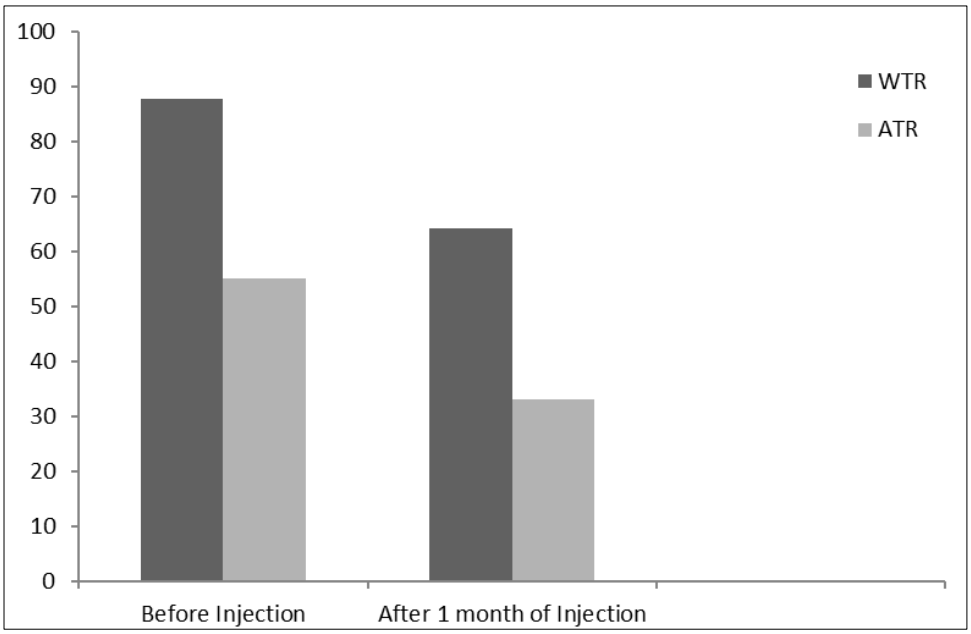


Fig 7: The mean corneal astigmatism before and after 1month of BTX-A in patients with Blepharospasm & Hemifacial Spasm With-the- rule astigmatism decreases and against-the rule astigmatism also decrease at 1 month.

There were no changes in Best Corrected Visual Acuity & Intraocular Pressure after the BTX-A (Table 3). The BCVA was 1.19±0.61 before giving injection &1.20±0.58 after 1 month of injection. Also the IOP was 13.87 mm of HG before giving injection &13.66±2.06 mm of HG after 1 month.

Table 3: Changes in Visual Acuity & Intraocular Pressure After injection of BTX- A in patients with Blepharospasm or Hemifacial Spasm (Mean±SD)

	Before Injection	1 month after injection
BCVA (Snellen)	1.19±0.61	1.20±0.58
IOP, mm of HG	13.87±2.21	13.66±2.06

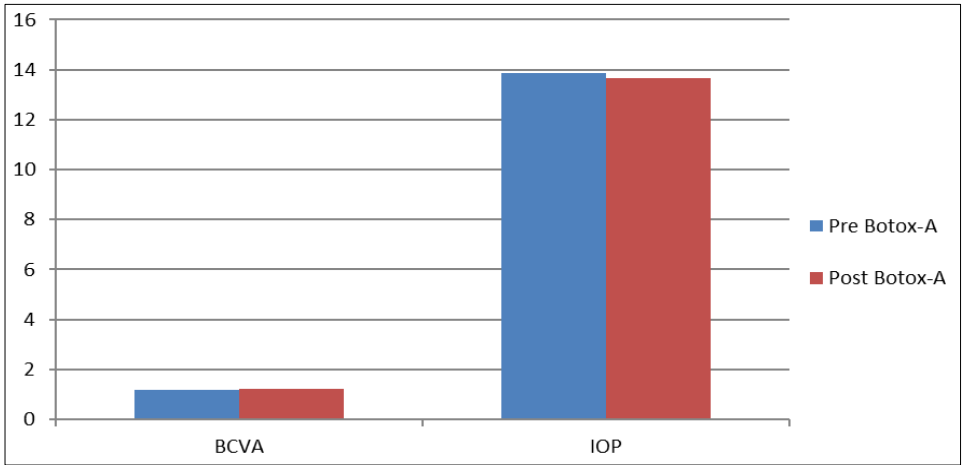


Fig 8: Comparison of Best Corrected Visual Acuity & IOP before & after 1 month of BTX-A in patients with HFS & BEB.

Whereas the TBUT was found to be significantly higher at 1 month after the injection (4.72±2.81 at pretreatment, 13.04±3.85 after1 month), The schirmer test values were significantly lower at 1 month after the injection (15.76±8.64 at pretreatment, 8.64±5.41 after 1 month) & The OSDI Score were also significantly decreased at 1 month after the injection (10.28±4.50 at pretreatment, 3.21±1.01 at 1 month after the injection.

Table 4: Changes of Dry eye tests Before & After 1 month injection of BTX-A in patients with Blepharospasm & Hemifacial Spasm.

	Before Injection	After 1 month of Injection
TBUT (in sec.)	4.72±2.81	13.04±3.85
Schirmer Test Score (mm/5 min.)	15.76±6.97	8.64±5.41
OSDI Score	10.28±4.50	3.21±1.01

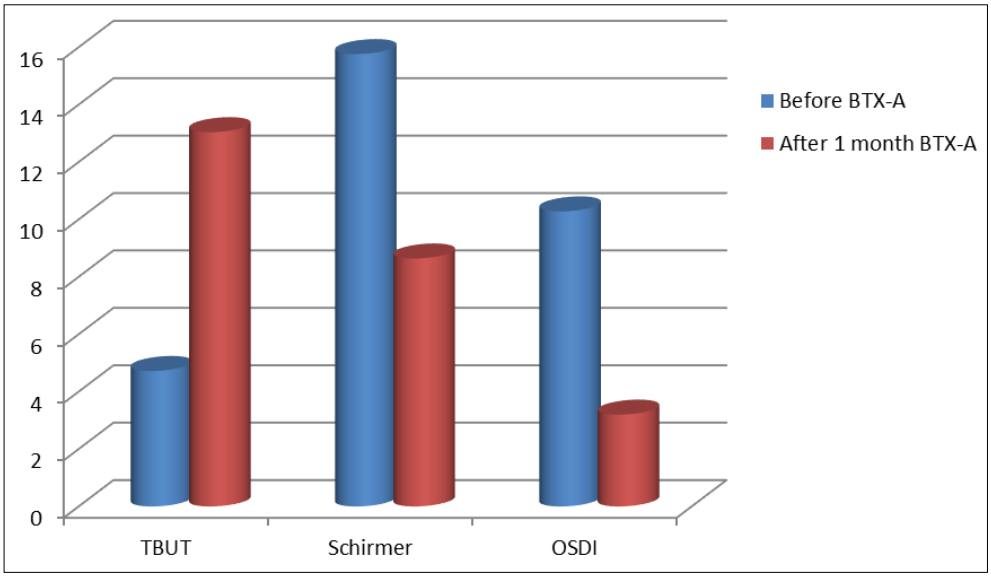


Fig 9: Comparison of the Dry eye tests &OSDI Score before & after 1 month injection of BTX-A in patients with Blepharospasm & Hemifacial Spasm.

In all of the patients Benign Essential Blepharospasm &Hemifacial Spasm the JRS Severity & Frequency improved significantly from before the Botox-A injection to 1 month after the injection. There was significant difference in Severity & Frequency between the pretreatment & after the 1 month of the injection (3.2±0.75 &2.73±0.75 pretreatment, 0.33±0.47 &0.47±0.48 after 1 month of injection respectively)

Table 5: Changes of Jancovic Rating Scale Consisting Severity & Frequency before & after 1 month injection of Botox-A in patients with Blepharospasm & Hemifacial Spasm.

JRS	Before Injection	After 1 month of Injection
Severity	3.2±0.75	0.33±0.47
Frequency	2.73±0.75	0.47±0.48

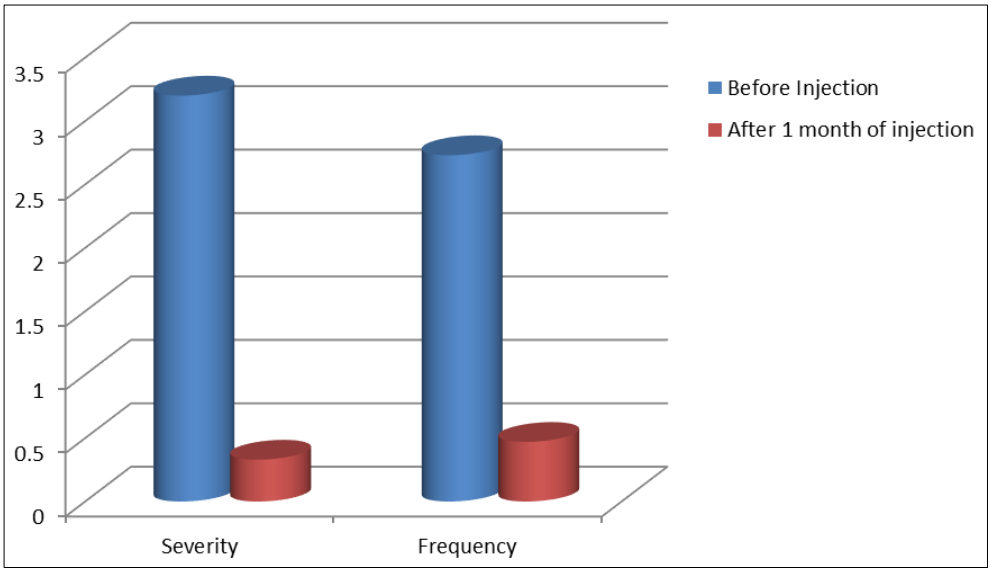


Fig 10: Significant differences of JRS's severity & frequency before & after 1 month of BTX-a in patients with benign essential blepharospasm & hemifacial spasm

Conclusion

In conclusion Botulinum Toxin –A injection therapy had an effect on disease severity, Tear Film parameters as well as OSDI scores & corneal astigmatism in patients with Benign Essential Blepharospasm & Hemifacial Spasm after 1 month of treatment. It is also known that the effect of Botulinum Toxin-A is temporary & repeated applications are required. Well this same study was continuing in our institute, which including Before; after 1 month & after 3 months of follow up, of patients with Benign Essential Blepharospasm & Hemifacial Spasm.

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