

CLINICAL SCIENCE

Botulinum toxin A treatment in patients suffering from blepharospasm and dry eye

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Background: Many patients with essential blepharospasm also show dry eye signs and symptoms. Botulinum toxin A is an effective treatment for reducing spasms in these patients. In this investigation, the effect of botulinum toxin A injections on tear function and on the morphology of the ocular surface in patients suffering from blepharospasm in combination with a dry eye syndrome was investigated.

Methods: Botulinum toxin A injections were applied to 16 patients with blepharospasm. All patients complained of dry eye symptoms and had reduced tear break up time values. A subjective questionnaire and ocular examinations including tear break up time, Schirmer test without local anaesthesia, and rose bengal staining were evaluated before, 1 week, 1 month, and 3 months after injection. Impression cytology was performed before, 1 month, and 3 months after botulinum toxin A treatment.

Results: Although all patients were relieved of blepharospasm after botulinum toxin injections, only three noticed an improvement in dry eye symptoms. Eight patients noticed no difference and five complained of worsening. Tear break up time was found to be increased 1 week and 1 month after injections. Schirmer test measurements were reduced up to 3 months. Rose bengal staining slightly increased 1 week after injections. Impression cytology showed no definite change in conjunctival cell morphology 1 month and 3 months after botulinum toxin A injections.

Conclusion: In the patients presented here suffering from blepharospasm and dry eye, botulinum toxin A injections were effective in relieving blepharospasm but were not successful in treating dry eye syndrome.

Botulinum toxin A injections are a well established treatment for blepharospasm. Botulinum toxin A, a dichain protein, is one of seven neurotoxins produced by *Clostridium botulinum*. The light chain endopeptidase component of botulinum toxin acts in the end plate of motor neurons where it cleaves SNAP-25, a protein involved in the fusion of acetylcholine containing vesicles with the presynaptic membrane.¹ When injected locally, it causes muscular paralysis by interfering with the release of acetylcholine at neuromuscular junctions.

Many patients with blepharospasm also suffer from dry eye symptoms and have reduced Schirmer test values.^{2–4} An increase in tear secretion and a decrease in dry eye symptoms have also been reported after periorbital botulinum toxin A injections for patients with Sjögren's syndrome associated with blepharospasm.⁵ Because of the reduction of lacrimal drainage after botulinum toxin A injections, this treatment has been suggested for dry eyes.⁶

In contrast, Price *et al*⁷ did not find any changes in Schirmer test results 1 week after injection compared with measurements taken before injection.

In this study, the effects of a standard dose of periorbital botulinum toxin A injections on tear function parameters, ocular surface morphology, and subjective dry eye symptoms were investigated up to 3 months in patients suffering from essential blepharospasm and dry eye syndrome.

PATIENTS AND METHODS

Botulinum toxin A (Dysport, Ipsen Biopharm, UK) was applied to 16 patients, three males and 13 females with an age range of 33–93 years (mean 67 years) with essential blepharospasm. The duration of the spasm was 7 months to 20 years. Ten patients had received repeated injections, the last injection dating back at least 6 months. All patients underwent neurological examination. Eight patients were

taking antidepressants, six patients antihypertensive drugs. Medication was unchanged during follow up. Further criteria for a patient's inclusion were typical symptoms of dry eye (dryness, burning, foreign body sensation, ocular pain, photophobia or easily fatigued eye) and a reduced tear break up time value according to the dry eye criteria by Lemp *et al* and Pflugfelder *et al*.^{7, 8} All patients gave informed consent before inclusion in this therapy and investigation.

The conventional treatment for essential blepharospasm using Dysport are 0.2 ml (40 units) injections to the upper and lower temporal areas of the orbital portions of the orbicularis muscle as well as 0.1 ml (20 units) injections to the muscle mid-way along the lower lid and to the upper medial part of the orbital portion of the orbicularis. Thus a standard dose of 120 units per eye was injected subcutaneously into these four periorbital locations.⁹

Each patient was asked for dry eye symptoms occurring several times a week and lasting for more than half an hour before, 1 week, 1 month, and 3 months after injections. The quality of symptoms was classified as absent, minimal, moderate, or severe. This questionnaire has been described as significantly correlated with the presence of keratoconjunctivitis sicca.¹⁰

Ocular examinations including tear break up time, Schirmer test without local anaesthesia, and rose bengal staining were performed before treatment, 1 week, 1 month, and 3 months after injection with botulinum toxin A.

Tear break up time (BUT) was measured by adding one drop of fluorescein obtained by wetting a fluorescein strip with non-preserved sterile saline to the inferior fornix. The mean value of three measurements was recorded. A BUT value of less than 5 seconds was considered pathological.

The Schirmer test was performed without anaesthesia using a commercially available 5 mm × 35 mm paper strip. Readings were reported in mm of wetting after 5 minutes. A reading of less than 5 mm was referred to as dry eye.

Table 1 Summary of clinical data and test results

	BUT (seconds)	Schirmer test (mm)	Rose bengal staining (score)	IC score
Pre	2.6 (1.0)	7.2 (6.9)	3.0 (2.7)	10.8 (4.6)
1 week	3.7 (1.8)*	3.8 (3.7)*	4.2 (2.8)	
1 month	3.7 (1.7)*	3.3 (3.2)*	3.9 (2.2)	11.3 (5.1)
3 months	3.0 (1.4)	3.6 (3.7)*	3.2 (2.5)	12.0 (4.9)

Each value shows average (SD) of all treated eyes. * = $p < 0.01$.

For rose bengal staining, one drop of 1% rose bengal solution was added to the inferior fornix and recorded in the temporal and nasal conjunctiva and cornea on a scale of 0 to 3 points according to the van Bijsterveld scoring system.¹¹ Thus, the maximum score obtained for one eye was 9. More than 3.5 points per eye were considered pathological.

Impression cytology was performed in all patients before treatment, 1 month, and 3 months after botulinum toxin A treatment. Sheets of cellulose acetate filter paper (type VC, 0.10 μ m, VCWP 04700 Millipore Corp, Bedford, MA, USA) were used to collect cells from the superior and inferior bulbar conjunctiva. The specimens were stained using the procedure previously described by Tseng¹² and examined under a light microscope. Between 0 and 3 points were added together from the following parameters to get the impression cytology score (IC score). The morphology of the epithelial cells, cell to cell contact, grade of squamous metaplasia (nucleus/cytoplasm ratio), appearance of nuclear chromatin (pycnosis, "snakes," fragmentation), keratinisation and distribution, number, and morphology of goblet cells were examined as well as number and type of inflammatory cells and mucous aggregation. A total of 0 to 7 points were typical for normal cell morphology, 8–14 points for slightly pathological, 15–21 points for moderate pathological finding, and 22–30 for intense pathological changes.

Data were analysed using the Wilcoxon rank test. A p value of 0.01 or less was considered statistically significant.

RESULTS

Before botulinum toxin A therapy, all patients presented with a break up time less than 5 seconds. Eight of 16 patients presented with pathological values for Schirmer test without local anaesthesia (< 5 mm) and rose bengal staining (score ≥ 3.5).

Impression cytology showed moderate epithelial squamous metaplasia in five patients, slight squamous metaplasia in nine patients, and a normal epithelial picture in only two patients. Reduced goblet cell density was observed in 15 patients before therapy and an inflammatory reaction was found in five patients.

Botulinum toxin treatment relieved blepharospasm in all patients (mean duration 3 months). Improvement or deterioration of the dry eye was judged by subjective and objective parameters. According to the questionnaire, three patients reported a decrease of dry eye symptoms. Eight patients noticed no difference and five reported an increase of symptoms. The reasons for this increase were a sagging of the lower lid in two patients leading to exposure of the ocular surface and a lower eyelid laxity leading to an entropion in one patient. In two patients, no other reason but a decrease in Schirmer test scores to pathological values could be found.

The tear function parameter BUT increased 1 week and 1 month after injections ($p < 0.01$). Schirmer test results were significantly reduced ($p < 0.01$) 1 week, 1 month, and 3 months after injections. Rose bengal staining increased 1 week after injections but not significantly ($p > 0.01$). The epithelial picture examined and interpreted by the impression cytology score remained identical 1 month and 3 months after injections (Table 1).

DISCUSSION

Essential blepharospasm is characterised by repeated forceful spasmodic contractions of the orbicularis oculi muscle frequently resulting in prolonged eyelid closure and severe visual disability. It has been hypothesised that essential blepharospasm is maintained by a vicious cycle within a yet unidentified central control area located in the region of the basal ganglia, mid-brain, or brainstem.¹³ Multifactorial stimuli such as light, emotion, stress, and other psychological factors contribute to the cycle.

Dry eye is a complex disease of the ocular surface caused by different disturbances of the natural function and protective mechanism of the external eye leading to an unstable tear film. Up to now there is not a single test which evaluates completely the dynamic system of the ocular tear film and ocular surface. It is necessary to interpret the results of a panel of different tests to analyse the multifactorial aetiology of this disease.^{7, 8}

Dry eye has often been reported in patients with blepharospasm.²⁻⁴ It is difficult to determine whether dry eye causes blepharospasm because the blinking rate increases to compensate for tear film instability or deficiency.¹⁴ On the other hand, blepharospasm could cause dry eye since the periodic blinking action of the eyelids is crucial for the maintenance and renewal of the precorneal tear film.¹⁵ Electrophysiological studies have confirmed abnormalities in the electrically induced blink reflex in patients with blepharospasm even in the absence of lid spasm.^{16, 17} Abnormal lid motion did not improve following treatment with botulinum toxin. In contrast, botulinum toxin treatment significantly altered blink lid lowering kinematics, and a significant decrease in the peak velocity of the blink downphase was observed.¹⁶

Botulinum toxin A has been suggested for dry eye therapy because of the reduction in lacrimal drainage after treatment.⁶ Paralysis of the orbicularis oculi muscle acts on the canaliculi and induces a decreased pump function during blinking. Therefore, botulinum toxin injection significantly lowered the blink output 3 weeks after treatment.⁶ This would result in an increased tear retention explaining the observed improvements in Schirmer test measurements.³

In our patients with blepharospasm, treatment with botulinum toxin A resulted in improved tear film break up time only. The ocular surface morphology judged by impression cytology remained unchanged. Significantly reduced Schirmer test values up to 3 months and slightly increased rose bengal staining 1 week after botulinum toxin A injection were observed. This is consistent with the findings of Dutton *et al*¹⁸ that dry eye is the most common side effect of botulinum toxin therapy for blepharospasm.

Lacrimal drainage capacity decreases with increasing age.⁶ As patients in our study were older (mean age 67 years), this could be an explanation for the difference in the Schirmer test results after treatment with botulinum toxin A compared with previous studies.^{3, 5} It is also possible that increased tearing after botulinum toxin A therapy described in literature^{3, 5} is caused by corneal exposure resulting from lower eyelid laxity.¹⁸ The absence of contractive forces around the walls of the lacrimal system may produce both epiphora and an associated keratoconjunctivitis as a result of a stagnant tear

meniscus and delayed tear clearance. This provides microorganisms with a good environment for replication and allows inflammatory products to accumulate.¹⁹

Another reason for decreased Schirmer test results might be a direct pharmacological effect of botulinum toxin on lacrimal gland tear production. Botulinum toxin A not only affects neuromuscular junctions but also autonomic cholinergic transmission during the systemic manifestation of botulism. Clinical presentation includes mydriasis, accommodation paresis, reduced salivary secretion, and reduced lacrimation. Therefore, potential indications for botulinum toxin A treatment in disorders of the autonomic nervous system include diseases associated with secretomotor hyperactivity such as pathological tearing (crocodile tears), hypersalivation, and hyperhidrosis.²⁰ Botulinum toxin A may affect lacrimal gland tear production directly by spreading along tissue planes.

Another reason for different results of botulinum toxin A therapy in the literature and presented in this study may be because two different types of commercially available botulinum toxin A preparations are used—Dysport and Botox. It was postulated that 1 unit of Botox is equivalent to 3–5 units of Dysport.²¹ Different investigators may use different injection techniques and may vary both the number and distribution of injections to reach a maximum of efficacy in relieving blepharospasm.^{3,9} The apparent difference in the potency of the two products and different or variant injection sites cause difficulties when comparing tear function parameters. To avoid variations in dosage and localisation of injections, a standard procedure was used in this investigation.

The lack of improvement in dry eye after effective treatment for blepharospasm with botulinum toxin A suggests that blepharospasm and dry eye are two independent diseases but can occur simultaneously. Although botulinum toxin improves blepharospasm, it does not restore normal tear function and ocular surface morphology. Even a deterioration of dry eye symptoms and signs can be observed. This should be kept in mind when treating patients suffering from blepharospasm in combination with dry eye.

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