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Original Article

An evaluation of the safety and efficacy of botulinum toxin type A (BOTOX) when used to produce a protective ptosis

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Abstract

Purpose: To evaluate the safety and efficacy of botulinum toxin type A (BOTOX, Allergan) when used to produce a protective ptosis in patients where a surgical tarsorrhaphy would otherwise be required.

Methods: A total of 21 patients entered into the study. Doses of 2.5 and 5.0 units of BOTOX were injected into the levator palpebrae superioris muscle through the eyelid. The patients were followed daily where practical until a ptosis developed and then monitored 1–2 weekly until the ptosis was resolved. Injections were repeated, if necessary, until the underlying condition had healed.

Results: Ptosis took an average ± SE of 4.0 ± 0.5 days to develop (range 2–8 days). Duration of ptosis was an average ± SE of 46.0 ± 12.1 days (range 1–206 days). The effective dosage was 5 units of BOTOX in 0.1 mL. In 16 patients, the ptosis produced by BOTOX was sufficient to allow the underlying disease to heal and a surgical tarsorrhaphy was avoided. One patient required a surgical tarsorrhaphy and three patients required other surgical intervention to correct the underlying condition. One patient was lost to follow up. Diplopia was seen in five patients but resolved in all cases.

Conclusions: BOTOX was a suitable alternative to a surgical tarsorrhaphy.

Key words: botulinum toxin, cornea, corneal ulceration, diplopia, protective ptosis.

Introduction

Recalcitrant corneal epithelial defects and persisting corneal exposure from lower VII nerve involvement are often treated by a surgical tarsorrhaphy when medical treatments are not effective. This procedure involves splitting the upper and lower lid margins with removal of the distal posterior lamella. The anterior lamella of the upper and lower lids are sutured together and the raw edges of the posterior segment form a scarred bonding over following weeks.[1] When reversing the tarsorrhaphy, the lid margins are left permanently scarred and both cicatricial entropion and trichiasis can be eventual problems.[2,3] A surgical tarsorrhaphy also does not permit easy viewing of the cornea or allow access for topical medication.[2,3] This procedure can be very effective in providing healing of persistent epithelial defects.

A temporary tarsorrhaphy can be performed by the local injection of botulinum toxin into the levator palpebral superioris muscle of the involved eye. Botulinum toxin has been effectively used in ophthalmic practice for the treatment of strabismus, hemifacial spasm and blepharospasm.[4–7] Although the use of botulinum toxin in producing a ptosis as a form of treatment for corneal ulceration and exposure has been mentioned in reviews on botulinum,[8–10] there has been only one major prospective study of the effects of the botulinum injection in producing a protective ptosis[2,3] and various case reports.[11–13] There have also been studies into botulinum toxin's use in upper lid retraction of Graves' ophthalmolopathy,[14] epikeratoplasty[15] and entropion of the lid.[16]

An open-label prospective multicentred study was performed to evaluate the safety and efficacy of botulinum toxin type A (BOTOX; Allergan, Gordon, NSW, Australia) when used to produce a protective ptosis in patients, where a surgical tarsorrhaphy would otherwise be required.

Methods

There were a total of 21 patients entered into the study from the ophthalmic unit at St Vincent's Hospital (patients 1/01–1/04) and the Corneal Unit at the Royal Victorian Eye

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Table 1. Patient data

Subject	Diagnosis	History/prior therapies
1/01	VII nerve palsy	CVA, HIV
	Oculomotor palsies	Pontine haemorrhage
1/02	VII Nerve palsy	CVA
1/03	Multiple cranial nerve palsies	
	V, VII, IX, X	
1/04	Herpetic keratitis, PED	Recurrent
2/01	PED following PK	PK × 2, Lamellar keratoplasty × 2
		Down syndrome
2/02	Herpetic keratitis, PED	
2/03	Sclerokeratitis, PED	PK 1995, keratolysis and glue 1996
		Fungal keratitis
2/04	Recalcitrant corneal ulcer	Neurotropic cornea following trigeminal ablation
		Recent M. chelonae keratitis
2/05	Psuedomonas keratitis	Bacterial keratitis and stromal melting
2/06	Recalcitrant corneal ulcer	Neurotropic cornea following trigeminal ablation
2/07	Contact related bacterial keratitis	
2/08	Caustic soda burn 1997, PED	Failure of epithelization despite contact lens
2/09	PED	Herpes Simplex keratitis 1996
		Bacterial keratitis 1996, PK 1997
2/10	Herpes simplex keratitis	PK 1990 and 1997
		Bandage contact lens
		Medial and lateral tarsorrhaphy 1995
2/11	Climatic droplet keratopathy	
	Pseudophakic bullous keratopathy	
	Bacterial keratitis – *Staphylococcus epidermis*	
2/12	Herpes simplex keratitis, PED	
2/13	Polypharmacia, PED	Bandage contact lens, unpreserved drops
2/14	Bacterial keratitis	Bandage contact lens
	Pseudophakic bullous keratopathy	
2/15	Herpes simplex keratits, PED	PK × 2
	Microbial keratitis – *Moraxcella*	
2/16	Chemical burn 1990	Descemetocoele, PK 1993
	Recurrent corneal ulceration	
2/17	Recurrent Herpes simplex keratitis	PK 1957, 1969, 1996

PED, persistent epithelial defect; PK, penetrating keratoplasty. Subjects 1/01–04 from St Vincent's Hospital and subjects 2/01–17 from the Corneal Unit at the Royal Victorian Eye and Ear Hospital.

and Ear Hospital (patients 2/01–2/17). Participation in this study was open to patients 12 years of age or older who required a surgical tarsorrhaphy. There were 12 men and nine women, aged 34–90 years (average 63 years).

The diagnosis of each of the patients is listed in Table 1. There were three patients (1/01, 1/02 and 1/03), who were grouped for primary corneal protection because of nerve palsies, and the other 18 were grouped as primary corneal pathology. The various underlying conditions had been present for 2–40 weeks with a mean ± SE of 6 ± 2 weeks.

The presence of any of the following excluded potential patients from participating in the study: scarring in the region of the levator palpebral superioris muscle; an upper lid cicatricial entropion or ectropion; a known hypersensitivity to any ingredient in the formulation; or the presence of infection or inflammation at the proposed injection site(s).

Doses of 2.5 and 5.0 units of BOTOX were injected into the levator palpebral superioris muscle through the eyelid. The patients were followed daily where practical until a ptosis was produced and then monitored 1–2 weekly until the ptosis was resolved. Injections were repeated until the underlying condition had healed (Fig. 1).

The development of the ptosis was tracked. The variables that were followed were: the number of injections and dose required to produce and maintain ptosis; the time until maximum ptosis occurred; when levator function and interpalpebral fissure returned to original measurements; improvement of underlying condition; other measurements required to promote protection and healing of the cornea (e.g. concomitant medications); complications; and whether the ptosis that developed was suitable in assisting the healing of the underlying condition thus preventing the need for tarsorrhaphy surgery.

The investigator performed all injections in a sterile setting. A vial of BOTOX was diluted to the desired units (2.5 or 5.0 units per 0.1 mL) to be injected by adding the appropriate amount of sterile non-preserved 0.9% sodium

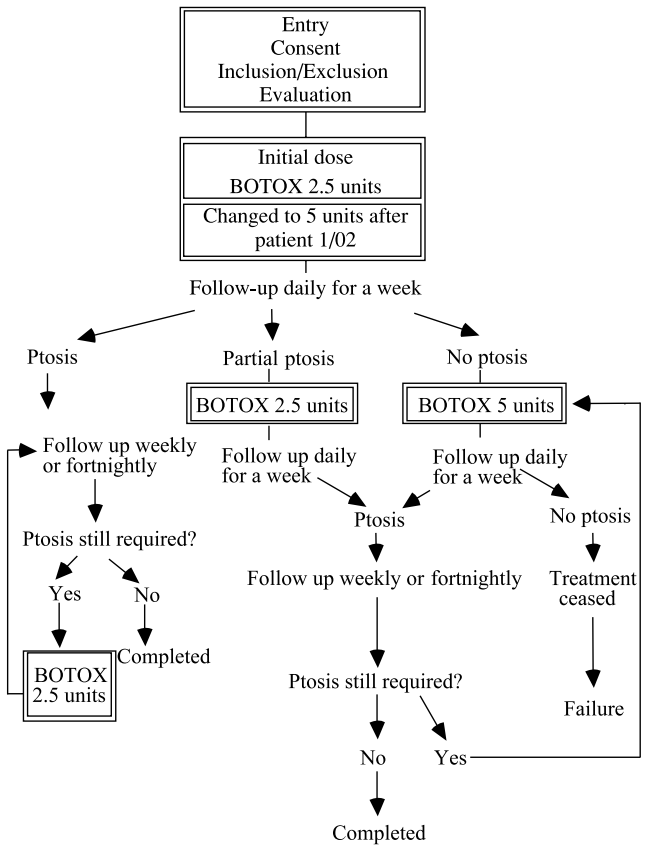

Figure 1. Study procedure.

chloride according to the provided dilution table. The manufacturer's directions were followed. From the diluted solution, at least 0.2 mL of the reconstituted BOTOX was drawn from the vial into a tuberculin syringe to fill the needle barrel. With the patient lying down, a 25-g needle (25 mm length) was attached to the tuberculin syringe and the needle was introduced just below the superior orbital rim to the hilt of the needle (at a depth of 25 mm) aiming backwards into the levator palpebral superioris. The aim was to make an orbital injection into the muscle belly of the levator palpebral superioris, not into the aponeurosis. Injecting 0.1 mL delivered the desired units. The remaining solution in the syringe was discarded. No anaesthetic or electromyographic control was required.

Results

Twenty-one patients were enrolled and included in the safety analysis. Sixteen patients were included in the efficacy analysis. The main reason for the discrepancy was that there were patients who received a second injection before the effect of the first injection could be evaluated, and hence were not eligible for the efficacy analysis.

Ptosis resulted in 16 out of 21 patients after injection of BOTOX. Four patients required a second injection to maintain sufficient ptosis to allow healing. A 'suitable' ptosis was defined as one that was sufficient to cover the area of affected cornea and assist healing of the underlying condition. The medically induced tarsorrhaphy allowed topical antibiotics and lubricants to still be delivered to the eye concerned. One patient required a surgical tarsorrhaphy and three patients required other surgical intervention to correct the underlying condition. One patient was lost to follow up (Table 2).

In the 16 patients who were suitable for the efficacy study, a suitable ptosis developed between 2 and 8 days with a mean ± SE of 4.0 ± 0.5 days. Once the suitable ptosis had established, it lasted a mean ± SE of 46.0 ± 12.1 days (range 1–206 days). The first injection only was used to calculate these figures so as to exclude any bias from possible variables induced from the repeat injections. Table 2 shows the data collected from all 21 patients.

It was clear from the early patients that an injection concentration of 2.5 units was not adequate to produce sufficient ptosis to allow healing of the underlying condition. The initial injection concentration was then increased to 5 units. Two patients received 2.5 units as a single injection, 12 patients received 5 units as a single injection, two patients received 7.5 units in two separate injections (2.5 and 5.0 units) and five patients received 10 units (5.0 and 5.0 units) in two separate injections. The effective dose was found to be 5 units in 0.1 mL.

Apart from those patients who were excluded from the efficacy analysis, the underlying corneal condition resolved in 14 patients while the temporary BOTOX-induced ptosis was present. In two of those patients, surgical intervention other than a surgical tarsorrhaphy was required. Patient 2/08, who suffered a caustic soda burn, required an amniotic membrane transplant and limbal stem cell transplant due to recurrence of epithelial breakdown, and patient 2/15, with Herpes simplex and Moraxcella keratitis, suffered a perforated desmetocoele requiring a penetrating keratoplasty. The other two patients in the efficacy study had the BOTOX protective ptosis performed for corneal protection while there was a VII nerve palsy present (Table 2). Ocular lubricants were required in 18 patients to assist corneal healing.

One patient was considered as a treatment failure due to subject intervention. Subject 2/01 had Down syndrome and a past history of penetrating keratoplasty (× 2), lamellar keratoplasty (× 2), tarsorrhaphy (× 3) and a recently infected central tarsorrhaphy. He interfered with the ptosis and cornea by rubbing with his finger and a surgical tarsorrhaphy was required.

The only treatment related adverse event reported was diplopia. The occurrence of this event was 24% (5/21 patients). In every case, the diplopia resolved without any additional intervention. No adverse event was recorded associated with administration of the study drug (Table 3). The vertical misalignment clinically behaved as a superior rectus muscle palsy. Case 1/03 had both vertical and horizontal misalignments, which were at least partly due to underlying multiple cranial palsies.

Table 2. BOTOX treatment data for all patients

Subject no.	No. injections	No. units	Time to ptosis from injection (days)	Duration of ptosis (days)	Efficacy trial	Underlying condition healed	Time to resolution (days)	Comment
1/01	1	2.5	7	8	Yes	Not relevant	Unknown	Protection of cornea
1/02	1	2.5	M	Ptosis never confirmed				
1/03	1	5	7	17	Yes	Not relevant	Unknown	Protection of cornea
	2	5	3	14				
1/04	1	5	4	206	Yes	Yes	210	
2/01	1	5	2	9	Surgical tarsorrhaphy			
2/02	1	5	3	11	Yes	Yes	196	
2/03	1	5	2	33	Yes	Yes	192	
2/04	1	5	3	102	Yes	Yes	105	
2/05	1	5	2	40	Yes	Yes	42	
2/06	1	5	2	54	Yes	Yes	56	
2/07	1	5	No					
	2	5	6	10	No*			
2/08	1	5	2	12	Yes	No	Not resolved	Surgical intervention
	2	5	4	7				
2/09	1	5	3	95	Yes	Yes	168	
	2	5	9	M				
2/10	1	5	4	17	Yes	Yes	98	
	2	5	7	56				
2/11	1	5	4	24	Yes	Yes	28	
2/12	1	5	No					
	2	2.5	7	21	No*			
2/13	1	5	8	49	Yes	Yes	94	
2/14	1	5	2	29	Yes	Yes	56	
2/15	1	5	2	50	Yes	No	Not resolved	Surgical intervention
2/16	1	5	5	1	Yes	Yes	33	
2/17	1	5	Incomplete					
	2	5	7	14	No*			

M, missing data. *Reinjected before effect of first injection could be evaluated.

Table 3. Side-effects of BOTOX administration

Subject no.	No. units	Time since injection (days)	Duration of adverse effect (days)	Description of adverse effect
1/03	5	1	Not resolved	Diplopia (vertical and horizontal)
2/02	5	84	175	Diplopia (vertical)
2/04	5	105	56	Diplopia (vertical)
2/05	5	24	18	Diplopia (vertical)
2/12	5	74	42	Diplopia (vertical)

Discussion

All patients in our study with persistent corneal epithelial defects had failed the normal paradigm of conservative treatment. In all cases infective causes were excluded, preservative-free medications were used when able and any blepharitis was treated, and despite this the defect had failed to heal.

There was one failure who required a surgical tarsorrhaphy because the patient interfered with his eye. BOTOX was helpful in all the patients included in the efficacy trial, except for two patients who required further surgical intervention other than a surgical tarsorrhaphy. BOTOX proved to be safe to use in the 21 patients. Diplopia, which resolved in all cases, was the only significant side-effect.

The only prospective trial of the use of botulinum toxin was by Adams *et al*. Their first report was of 15 patients[2] and the second report was after their patient base had expanded to 25 patients.[3] The study method and patient selection was similar to our study. The botulinum toxin used was supplied by the vaccine research and production laboratory PHLS CAMR, Porton Down, Wiltshire, England.

Using dosages of equivalent to 2.5 units (62.5×10^{-5} g), out of the 25 patients, complete ptosis was reported in 15 patients after one injection (60%), compared to 16 out of 21 patients in our study (76%). In three more patients there

was complete ptosis after another dose of toxin. The time to complete ptosis was a mean of 3.6 days, compared to our average 4.0 days. Duration of the ptosis was a mean 16 days, compared to our 46.0 days.

Impression cytology revealed that the conjunctival epithelium improved in patients with corneal ulceration, showing an increase of goblet cells, loss of inflammatory cells and a move toward more normal conjunctival morphology. There was no change seen in the conjunctivae of patients with lower motor neuron VII nerve palsy.[3]

Side-effects reported in the study by Kirkness *et al.* included transient underaction of the ipsilateral superior rectus muscle (17 patients), for a duration of 3–20 weeks (mean 6 weeks).[2,3] Three patients experienced diplopia, as the underaction wore off prior to the return of the levator function in most cases. Haemorrhage at the site of the injection occurred in one patient.

There are various case reports concerning the use of botulinum toxin for a protective ptosis.[11,12,14,15] Some of these included the use of higher doses, but there was no mention of side-effects. Heyworth and Lee reported three cases in which the superior rectus weakness was permanent.[17] In these cases, 7.5 units in 0.3 mL were used to inject the superior rectus muscle. The authors proposed either that a prolonged period of occlusion may have caused a breakdown of fusion, or that there was contracture of the ipsilateral antagonist muscle. They recommended that latent deviations be searched for in order to pick those at risk of this complication as a result of prolonged occlusion.[17]

Based on our findings, caution should be exercised in using BOTOX-induced ptosis in eyes with good vision. Corneal protection is the primary goal in order to preserve vision.[18] There has been a suggestion to administer botulinum toxin into the levator via the transconjunctival route,[18] but this may lead to increased superior rectus underaction.

People with severe ocular surface disease have poor vision. Those who are having the botulinum toxin injection in order to heal a corneal defect are likely to be unaware of any diplopia. Hence, the incidence of underaction of the superior rectus could be higher.[17]

Gravity may be important for the temporary ptosis to be effective. Our observation was that patients confined to supine position do not have as effective protection as mobile patients. Adequate coverage of the cornea requires good mobility of the upper lid and this technique should be used with care if scarring is suspected in the vicinity of the levator palpabral superioris muscle. Cicatrization of the lower lid would be another contraindication if corneal coverage is not adequate.[2]

The mechanism of action of protective ptosis is unclear. At least there is prevention of epithelial drying, especially in the facial palsy patients. Once a protective ptosis is established, there would be reduced trauma to epithelial cells by decreased eyelid movement. In addition, we suspect that growth factors and cytokines released from tarsal conjunctival vasculature would aid healing of the epithelium and that the close proximity of the vessels of the conjunctiva to the indolent ulcer would allow transfer of these factors. Conjunctival morphology may also be altered. Increased contact time with lysosymes and growth factors in tears due to reduced evaporation may also be important.

It should be noted there is a concentration difference between the USA-manufactured and UK-manufactured botulinum.[19] No ideal dosage of BOTOX has been examined by a trial.

Diplopia may be a significant problem, but is confined to patients with good vision and is usually not permanent. Gravity may be important for the temporary ptosis to be effective, as we observed that patients confined to supine position did not have as effective protection as mobile patients.

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