

Evaluation of efficacy and safety of botulinum toxin type A injection in patients requiring temporary tarsorrhaphy to improve corneal epithelial defects

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Abstract

• **AIM:** To evaluate the efficacy and safety of botulinum toxin type A (Dysport, (Ipsen Biopharm Ltd, Wrexham, UK)) injection in patients requiring temporary tarsorrhaphy to improve corneal epithelial defects.

• **METHODS:** Thirty patients were enrolled into the prospective study between March 2007 and September 2009. Doses of 15 and 30U of Dysport were injected into the levator palpebrae superioris muscle through the eyelid. The patients were followed daily until completion of ptosis and then 1-2 weekly until complete resolution of levator function and improvement of corneal condition.

• **RESULTS:** Ptosis took 2.64 ± 1.85 days to be completed (range 1-9 days) and lasted for 12 ± 2.19 weeks. For patients with seventh nerve palsy, 30U Dysport was appropriate to produce sufficient ptosis whereas in other patients 15U of toxin was sufficient. In 83.3% of patients ptosis was sufficient for complete recovery of corneal epithelium and 16.7% required a second procedure (Amniotic membrane transplantation, conjunctival flap). There was a direct correlation between age and duration of ptosis. In patients with seventh nerve palsy, the amount of resultant ptosis was significantly lower than that of other patients. The only adverse effects of injection were superior rectus underaction (33.3%) and diplopia (16.7%) which resolved in all patients without any intervention.

• **CONCLUSION:** Dysport injection is a safe and effective substitute for surgical tarsorrhaphy with fewer complications.

• **KEYWORDS:** botulinum toxin type A; temporary tarsorrhaphy; temporary tarsorrhaphy

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INTRODUCTION

Tarsorrhaphy is the closure of the eyelids, either temporarily or permanently^[1]. It is often performed in the management of various problems such as corneal ulceration or exposure, persistent corneal epithelial defects secondary to neurotrophic keratopathy, exposure keratopathy, dry eye syndrome, and progressive corneal melting^[1,2]. It is also performed in patients susceptible to corneal ulceration because of 5th or 7th nerve palsies^[2]. Tarsorrhaphy decreases the evaporation rate of tears by decreasing the palpebral fissure width. In addition, immobilization of the lid over the epithelial defect decreases the traumatic effect of the moving lids on the healing epithelium^[1]. Surgical tarsorrhaphy involves splitting the upper and lower lid margins with removal of the distal posterior lamella. The anterior lamellas of the upper and lower lids are sutured together and the raw edges of the posterior segment form a scarred bonding over following weeks. This procedure has some complications including permanently scarred lid margins, cicatricial entropion^[3], trichiasis, and distichiasis. Adhesion between upper and lower lids after tarsorrhaphy removal, premature opening, pyogenic granuloma of the eyelid, keloid formation^[1], focal cellulitis, cheese wiring of the sutures, and skin breakdown^[4] are the other reported complications of surgical tarsorrhaphy. In addition, this procedure does not permit easy viewing of the cornea or allow access for topical medication^[3].

Botulinum A toxin injection into the levator palpebrae muscle offers a simple procedure for creation of chemical tarsorrhaphy and corneal protection^[2]. Botulinum toxin has been effectively used in ophthalmic practice for the treatment of reflex eyebrow elevation after ptosis repair,

lower lid entropion, management of glabellar rhytides, strabismus, hemifacial spasm, and blepharospasm [2]. This study compares efficacy and safety of botulinum toxin type A injection with temporary tarsorrhaphy in patients that had corneal epithelial defects requiring temporary tarsorrhaphy.

MATERIALS AND METHODS

Materials In a prospective study between March 2007 and September 2009, patients with recalcitrant corneal epithelial defects or those susceptible for corneal ulceration were included. All of the patients had been treated with conservative treatments (preservative-free lubricants, bandage contact lens) and appropriate antibiotics (for ulcers) for at least 2 weeks and because of unresponsiveness to these treatments were considered for performing temporary tarsorrhaphy. Exclusion criteria included; upper lid scar, cicatricial entropion or ectropion, known hypersensitivity to botulinum toxin or any ingredient in the formulation, established 7th nerve palsy, high myopia or presence of staphyloma, infection or inflammation at the site of injection, previous orbital trauma with untreated sequelae, proptosis, systemic diseases on which botulinum toxin has unfavorable or unknown effect, and pregnancy or breast feeding. Thirty patients were enrolled in the study including 17 men (56.7%) and 13 women (43.3%)

Methods A vial of 500U Dysport (Ipsen Biopharm Ltd, Wrexham, UK) was diluted by adding 2.5mL non-preserved 9mL/L sodium chloride slowly to reach the desired concentration of 200kU. 0.1mL of this solution was drawn into the insulin syringe. After scrubbing the upper lid with Bethadine solution, a 23-g needle (30mm length) was attached to the syringe and the needle was introduced just below the superior orbital rim in the mid-pupillary plane to the middle of the needle (at a depth of 15mm). Then 0.075mL (15U Dysport) of the solution was injected and the remaining in the syringe was discarded. During the injection, the eye was kept open and in primary position. The patients were followed daily until ptosis was produced and then monitored 1-2 weekly until complete recovery of levator function and ptosis. If the corneal pathology had not been healed until elimination of ptosis or appropriate ptosis didn't occur within 1 week of the first injection, the injection was repeated. The patients were continued on appropriate topical medications as prescribed by the corneal surgeon. The extent of exposure keratopathy and corneal pathology was monitored by the corneal surgeon with fluorescein staining or measurement of epithelial defect at each visit. It was observed that in first 2 patients with 7th nerve palsy, 15U of Dysport is not sufficient to produce appropriate ptosis, and a second injection was required. Therefore, since then, for patients with 7th nerve palsy 30U Dysport was injected

initially. All of the injections were performed by one surgeon in the clinic in an outpatient basis, and were followed between 8 and 18 weeks. The first two patients with 7th nerve palsy who underwent 2 injections were excluded from efficacy analysis of some variables.

RESULTS

Seventh nerve palsy existed in 6 patients (20%). In all of the patients (but the first 2 with 7th nerve palsy) 1 injection (30U in patients with 7th nerve palsy and 15U in others) was sufficient to produce appropriate ptosis and there was no need to repeat the injection. Ptosis started in the first post-injection day in all of the patients and in 28 patients with one single injection maximal ptosis developed between 1 to 9 days with a mean±SD of 2.6±1.8 days. Ptosis lasted for a mean±SD of 12.0±2.2 (range 8-17) weeks. In 24 patients (80%) corneal pathology was persistent epithelial defect (neurotrophic, dry eye, keratitis) and in 6 patient (20%) pathology was punctate epithelial erosion (PEE). In general, in 25 patients (83.3%) corneal epithelium improved completely while ptosis was present and 5 patients required secondary surgical intervention (Amniotic membrane transplantation or conjunctival flap). In patients responsive to treatment, the mean ± SD time to improve corneal condition was 26.2 ±12.2 (range 11-60) days. Corneal condition improved in 19 patients with persistent epithelial defect (79.1% of them) and in 6 patients with PEE (100%). There was no statistically significant difference between males and females in duration of corneal epithelial defect, duration of ptosis, time to complete ptosis, duration of diplopia, and amount of ptosis but corneal condition improved in 70.6% of men and 100% of women with significant difference ($P=0.03$) though severity and etiologic factors in two groups were not matched.

Amount of ptosis was a mean±SD of 9.5±0.7 (range 8-10) mm. In patients with 7th nerve palsy, despite injection of 30U Dysport, this amount was 8.5±0.8 mm and in other patients (injection of 15U Dysport) it was 9.8±0.4 mm and the difference in 2 groups was significant ($P=0.01$). In addition, in patients with 7th nerve palsy, maximal ptosis occurred in a mean±SD of 4.0±2.7 days that it was longer than this time in other patients (2.4±1.6 days) but there was no statistical significance ($P=0.11$). There was a significant direct correlation between age and duration of ptosis (Pearson correlation = 0.416, $P=0.02$) and a reverse but not statistically significant correlation between age and time to maximal ptosis (Pearson correlation = -0.241, $P=0.19$).

The only treatment related adverse event was superior rectus underaction which occurred in 10 patients (33.3%) and lasted 7.8±1.8 (range 4-10) weeks but only 5 of them (16.7% of total) reported diplopia during manual retraction of ptotic

eyelid that lasted 8.0 ± 1.4 (range 6-10) weeks. In all cases, the diplopia resolved without any additional intervention. In one patient, nasolacrimal duct obstruction occurred in the same eye 4 months after injection and in one patient with 7th nerve palsy due to cerebellopontine angle surgery, herpetic epithelial keratitis occurred 15 days after injection while the corneal condition had healed.

DISCUSSION

All 30 patients in the study had failed conservative therapy, and after that, they were considered for temporary tarsorrhaphy. After explanation about two procedures, all of the patients preferred to have botulinum toxin injection instead of tarsorrhaphy and then an informed consent was taken. Ptosis started in the first post-injection day. Despite injection of 30U Dysport in patients with 7th nerve palsy (compared with 15U in others), palpebral fissure height did not reach to zero in them, however appropriate ptosis was achieved. Ptosis secondary to neuroparalysis of levator palpebrae muscle is attributed to some factors: gravity which pulls down the lids (in Ellis' study^[3], patients confined to supine position did not have as effective protection as mobile patients), tonicity of orbicularis muscle, and elasticity of palpebral tissues. Because of decreased orbicularis tone and lower lid ectropion, some degrees of lagophthalmos still remained in patients with 7th nerve palsy. Also, in these patients the amount of ptosis was significantly lower than others and completion of ptosis occurred more slowly which can be attributed to decreased counter-effect of orbicularis muscle secondary to decreased innervation by 7th nerve. In patients with upper lid scar, due to decreased elasticity of palpebral tissues, ptosis secondary to chemodenervation may be reduced. Duration of ptosis vary considerably in various studies as it was 6.5 weeks in Ellis' ^[3], 8.1 weeks in Adams', 8.5 weeks in Kirkness', and 9.2 weeks in Naik's study^[5]. This period was 12 weeks in this study which was more consistent with that of Gusek-schneider (12.4 weeks)^[6].

Reported side effects of botulinum toxin injection include preseptal hemorrhage^[2], superior rectus underaction and diplopia. In our study, the only side effect observed was superior rectus underaction and diplopia, which occurred in 33.3% and 16.7%, respectively. This discrepancy in the occurrence of diplopia and superior rectus underaction is because of poor vision in most patients with corneal pathology that leads to ignorance of the image formed in the deviated eye. By reviewing other studies it was observed that occurrence of superior rectus underaction (and diplopia) is related to the depth of injection into the orbit. In Adams' and Heyworth's^[7] studies in which injections were performed at the depth of 25mm, the incidence was 80%, but in the Naik's study^[5] in which injections were performed at the depth of a

half inch, it did not occur in any patient, however they used 10-15 units Botox, which is equivalent to about 30-45U Dysport which is higher than the dose we used. Also in Adams' study, diplopia persisted in 2 patients after resolution of ptosis and Heyworth^[7] reported 3 cases of permanent superior rectus underaction that required strabismus surgery. It has been presumed that prolonged breakdown of fusion or contracture of ipsilateral inferior rectus is the cause of permanent cases of diplopia^[7]. It is recommended that latent deviations be searched for in order to pick those at risk of this complication as a result of prolonged occlusion. Successful improvement of corneal pathology differs in various studies. Corneal pathology improved in 61.8% of patients in Gusek-Schneider's study^[6] and 76% of patients in Ellis' study^[3]. In our study in 83.3% of patients corneal pathology improved including 100% of patients with corneal erosion and 79.1% of patients with corneal epithelial defect. In 3 patients unresponsive to the procedure, the diagnosis was persistent epithelial defect (PED) after herpetic keratitis and in 2 patients, diagnosis was PED with bacterial keratitis that required Amniotic membrane transplantation (3 cases) and conjunctival flap (2 cases). These results are comparable to the results observed in Cosar's study^[1] that performed tarsorrhaphy in these patients and reported a success rate of 90.9% in improving the corneal epithelial defects. However, a randomized clinical trial should be designed to compare these two procedures after matching two groups otherwise.

Botulinum toxin type A and type B are composed of a 150-kDa polypeptide consisting of a light chain and heavy chain^[8]. When the toxin is internalized into the nerve terminal, the light chain exerts the paralytic effect of Botulinum toxin by inactivating a group of proteins (SNARE complex) that are responsible for the fusion of vesicles containing the neurotransmitter acetylcholine (ACh) with the nerve cell membrane and thereby blocking the release of ACh into the neuromuscular junction^[9]. Approximately 2 months after administration of Botulinum toxin, new nerve terminal sprouts emerge, and these extend toward the muscle surface to form a physical synaptic connection with the previous neuromuscular junction. The clinical duration of effect which is approximately 3-4 months, corresponds to the time that is required for new sprouts to grow from the nerve root to re-establish the motor endplate^[10]. In this study, there was a direct correlation between age and duration of ptosis so that the function of levator palpebrae muscle returned to normal more rapidly in younger patients. We can presume that this sprouts of nerve terminal forms more rapidly in younger patients and it can be suggested to use lower doses of toxin in older persons. In addition, we observed that maximal ptosis occurred more rapidly in older patients

(albeit not significant) that it could be attributed to preexisting aponeurotic dehiscence, which is common in elderly. All of the injections performed in the clinic and except in 5 patients unresponsive to treatment, in 83.3% of the patients admission of the patients and need for an operating room was eliminated. Facility of corneal examination and more effective applying topical drugs were other advantages. In one patient, nasolacrimal duct obstruction occurred in the same eye 4 months after injection. There is no similar report in the literature but we can propose that effect of the toxin on periocular muscles leads to decreased tear flow through tear drainage system resulting in concentration of tear in the lacrimal sac and obstruction in susceptible patients. Finally, Ptosis secondary to botulinum toxin injection is an efficacious and safe substitute for surgical tarsorrhaphy with fewer complications that most of them resolve without additional intervention. Superior rectus underaction is one of its most common adverse effects that can be prevented by decreased depth of injection. In patients with seventh nerve palsy, a higher dose of toxin is required and duration of ptosis in these patients and younger ones is shorter than others. In older patients, we can use lower doses of toxin to produce desired effects.

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