Original article

Successful treatment of lower eyelid epiblepharon by injection of botulinum toxin A in patients under two years of age

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Abstract

Introduction: Epiblepharon is characterized by a cutaneous horizontal fold adjacent to the lid margin. Some cases showed spontaneous resolution, others required surgical treatment. We propose a medical treatment with botulinum toxin type A (BTX-A). **Objective:** To provide clinical evidence of the usefulness of botulinum toxin type A (BTX-A) in patients with lower eyelid epiblepharon. **Subjects and methods:** This was a prospective, non-randomized, non-masked study. Patients with lower eyelid epiblepharon with corneal eyelash contact were included in the study. The scale proposed by Khwarg & Lee (1997) was used to assess the epiblepharon clinical evaluation. A single dose of 12.5 IU of BTX-A (Dysport ®) was directly injected into the medial pre-tarsal orbicularis muscle region in the lower eyelid. Patients were evaluated before the injection and at 1, 4, 12 and 24 weeks after the injection. We performed descriptive statistics and Wilcoxon Signed Rank Test, comparing prior injection measurements to post injection measurements at the 24th week. A $p < 0.05$ was considered statistically significant. Each eye was separately analyzed. **Results:** Fourteen eyes of seven Hispanic patients were treated, five female and two male. The mean age was 8.4 months (4 - 14 months). The height of the skin-fold, the area of the cornea touched by the cilia and the symptoms score improved after the first week of BTX-A injection and remained so until the end of study ($p < 0.05$). No major complications were noted. **Conclusion:** The effect of a single 12.5 IU injection of BTX-A (Dysport ®) into the medial orbicularis muscle portion in the lower eyelid epiblepharon patients successfully improves the clinical signs and symptoms.

Keywords: epiblepharon, botulinum toxin, lower eyelid

Introduction

Epiblepharon is characterized by a cutaneous horizontal fold adjacent to the lid margin, in which the underlying orbicularis muscle of the lid margin misdirects the lashes towards the eye causing ocular irritation and corneal erosion. The medial portion of the lower eyelid is most commonly affected and the condition is almost always bilateral. The prevalence reported in oriental infants varies from 46 to 52.5 % in children younger than 1 year (Khwarg & Lee, 1997).

The etiology of epiblepharon has not yet been established. Some authors have proposed that it is due to a congenital absence of the insertion of lower-eyelid retractors to the skin and orbicularis muscle or an insertion very close to the lid margin. Others support the combination of orbicularis muscle hypertrophy with an extra skin fold (Jordan, 1993).

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It is well known that almost all cases are self-limited by the age of four or five years (Noda et al 1989). Meanwhile, a conservative treatment with eye lubricants is indicated for preventing ocular surface damage. Surgery is only indicated when there is significant corneal injury caused by the rubbing of the eyelashes and usually involves the removal of the skin and some pre-tarsal orbicularis muscle in the affected eyelid. Although the surgery is almost always successful and complications are unusual, under correction or recurrence rates range from 4.9 to 23 % and the potential risk of the surgical and anesthetic procedures should be considered (Sundar et al, 2010).

The main feature found in epiblepharon is the orbicularis muscle hypertrophy. BTX-A has been proven to weaken the muscle fibers in other eyelid conditions of similar patho-physiology. Steel et al (1997) have reported the improvement of involutive entropion with BTX-A. Christiansen et al (2004) used 5 BTX-A IU in a child with congenital entropion with successful results without major complications. Both authors applied the BTX-A in the orbicularis muscle of the affected eyelid in order to decrease the muscle contraction. There are five commercially available preparations of BTX-A: onabotulinumtoxinA (ona-BoNT/A; Botox®, Allergan, Inc, Irvine, CA), abobotulinumtoxinA (abo-BoNT/A; Dysport ® Ipsen LTD, Wrexham, UK), BTXA (Lanzhou Institute, China), incobotulinumtoxin A (inco-BoNT/A; Xeomeen, Merz Pharmaceuticals, Frankfurt am Main, Germany) and Neuronox (nue-BoNT/A; MEDYTOX Inc., Cheonwon-gun, South Korea). Despite widespread clinical use, comparative dose ratios or conversion factors of BTX-A formulations remain controversial because they have been shown to have differences in efficacy and systemic effects (Kim et al 2013). Hexsel et al (2008) reported similar field effects at a dose equivalence of 2.5:1.0 IU (Dysport®:Botox®) for both muscle and sweat gland activity. Bearing in mind that both authors, Steel et al (1997) and Christiansen et al (2004), applied 5 IU of onabotulinumtoxinA (ona-BoNT/A; Botox®, Allergan, Inc, Irvine, CA) and based on the reported conversion ratio observed by Hexsel et al (2008) between onabotulinumtoxinA (ona-BoNT/A; Botox®, Allergan, Inc, Irvine, CA), abobotulinumtoxinA (abo-BoNT/A; Dysport ® Ipsen LTD, Wrexham, UK), we decided to apply a single dose of 12.5 IU of Dysport ® BTX-A (corresponding to 5UI Botox®) into the medial region of the orbicularis muscle in the lower eyelid in patients with epiblepharon to ease symptoms and prevent ocular surface complications related to this disease.

Subjects and methods

Patients younger than two years of age with lower eyelid epiblepharon were included in the study. Patients with systemic diseases and any other eyelid malpositions, eyelid trauma or previous eyelid surgery were excluded; patients with an incomplete follow-up were eliminated from the study. Informed and signed consent was obtained from the child's parents. In all patients the clinical evaluation of epiblepharon was made using the scale proposed by Khwarg and Lee (1997) in which three parameters are measured (Table 1): 1) height of skin fold, 2) the area of the cornea touched by the cilia and, 3) the area of corneal erosion using fluorescein staining (BioGlo Sterile Strips, CA, USA). Treatment consisted of injecting a single dose of 12.5 IU of BTXA (abo-BoNT/A; Dysport ® Ipsen LTD, Wrexham, UK) into the medial region of the hypertrophied orbicularis muscle about 3 - 4 mm below the eyelash margin of the affected lower eyelid. Dysport ® is provided in a glass vial containing 500 IU, which was diluted with 2 ml of 0.9% saline solution resulting in a concentration of 25 units in 0.1ml. All the procedures were performed at the office using topical tetracaine hydrochloride 0.5 % eye drops as ocular surface anesthetic (Ponti-Ofteno, Sophia, México) with appropriate child immobilization. The puncture site was cleaned by making a smooth circular pass over the site with a 70 % alcohol pad allowing the skin to dry before proceeding. Each injection consisted of 12.5 IU (0.05 ml) of diluted BTX-A preparation applied directly into the affected lower eyelid using a syringe with a 31-G insulin needle (Plastipak, Edo. De

México, Mexico). All patients received BTX-A from the same preparation vial, and only one surgeon (ANC) applied the injection in all cases. A 0.2 % tobramycin eye ointment (Trazil-ofteno, Laboratorios Sophia, Mexico) was applied in a single dose after the injection.

After the BTX-A injection, patients were monitored at 1, 4, 12 and 24 weeks. At each visit, ophthalmological evaluation of the grade of epiblepharon was done according to the Kwarg and Lee (1997) scale. The clinical epiblepharon assessment was made by the same surgeon (CYC).

Each eye was evaluated separately and the collected data was analyzed using the Wilcoxon Signed Rank Test, comparing measurements of the skin fold height, the corneal area touched by the cilia (corneal touch) and the corneal erosion area prior to the injection to the with the same variables measured at the 24th week after the injection. A $p < 0.05$ was considered statistically significant. SPSS/PC+ software (version 17 SPSS Inc., Chicago, IL, and U.S.A.) was used for the statistical analysis.

The study was approved by the Internal Review Board of our institution and the tenets of the Declaration of Helsinki were followed.

Results

Fourteen eyelids of seven patients, all of them Hispanic (2 male and 5 female), with a mean age of 8.4 months (range 4 - 14 months) were included in the study. The seven patients completed the follow-up period and in all cases the epiblepharon had affected both the lower eyelids. The results of Khwarg & Lee scale are summarized in Table 1. The prior- injection skin fold height measurements showed that most of the patients were in class III, RE 4 eyelids, 57 %, LE 5 eyelids 71 %; at the end of the study, most of the RE and LE showed improvement to class II, 4 eyelids, 57 %, and 5 eyelids, 43 % respectively. The prior-injection measurements of the corneal area touched by the cilia were mostly categorized as class III, 4 RE, 57 % and 5 LE, 71 %. At the 24th week, the measurements of both the eyelids improved considerably to that of class I, 5 RE, 71 % and 5 LE, 71 %. When comparing prior injections measurements to the 24th week measurements of these two categories using the Wilcoxon Signed Rank Test, statistical differences were found in both ($p < 0.05$). In our study, only one patient presented with corneal erosion at the beginning of the study, classified within class II in both the eyelids. This patient showed an improvement to class I during the first week after treatment, and remained thus until the end of the study. We noted that most of the patients began showing clinical improvement in both the height fold skin and corneal touch area from the first week after injection, which continued and remained stable until the end of the study (Figures 1 and 2). All the injections were successfully applied in the office without the need for any sedative maneuver and only self-limited eyelid hematomas at the site of injection were seen. We did not observe any disturbance in ocular motility, secondary ectropion or any other complication.

The numbers, in the tables, represents the number of eyelids included. As we can see, at the 24th week, most patients moved toward class I of each measurement, and statistical differences were found in the skin fold height and corneal touch when comparing prior injection measurements to measurements at 24th week after the injection (*).

Table 1

Comparison of skin fold height, corneal area touched by cilia (corneal touch) and corneal erosion measurements before BTX-A injection (Pre Tx) and at the 24th week after the injection:

	Skin fold height		Corneal touch		Corneal erosion	
Class ++	PreTx	24 wks*	PreTx	24 wks*	PreTx	24 wks
	RE LE	RE LE	RE LE	RE LE	RE LE	RE LE
I	0 0	2 3	1 1	5 5	6 6	7 7
II	2 1	4 3	2 1	2 2	1 1	0 0
III	4 5	1 1	4 5	0 0	0 0	0 0
IV	1 1	0 0				
Total	7 7	7 7	7 7	7 7	7 7	7 7

++ Morphologic eyelid description and classification.- (Khwarg & Lee 1997)

RE $p = 0.004$, LE $p = 0.014$.

n = 14 eyelids. RE = right eye, LE = left eye

Height of skin fold scale

Class I - The highest line of skin fold is located below the lower eyelid margin.

Class II - The skin fold is just below or on the lower eyelid margin, without concealment of the eyelid margin.

Class III - The skin fold is above the lower eyelid margin with concealment of less than the medial third of the eyelid margin.

Class IV - The skin fold is above the lower eyelid margin with concealment of more than the medial one third of the eyelid margin.

Corneal touch scale:

Class I - Inverted cilia touching less than medial one third of the cornea.

Class II - Inverted cilia touching less than medial two thirds of the cornea.

Class III - Inverted cilia touching more than two thirds of the cornea.

Corneal erosion scale:

Class I - No corneal erosion.

Class II - Less than the medial one third of the cornea is eroded.

Class III - More than medial one third of the cornea is eroded.

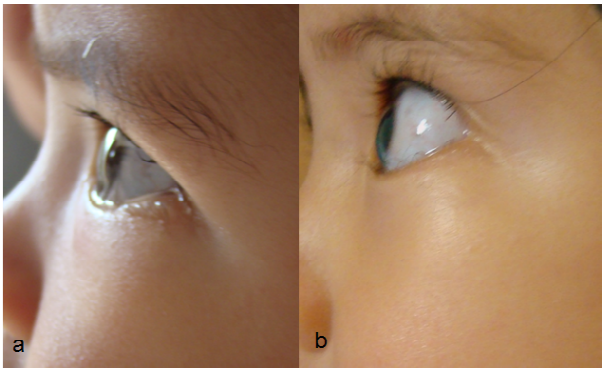

Figure 1a and 1b

Discussion

Epiblepharon is not an uncommon disease seen in our practice. This entity is self-limited in most cases at around two years of age. Within this period, the patient usually presents irritative signs and symptoms due to the ocular surface eyelash contact. Symptomatic treatment with ocular lubricants is usually indicated. When the symptoms persist or corneal complications occur despite the use of lubricants, surgical treatment is indicated. Although the surgical treatment is highly successful, results could sometimes be unpredictable and complications related to the surgical and anesthetic procedures may arise.

Searching for an alternative procedure to surgery, Naik et al (2010) treated a 4-month-old infant with epiblepharon with medial eyelashes touching with an injection of 0.2 ml of hyaluronic acid gel (Juvederm Ultra) in the sub-orbicular plane in the valley above the abnormal skin fold. He observed an immediate out-turning of the eyelid, which persisted until the fourth month.

In this study, we also propose a non-surgical treatment to improve the clinical signs of patients with epiblepharon by applying 12.5 IU of BTX-A directly to the hypertrophied orbicularis muscle.

We demonstrated in our epiblepharon patients that BTX-A improves the eyelid skin fold, the area of corneal touch by cilia and corneal erosion area. These changes were seen since the first week of application and remained during the whole study period. This will ultimately impact on ocular symptoms, the appearance of ocular complications, such as conjunctival squamous metaplasia, corneal erosion and ulceration.

One of the major advantages of this procedure is its simplicity, and that it is a non-invasive treatment that can be performed by any ophthalmologist. The treatment is reversible due to the period of action of BTX-A which is of six months on average. Most epiblepharon patients will have a spontaneous resolution within the first two years of life. With the BTX-A application we are providing the patient with a symptom-free period before the spontaneous resolution appears. Deka et al (2011) used BTX-A for the treatment of lower lid entropion. In his study, three children with congenital entropion were included. The author stated that botulinum toxin is a safe and effective procedure for correction of

senile entropion and some cases of congenital entropion, and no complications or side effects of this treatment were noticed. We also did not find any complications related to diffusion of the toxin to the adjacent tissues, especially disturbances in eye motility or lower eyelid misdirection.

Conclusion

The present study demonstrates that a single dose of 12.5 IU of BTX-A, abobotulinumtoxin A (abo-BoNT/A; Dysport ® Ipsen LTD, Wrexham, UK) injected into the medial region of the hypertrophied orbicularis muscle of the affected inferior eyelid is a safe procedure that improves the clinical eyelid signs of epiblepharon and eventually will alleviate ocular symptoms and will prevent ocular surface complications in patients with lower eyelid epiblepharon.

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