Botulinum Toxin in Refractory Epiphora

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Introduction

The lacrimal gland is innervated by the cholinergic fibers of the seventh cranial nerve. Injection of botulinum toxin A (BTA) in the lacrimal gland is hypothesized to decrease the tear production by blocking presynaptic release of acetylcholine into neuromuscular end plates of cholinergic nerve fibers [1]. Therefore, injection of BTA into the lacrimal gland can be an alternative treatment for epiphora due to severe gustatory hyperlacrimation, unsalvageable proximal lacrimal drainage system obstructions, and refractory functional epiphora. Studies about the use of BTA injection in the lacrimal gland for the treatment of gustatory hyperlacrimation [2–13], and functional epiphora [14] have been published in the literature. Results of BTA injections in patients with epiphora owing to obstruction of proximal lacrimal apparatus have been also reported [13, 15, 16]. Encouraging results have been presented when the efficacy of BTA injection into the lacrimal gland was compared with conjunctivodacryocystorhinostomy (CDCR) in treatment of epiphora for complete proximal lacrimal drainage obstructions [17]. This chapter will discuss BTA properties, mechanism of action, and injection techniques into the lacrimal gland and complications.

Botulinum Neurotoxin

Botulinum toxin is the poisonous exotoxin of *Clostridium*. The bacterium *Clostridium botulinum* produces eight antigenically distinct exotoxins. Serologic types include A, B, C, D, E, F, and G. Type E is also produced by *C. butyricum*. Type F is produced by *Clostridium baratii* [18]. Type A, B, and E botulinum toxins are colorless, odorless, and tasteless. Only these three types of toxins affect humans and can cause systemic botulism. Type A is the most potent toxin, followed by types B and F. Each botulinum toxin is synthesized as a single-chain protein, which is inactive until it is cleaved by bacterial proteases into its active form. The active botulinum toxins are composed of two chains: one heavy chain joined to a light chain by a relatively weak disulfide bond, which contributes to the instability of the molecule. The toxin is inactivated by heat and multiple environmental factors [18, 19].

Mechanism of Action

Botulinum toxin blocks the release of acetylcholine from its vesicles at the presynaptic nerve terminal. It also inhibits release of acetylcholine at the autonomic ganglia, postganglionic parasympathetic, and sympathetic nerve endings. The different serotypes bind to different sites on the motor neuron terminal. The heavy chain functions both as a channel and a companion to bring the light chain across the endosomal membrane and then into the cytosol in the presynaptic region. The light chain then acts inside the cell on synaptosomal-associated protein receptor proteins (SNARE) to block the release of the vesicle-bound neurotransmitter acetylcholine from nicotinic and muscarinic nerve endings. Muscle weakness does not become evident immediately but takes 2–4 days, due to the continued release of acetylcholine from vesicles that have not been blocked by the toxin. Recovery of muscle activity typically begins 3–4 months after injection and is thought to occur due to the regeneration of new end plate units [19].

Commercial Preparations

Doses of all commercially available forms of botulinum toxin are expressed in terms of units (mouse units). The standard measurement of the potency of the toxin is one interna-

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tional unit (IU), which is the amount of toxin that kills 50% of a group of 18–20 female Swiss-Webster mice (LD50) when injected intraperitoneally. The LD50 in humans is estimated to be approximately 2730 IU [18, 20, 21].

Ona-botulinum toxin A, commercially available as BOTOX® and BOTOX® Cosmetic (Allergan plc (NYSE: AGN, Dublin, Ireland), is a dry, protein crystalline complex of botulinum toxin A which contains 50 or 100 units per bottle. Abo-botulinum toxin A, commonly marketed as Dysport® (Ipsen, Slough, UK), and Inco-botulinum toxin A as Xeomin® (Merz Pharma GmbH & Co. KGaA, Germany).

The onset of effect takes 24–48 h and maximum effect is achieved at 7–10 days. The effect usually lasts 4–6 months. Repeated injections may delay the onset, but sometimes a more protracted effect may occur.

Botulinum toxin B has a faster onset of action, better diffusion into tissues, and prolong action as compared to BTA; however, they have not been used for lacrimal gland injections, mainly due to the evidence of inflammatory response in animal models and also because its potency is less that BTA [19, 20].

Reconstitution and Storage

Botulinum toxin A is recommended to be reconstituted with sterile non-preserved 0.9% NaCl solution before injection and must be kept at 4 °C until injection. It has to be injected within 4 h after reconstitution for maximum activity. The weak disulfide bonds between the two chains of the toxin render it fragile under mechanical stress such as frothing when diluting and agitating the liquid inside the vial. BTA is used for lacrimal glandular injections.

Table 40.1 shows the approximate botulinum toxin A concentration with various volumes of diluent used for two most commonly used commercial forms: Botox® and Dysport® [18–23].

The concentration of the botulinum toxin depends on the amount of diluent in the vial which can be determined by the physician. The usual concentrations used for lacrimal gland are 1.25–2.5 units/0.1 ml.

Table 40.1 Botulinum toxin A concentration with various volumes of diluent

0.9% NaCl added (ml)	Botox® dose (U/0.1 ml)	Dysport® dose (U/0.1 ml)
1	10	50
2	5	25
4	2.5	12.5
8	1.25	6.25
10	1	5

Warning and Contraindications

It is important to note that the use of BTA for refractory epiphora is not yet FDA approved. Hence, it would be wise to point out that this is an off-label use of botulinum neurotoxin, and adequate prior informed consent is necessary. Pregnancy and lactation, neuromuscular junction disorders (*Myasthenia gravis*), peripheral motor neuropathies, active infections, and hypersensitivity to any of the contents are well-known contraindications for use of botulinum toxin.

Rationale for Its Use in Epiphora

Botulinum neurotoxin has been used to control hypersecretion from glands supplied by cholinergic neurons in the head and neck area [23]. Since the lacrimal gland is innervated by the cholinergic fibers of the facial nerve, injection of botulinum toxin A (BTA) in the lacrimal gland decreases tear production by blocking presynaptic release of acetylcholine into neuromuscular end plates of cholinergic nerve fibers [1]. Therefore, injection of BTA in the lacrimal gland has been investigated as an alternative symptomatic treatment to stop epiphora temporarily, in gustatory hyperlacrimation and in anatomic and functional lacrimal drainage blockage.

In 1998, Borojerdi and colleagues injected botulinum neurotoxin into the lacrimal gland to treat hyperlacrimation in two patients and into the orbital portion of the orbicularis oculi muscle in ten patients with abnormal facial movements post facial palsy. Two patients who received injections into the lacrimal gland had complete recovery of the epiphora, whereas half of those who received orbicularis oculi muscle injections had shown reduced lacrimation [2]. Eleven peer-reviewed articles followed since 1999, where botulinum neurotoxin injections into the lacrimal gland either had a temporary yet complete relief or decreased epiphora [3–13].

Whittaker et al. [14] showed decrease in epiphora in 14 patients with functional lacrimal outflow obstructions with anatomical patency of the drainage apparatus. BTA injections in patients with epiphora owing to anatomical obstructions of lacrimal apparatus have also been reported [13, 15–17].

Injection Technique and Dose

Purified BTA injection in the lacrimal gland can be easily performed under topical anesthesia with proparacaine 0.5%. It is preferable to get high concentration in small volume to minimize the spread of neurotoxin to the vicinity of the injection site.

The upper eyelid is retracted with a finger, and the patient can be asked to look extreme inferomedially to expose the palpebral lobe of the lacrimal gland. Alternatively, the eyelid

can also be everted with a Desmarres retractor. Although both transcutaneous and transconjunctival approaches can be used, the authors prefer the latter. The reasons being direct visualization of the gland and also the chance of spread into surrounding tissues is less. BTA is injected into the lacrimal gland, as seen in Figs. 40.1, 40.2, and 40.3. Tuberculin syringes with 27–30-gauge needles are preferred which allow more painless and accurate injections into the gland with relatively low risk of bleeding. The dose of the drug injected can vary from 1.25 U/o.1 ml–5 U/0.1 ml. The authors of this chapter prefer to start from 2.5 units and escalate if needed based on the response. Kaynak et al. have shown that a dose of 4 U/o.1 ml was effective in 70% of the patients at 15th post-injection day, with no epiphora or a grade 1–2 Munk score [17]. The patients who do not respond at the second week can be injected a second dose of botulinum neurotoxin before labeling them as non-responsive.

Post-injection Assessment

Assessment is preferably performed at 1 week and 1, 3, and 6 months post-injection. Apart from subjective measures like the Munk scoring, Schirmer tests must be done prior to BTA injections since the tear production was reported to significantly decrease in majority of the studies and can potentially lead to dry eyes. Other measures like tear meniscus assessment can provide finer objective outcomes with BTA.

Outcomes and Complications

Since 1998, a total of 51 patients with gustatory hyperlacrimation (or crocodile tear syndrome) have been treated with BTA injections into the lacrimal gland [2–13]. All of these studies reported complete or near-complete resolution of aberrant tearing within 1–2 weeks of treatment. Only infrequent and reversible complications such as ptosis, lagophthalmos, diplopia, conjunctivitis, and dry eye were observed.

A study by Nava-Castaneda et al. [10] reveals that a 2.5-U BTA injection into the palpebral lobe of the lacrimal gland diminishes epiphora due to gustatory hyperlacrimation from the first week and may last up to week 24. Baranano and Miller [8] reported a patient with gustatory lacrimation who has been successfully managed for 3 years with injections of BTA every 8–11 months, suggesting that multiple injections continue to impact epiphora.

BTA has also been used to minimize symptomatic tearing in patients with lacrimal obstruction [13, 15, 16] and functional tearing [14]. Wojno [13] has published that 63% of patients with lacrimal outflow obstructions, mostly or completely improved with 2.5 units of BTA. This outcome has improved to 71% with an additional 2.5 units of BTA to those with less than maximal improvement. Underlying pathologies in these patients has not been elaborated. Ziahosseini et al. [15] have injected BTA into the lacrimal glands of 22 eyes of 17 patients of troublesome epiphora with a mean age of 70.3 years. Etiologies included canalicular obstructions, nasolacrimal duct (NLD) obstructions and epiphora after punctal cautery. In their symptoms 60% had improvement and a significant improvement in Munk scores effective for 10 weeks. Because advanced age, frailty, and coexisting morbidities often make attending clinics difficult for elderly patients, BTA was suggested as a useful alternative to surgery in this group of patients. The patients who were initially given doses more than 2.5 units with no complications had subsequently achieved similar improvement with 2.5 unit injections, suggesting that higher doses may not produce superior outcomes. They did not observe any side effects with higher doses, except that the symptoms in one patient with associated recurrent cicatricial ectropion deteriorated after 2.5 units. This patient improved after ectropion repair. The message is that eyelid malpositions, if any, should be addressed first before BTA use.

Proximal obstruction of the lacrimal drainage system in children is also difficult to treat with surgical options. CDCR with Jones tube is rarely performed in children with a higher complication rate. Excellent patient co-operation and compliance is required. Eustis and Babiuch presented that they have successfully treated epiphora in three children (8, 9, and 16 years old) for 6–13 months [16].

Kaynak et al. published that BTA to lacrimal gland may be an alternative to CDCR in proximal obstruction related epiphora with similar outcome and less complications up to 6–12 months resolution of symptoms, and repeated injections are effective in resolving the symptoms [17].

Whittaker et al. [14] investigated the usefulness of BTA in patients with functional epiphora and achieved reduction in epiphora after transconjunctival injections of 2.5–5 units of BTA in the palpebral lobe of the lacrimal gland in 86% of patients, with the effect persisting in 66% of patients for 3 months. Two patients in this group encountered transient ptosis and diplopia.

Montoya et al. [5] suggested that a transconjunctival injection was preferred due to the ability to directly visualize the lacrimal gland during injection. Falzon et al. [12] published their meta-analysis where they have found the transconjunctival approach to be associated with fewer complications [12].

BTA has been used safely with no long-term side effects. Neither apparent benefits of higher doses nor actual dose or concentration comparisons have been published. Demetriades et al. [1] reported that no evidence of histological changes, particularly no inflammatory response, have been observed in the lacrimal glands of rabbits following injections of 1.25 and 2.5 units of BTA [1]. Kim et al. [24] have also reported similar findings and found it safe. The absence of histological changes in orbicularis oculi muscle

following BTA injections for blepharospasms is also documented [25]. However, lacrimal gland injections of botulinum neurotoxin B (BTB) in animal models have caused ocular surface changes such as corneal fluorescein staining and significantly decreased tear production with ocular surface inflammation [26].

Up to 10% of patients eventually develop antibodies to the toxin; this occurs more frequently in those who receive larger doses at more frequent intervals. This resistance is believed to result from the production of antibodies to the toxin over time. However, this does not appear to be the case in glandular disorders [27].

Conclusion

Botulinum toxin A injection into the lacrimal gland is an evolving treatment modality for controlling epiphora due to gustatory hyperlacrimation, refractory epiphora secondary to unsalvageable lacrimal drainage, and troublesome functional epiphora. Further studies are required to determine the optimum dose, concentration, and route of delivery [28].

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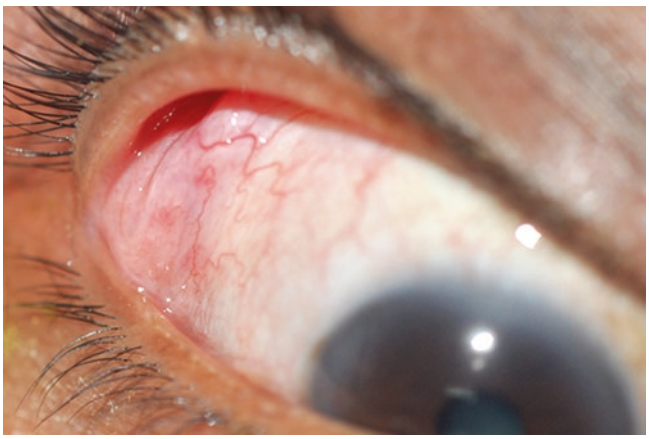

Fig. 40.1 Exposing the palpebral lobe of the lacrimal gland

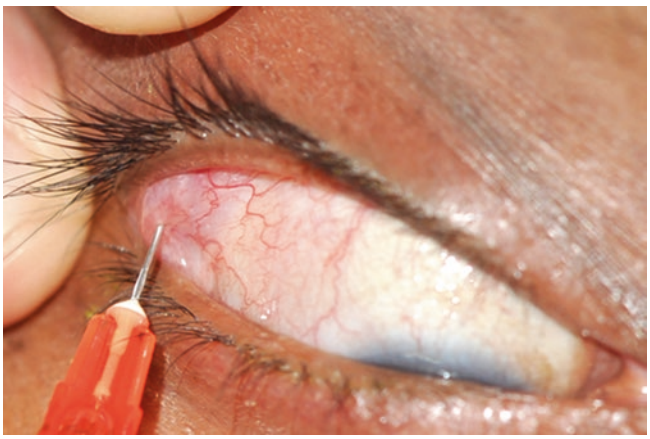

Fig. 40.3 Needle well set within the lacrimal gland tissue. Note that level of the needle and its distance from the ocular surface

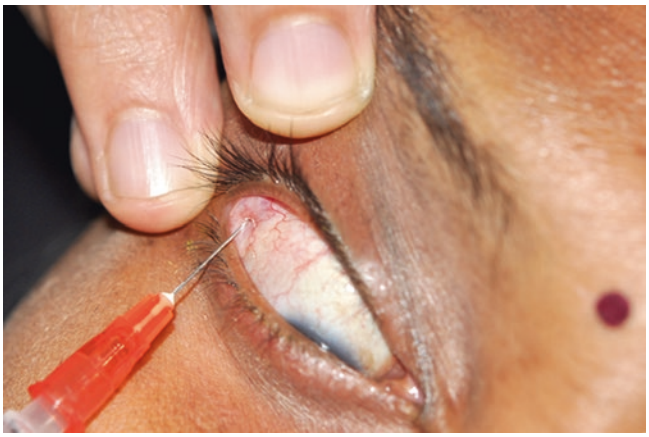

Fig. 40.2 BTA injection under direct visualization