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Lacrimal gland botulinum toxin injection for epiphora management

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Abstract

Purpose: Epiphora remains an often difficult to manage ocular complaint for ophthalmologists in all subspecialties. This review seeks to examine the safety and efficacy of botulinum toxin injection for management of chronic epiphora.

Methods: The authors conducted a Pubmed search for studies on the use of lacrimal and transplanted salivary gland botulinum toxin injections for the management of epiphora within the past 20 years. Studies included had a minimum of four glandular injections.

Results: The authors identified 14 studies and divided them by indication for injection; either functional epiphora, non-functional epiphora, or mixed studies. Seven studies examined injections for cases of functional epiphora, four for non-functional epiphora, and four for mixed cases. The number of glandular injections reported ranged from 4 to 65. Side effects reported were limited to diplopia, eyelid or lacrimal gland hematoma, papillary conjunctivitis, dry eye, ptosis, and bleeding.

Conclusions: Glandular botulinum toxin injection should be considered as a viable treatment strategy for both functional and nonfunctional epiphora. From the studies reviewed, botulinum toxin injection was shown to be effective in both children and adults. Injection can be performed in the outpatient setting, is minimally invasive, technically easy to administer, has a favorable side effect profile, and good efficacy. Furthermore, repeat injections can be performed with similar efficacy.

Keywords

Botulinum toxin injection; epiphora management; glandular botox injection; lacrimal gland botox injection

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Presentations

The content of this manuscript has not been presented or published elsewhere in any medium.

Introduction

Epiphora is a chronic condition that reportedly affects as many as 14% of the population over 40 years of age.[1] Patients experiencing this relentless ocular symptom report significant decreases in quality of life. Despite its severity, this condition remains difficult to manage for many ophthalmologists.[2]

Epiphora can be separated into two broad categories based on etiology: arising from either decreased tear outflow or hyper-secretion from the lacrimal gland. These two etiologies are often subdivided in the literature as non-functional and functional epiphora, respectively. Functional epiphora here refers to lacrimal drainage dysfunction in the presence of anatomical patency.[3] In contrast, epiphora resulting from any obstruction or other cause of decreased outflow within the lacrimal system can be characterized as non-functional epiphora. Decreased outflow may result from either lid malposition, decreased blink function, or outflow obstruction. Obstruction may result from a variety of causes including congenital ductal obstruction, prior inflammation due to infection or other inflammatory disorder, anatomic obstruction due to a tumor or other mass, and trauma. Hypersecretion results from overactivation of the lacrimal gland, especially reflex tearing. Causes include gustatory epiphora resulting from aberrant 7th nerve regeneration and reflex epiphora from ocular surface trauma or stimulation. Still, the disorder can be thought of as an interplay between these two non-mutually exclusive causes, wherein the overall aqueous tear influx and outflux of the lacrimal system must remain in balance to work effectively and any alteration to the equilibrium can result in dysfunctional epiphora.

Surgical management of epiphora focuses on relieving partial or total canalicular obstruction in the lacrimal system through canalicular trephination and/or silicone stent placement, and dacryocystoplasty with balloon dilatation depending on patient preferences, characteristics, and the location and etiology of the obstruction.[4-6] Blockage of the lacrimal system can occur anywhere along the tear drainage pathway from puncta and cana- liculi, to the nasolacrimal duct. Dacryocystorhinostomy (DCR) remains a mainstay of treatment for nasolacrimal duct obstruction (NLDO), while conjunctivodacryocystorhinostomy (CDCR) can be utilized for more proximal obstruction of the lacrimal system including severe canalicular obstructions. Still, success rates of these procedures are quite varied. Success rates of DCR are high, approaching roughly 85–99%.[7-9] Comparatively, CDCR results in higher risk of postoperative complications including corneal abrasions, diplopia, bleeding, infection, tube malposition and/or extrusion, and is associated with a need for regular follow up and maintenance.[4,10,11] One large systematic review showed infection rates approached 3% on average for CDCR with a range from 2 to 20% depending on the surgical approach.[10] Also, some patients may not be ideal surgical candidates depending on age, functional status, and presence of other co-morbidities including malignancy. These surgical procedures do little to address the cause of epiphora in patients with hyperlacrimation due to causes including abnormal seventh nerve regeneration and subsequent gustatory epiphora. However, complete excision of the palpebral lobe of the lacrimal gland has also been described for epiphora management.[12] Medical management of epiphora includes either use of systemic anticholinergics or observation with reduction of ocular surface disease findings by addressing co-existent dry eye. However, each of these treatment modalities

either carry various systemic side-effects or leave the patient with continued bothersome symptoms, respectively. Though DCR has high rates of success, some patients still suffer from chronic epiphora following surgery and would benefit from adjunctive treatment options. Non-surgical alternatives have been increasingly sought after. One such treatment option is botulinum toxin A injections of the lacrimal gland.

The annual incidence of symptomatic epiphora in adults resulting from acquired lacrimal outflow obstruction has been reported as high as 30.47 per 100,000.[13] One large epidemiologic study reviewing adult health data from the Mayo Clinic hospitals in Olmsted County, Minnesota between 1976–2000 found the most common cause of acquired epiphora was nasolacrimal duct obstruction at a rate of approximately 20.24 per 100,000.[13] Furthermore, obstruction more often affects women compared to men at an annual incidence rate of 26.10 compared to 13.29 per 100,000.[13] Still, there is little literature examining rates of non-functional epiphora in the adult population. Another epidemiologic study in Britain suggested epiphora rates in young children may reach as high as 20%.[14] In children, non-functional epiphora is the most common, often resulting from a membranous obstruction at the lower end of the lacrimal system near the valve of Hasner. This form of epiphora usually resolves spontaneously by the end of the first year of life.

Botulinum toxin was first purified in 1897, with seven different serotypes eventually identified.[15,16] The toxin works by inhibiting the presynaptic release of acetylcholine at the neuromuscular junction and by autonomic nerve fibers. This ultimately results in a decreased concentration of post-synaptic acetylcholine receptors and subsequent muscle weakening.[17] In the field of ophthalmology, botulinum toxin is commonly used to treat strabismus, blepharospasm, and hemifacial spasm. The use of botulinum toxin injection in medical treatments first started in 1970s, with the use of Botulinum Toxin A in animal trials.[18] Dr. Allen Scott, an ophthalmologist was one of the first medical professionals to utilize the toxin as a medical treatment.[19] The use of botulinum toxin for injection has been proven to be a safe procedure after over 40 years of use. Initial utilization of the purified toxin in ophthalmology included intramuscular injections for cases of strabismus.[18] Frueh, Felt, Wojno, and Musch first described the use of botulinum toxin, previously known as oculinum for treatment of benign blepharospasm in 1984.[20] There is also interest in using botulinum toxin to treat epiphora by injecting the lacrimal gland.[21-23] Here, the inactivation of acetylcholine release from postganglionic parasympathetic secretomotor fibers lead to decreased tearing.[16]

The purpose of this review is to examine the safety and efficacy of botulinum toxin injection for management of chronic epiphora.

Methods

The authors conducted a PubMed search utilizing MeSH terms for articles detailing lacrimal gland botulinum toxin injection for management of epiphora. Search terms included epiphora, tear(s), lacrimal, lacrimal gland, botulinum toxin, botox and botulinum toxin A. The search was limited to articles published within the past 20 years prior to February 1 2021. The search returned 134 results, which the researchers further delimited by relevance

to botulinum toxin injection of the lacrimal or transplanted salivary glands for management of epiphora. Data collected included subject number, study type, indications for injection, injection technique, injection location, dosing, injection frequency, outcomes, and reported side effects. Articles with fewer than four glandular injections were excluded from the study to ensure larger sample sizes. Fifteen studies met all above criteria for inclusion. For the purposes of this review, the discussion of cases was divided by functional or non-functional causes.

Results

Functional epiphora

Seven studies detailing botulinum toxin injections for the treatment of functional epiphora were included in the review.[21,23-28] A detailed summary of each study is provided in Table 1. The studies enrolled between 2 and 42 subjects for a total number of 119 glandular injections and a median of 14 subjects among the studies. Indications for injection included paroxysmal lacrimal hypersecretion, aberrant 7th nerve regeneration, facial palsies, gustatory epiphora and submandibular gland transplant complicated by epiphora. One study utilized incobotulinum toxin A injections (Xeomin®, MERZ Pharma, Frankfurt, Germany), while three studies used abobotulinum toxin A (Dysport®, Ipsen Ltd, Slough, United Kingdom), and four used onabotulinum toxin A (Botox®, Allergan Inc, Irvine, California, USA). A transconjunctival direct injection into the palpebral lobe of the lacrimal gland was solely utilized in three studies, one study utilized solely transcutaneous injections into the lacrimal or transplanted submandibular gland, two studies used a combination of transcutaneous and transconjunctival injections, and one study reported transcutaneous injections into transplanted submandibular glands. Initial injections included 97 (82%) transconjunctival lacrimal gland injections, six (5%) transcutaneous lacrimal gland injections, and 16 (13%) transcutaneous transplanted submandibular gland injections. Dosing ranged from 2–15 units for lacrimal gland injections, while submandibular gland injections were reported between 15 and 1200 units. Keegan *et al.* did not comment on the reasoning behind such a large dose of botulinum toxin A utilized in this study, though 1200 units was a large outlier compared to other studies.[25] Reinjections were reported in five studies (n = 48, 40%). Varied metrics were analyzed to evaluate the efficacy of the injections in each study including Munk Scores, Schirmer's test, and patient reported subjective symptom improvement. The Munk Score is a standardized scoring system from 0 to 4 for grading epiphora based on patient reported handkerchief usage for symptom management. A Munk Score mean reduction of 2.68 was reported in one study.[23] Improvement in Schirmer's Test was reported in six studies.[21,23-26,28] Two studies commented on objective decrease in mean Schirmer test values in patients at 1 month follow up.[23,26] Nava-Castaneda *et al.* reported a decrease in mean Schirmer test values of 7.4 mm (n = 15).[26] Comparatively, Girard *et al.* reported a decrease of 9 mm (n = 60) in mean Schirmer values. Together, these studies reported a mean decrease in Schirmer test values without anesthesia of 8.7 mm at 1 month follow up. Finally, five studies noted patient reported improvement in epiphora.[21,23,25,27,28] Four studies commented on the duration of symptomatic improvement ranging from four to six months.[21,26-28] Side effects reported included ptosis (n = 8, 7%), diplopia (n = 8, 7%), lacrimal gland hematoma (n = 2, 2%), and dry eye syndrome (n =

3, 3%). The complication rate for transconjunctival injections was 15% (n = 15), 38% (n = 6) for transcutaneous lacrimal gland injections, and 0% (n = 0) for submandibular gland injections.

Non-functional epiphora

Four studies evaluated the efficacy of botulinum toxin injections for nonfunctional epiphora.[29-32] Summaries of these studies are included in Table 2. Between three and 38 patients (mean 19.5, median 18.5) were studied for a total number of 72 subjects. Patient ages ranged from eight to 93 years old. Indications for injection included canalicular or common canalicular obstruction, nasolacrimal duct stenosis, both treatment naive and after failed medical or surgical treatment, and epiphora after punctal cautery. In three studies, injection was the only intervention studied. Kaynak *et al.* conducted a non-randomized, comparative study with patients electing either CDCR with permanent Metaireau tube insertion (n = 18, 47%) or onabotulinum toxin A injection in the palpebral lobe of the lacrimal gland (n = 20, 53%).[31] All four studies utilized transconjunctival approach for injections. Mean injection dosage across the four studies was 4.2 units, range 1.25–10.0 units. Twenty-eight (39%) patients required a single injection only.[29-31] The remainder of patients required multiple injections, and a small subset of patients (n = 9, 12%) required up to five injections.[29,30] For patients requiring re-injection, mean interval between injections ranged from four to ten months. For three of the studies, outcomes measured included Schirmer reduction, Munk Score reduction, and reported subjective improvement by patients. One study reported Schirmer reduction in 89% of patients.[29] Mean reduction in Munk Score was 2.75 for three studies.[29-31] Comparison of CDCR and botulinum toxin A injection by Kaynak *et al.* found statistically significant improvement in epiphora compared to pre-intervention mean Munk scores but no statistically significant difference between the two intervention groups.[31] Measures for reporting patient subjective symptom improvement varied by study, with some studies remarking on overall patient satisfaction and others quantifying degree of subjective improvement. Eustis and Babiuch reported on subjective improvement only.[32] All four studies noted the mean duration of epiphora-free period, ranging from three to twelve months. All studies noted some degree of subjective improvement in all patients. Complications of injection were transient and included ptosis (n = 13, 17%), esotropia (n = 2, 3%), diplopia (n = 2 3%), upper lid hematoma (n = 1, 1%), and papillary conjunctivitis (n = 1, 1%). Side effects in all four studies were reported to resolve within four weeks and are further discussed below. For patients undergoing CDCR, tube dislocation was seen in nine patients (50%), and granuloma formation causing tube obstruction was seen in four patients (22%).

Mixed studies

Four studies in this review assessed botulinum toxin injections for both functional and non-functional epiphora. A detailed summary of each study is included in Table 3. The studies evaluated between 31 and 46 patients for a total of 182 injected lacrimal glands.[22,33-35] Patient ages ranged from eight to 94 years old. Non-functional indications for injection included proximal and common canalicular obstruction, inoperable nasolacrimal duct obstruction due to nasal cancer or other condition, punctal stenosis, and post traumatic obstruction. Functional indications included functional nasolacrimal duct

obstruction, gustatory epiphora, seventh nerve palsy, and hypersecretion. Three studies utilized onabotulinum toxin A injection via a transconjunctival approach.[22,33,34] One study utilized prabotulinum toxin A (Nabota®, Daewoong Pharmaceutical, Seoul, Korea) in either a transconjunctival or transcutaneous lacrimal gland injection.[35] Two studies used injection doses of 2.5 units for all injections.[22,33] One study utilized injection doses of 3 units.[35] Singh *et al.* used doses of 2.5 and 5.0 units based on surgeon preference for a median dose of 2.5 units for functional epiphora and 5.0 units for nonfunctional epiphora.[34] Across the four studies 83 (46%) re-injections were reported. In the two studies dividing patients by functional and nonfunctional indications 61% (n = 22) of patients with functional epiphora received at least one additional injection compared to 43% (n = 22) of patients with nonfunctional epiphora. In these studies, subjective duration of effect was reported with a mean of 3 months (range 2 to 4 months).[22,34] Mean and median Munk score reductions were reported in three studies.[33-35] Singh *et al.* noted greater reduction in Munk score in the functional group compared to the nonfunctional group, but the difference failed to achieve statistical significance.[34] Schirmer reduction was reported in two studies.[33,35] One study assessed patient subjective symptom reduction only, and found that overall, 74% of patients felt epiphora was 'mostly or completely improved,' without a significant difference between functional and nonfunctional groups.[22] Lee *et al.* separated patients by route of injection and found no statistical difference between efficacy and side effects in patient receiving either transconjunctival versus transcutaneous injections.[35] Complications across all four studies included ptosis (n = 20, 14%), dry eye syndrome (n = 1, 1%), and diplopia (n = 4, 3%). Epiphora was attributed to nonfunctional etiology in approximately 65% (n = 93) of patients. All four studies noted a duration of effectiveness, with a range from three to five and a half months.

As presented above, reported side effects in all studies included diplopia, esotropia, eyelid or lacrimal gland hematoma, papillary conjunctivitis, dry eye, ptosis, and bleeding. These are detailed in Table 4. 65 out of 317 subjects (21%) experienced at least one side effect related to the glandular botulinum toxin A injections. However, each reported side effect was transient in nature, with resolution within at least eight weeks post injection. Furthermore, no cases of infection were reported in any of the studies. Ptosis and diplopia were the most common side effects reported affecting 41 (13%) and 18 (6%) patients, respectively. The distribution of side effects was roughly equal between the patients with functional versus non-functional epiphora.

Discussion

Epiphora results in a major impact to patient reported quality of life measures.[2,36] Kafil-Hussain and Romona reported patients suffering from chronic epiphora experience the same, if not greater decrease in vision related quality of life than patients awaiting second cataract surgery.[37] Though surgical management of the disease has been shown to improve patient reported quality of life, it still represents a costly approach, while also carrying the risk of side-effects associated with surgery including bleeding, infection, tube malposition, or extrusion.[4,10,31] The purpose of this study was to evaluate the safety and effectiveness of glandular botulinum toxin injection in the treatment of epiphora.

Our findings suggest that botulinum toxin injection represents a safe, minimally invasive, and effective treatment for the management of epiphora. Table 4 shows a summary of findings grouped by etiology. The injections can be utilized to treat both functional and non-functional cases of epiphora without changes in efficacy. Subjective improvement was reported in nearly all the studies involved, with values reported ranging from 67 to 100%. Both Wojno *et al.* and Singh *et al.* compared groups by etiology of epiphora.[22,34] Singh *et al.* found no difference in median Munk score reduction between the functional and non-functional groups.[34] Wojno *et al.* noted subjective improvement in all patients in both groups.[22] Side effects between the two etiologies were also nearly equal, with 18% (n = 21) of patients in the functional group and 21% (n = 19) of patients in the non-functional group experiencing side effects. Thus, there appears to be little difference in overall efficacy and side effects in cases of both functional and non-functional epiphora treated with botulinum toxin A injections.

Similarly, the studies appear to show no difference in efficacy when comparing transconjunctival versus transcutaneous injection of botulinum toxin A. Eleven studies utilized direct, transconjunctival injections into the palpebral lobe of the lacrimal gland.[21-23,26,27,29-34] Four studies reported transcutaneous injections or a combination of the two approaches.[24,25,28,35] The most common complication reported across all studies was transient ptosis. Five of the thirty-four patients (mean rate 15%, range 0–50%) injected via transcutaneous approach were reported to develop ptosis. Among the studies utilizing the transconjunctival approach, mean rate of ptosis reported was 10% (range 0–40%). In a randomized controlled trial comparing transconjunctival to transcutaneous botulinum toxin A injections, Lee *et al.* found temporary ptosis and diplopia occurred in 10.7 and 8% of cases in the transconjunctival and transcutaneous groups, respectively, with no significant intergroup difference.[35] A meta-analysis by Falzon *et al.* showed transconjunctival route to have lower complication rate in patients treated for gustatory lacrimation.[38] Our review shows a higher rate for transcutaneous injection, likely due to small sample size. Advantages of the transconjunctival approach include direct visualization of the lacrimal gland leading to decreased risk of ptosis, superior rectus palsy, and iatrogenic globe rupture.[23] Furthermore, decreased doses may be utilized during transconjunctival injection.[26] Disadvantages include the need for eyelid retraction through either placement of a retractor and/or eyelid inversion, and possible increased risk of subconjunctival hemorrhage.[31] Side effects reported in the included studies were limited to diplopia, eyelid or lacrimal gland hematoma, papillary conjunctivitis, dry eye, ptosis, and bleeding. All side effects were transient in nature. No cases of infection were reported in the included studies.

Kaynak *et al.* described side effects in patients undergoing dacryocystorhinostomy in their study comparing the two treatment modalities including Metaireau tube dislocation in 9 cases (50%), tube obstruction with granuloma formation in 4 cases (22%) and failure to control a patient's epiphora in a single case (6%).[31] Of note, Metaireau tubes are poly-N-vinylpyrrolidinone coated, silicone tubes that can be used in lieu of pyrex tubes in CDCR.[39] This tube is not currently approved by the FDA in the United States. Half of the patients undergoing CDCR were dissatisfied due to complications and extensive follow up requirements. Interestingly, Ahn *et al.* also noted a significant association between risk of complication and degree of difficulty in elevating the upper eyelid for injection. Patients

requiring a Desmarres retractor to expose the lacrimal gland were more likely to develop ptosis and diplopia. Despite risk of infection, tube extrusion, intrusion, or malposition, CDCR still offers a time-tested, effective surgical management for this chronic problem.[40-42] One large systematic review of 54 studies evaluating CDCR for treatment of epiphora related to canalicular obstruction noted an average efficacy rate among studies of 88.9% (n = 2555).[10] Thus, both botulinum toxin A injection and CDCR are viable alternatives for the treatment of chronic epiphora depending on surgeon preference and patient specific factors including age and indication.

One consideration regarding use of of botulinum toxin A injections for treatment of epiphora is the need for long-term follow up and potential repeat injections for continued successful management of the condition. Even with successful control of the symptoms, patients would still need to attend follow up appointments every few months for repeat injections, thereby increasing the overall costs of this approach. Interestingly, the duration of effects reported in most studies was between four to six months, with one study reporting a duration of twelve months.[31]

The physiological duration of effect of botulinum toxin on motor end plates in humans has been shown in various studies to be around two-three months.[43,44] However, injections for the treatment of autonomic driven processes through the action of acetylcholine, such as hyperhidrosis, have been shown to provide a longer duration of effect, lasting between 6 and 12 months.[45-47] This differing duration of action may account for the overall increased duration of effects reported by many of the studies included in this review. This finding also suggests that patients choosing to undergo botulinum toxin injections for management of epiphora may only require bi-annual visits for repeat injections.

Botulinum toxin A injection for epiphora due to functional and nonfunctional etiologies was found to be safe, with limited and transient side effects reported across all studies. Thus, lacrimal gland botulinum toxin injection should be considered as a viable treatment strategy for both functional and nonfunctional epiphora. From the studies reviewed, botulinum toxin A injection was shown to be effective in patients from eight to 94 years old. Injection can be performed in the outpatient setting, is minimally invasive, technically easy to administer, has a favorable side effect profile, and good efficacy. Furthermore, repeat injections can be performed with similar efficacy. Risks and complications associated with anesthesia and lacrimal surgery itself may be avoided in adolescents and adults. However, is important to consider that young children may still require sedation or anesthesia to undergo injection. For elderly patients who are poor surgical candidates, or those with inoperable conditions such as nasal cancer or other malignancy, injection may be a desirable treatment option. Injection also reduces the need for extensive follow-up after surgery. Botulinum toxin injections would be inappropriate as a primary treatment modality to address dacryocystitis or masses of the canalicular/nasolacrimal duct. These injections however could provide a useful adjunctive treatment for patients who have had anatomic and functional success from surgery but continue to have epiphora.

To the authors' knowledge, there are no studies comparing the cost effectiveness of botulinum toxin to that of surgical interventions for the treatment of nonfunctional epiphora.

Direct comparison may prove challenging given costs of facilities, equipment, drugs and supplies, and doctors vary by institution and geographic location. Additionally, the length of follow-up time, repeat procedures or revisions, and patients' subjective improvement of quality of life should also be considered when assessing cost effectiveness. One retrospective review comparing cost-efficiency of endoscopic and external dacryocystorhinostomy (DCR) found the cost of external DCR to be approximately £1656 ($2297.72 USD) in the United Kingdom in 2007.[48] From the 2020 Charge Description Master (CDM) at a large academic university in the Midwest, nasolacrimal duct probing with insertion of stent is listed at $5,055.00.[49] It can be assumed that the cost of CDCR are similar if not higher. The Allergan Botox® wholesale acquisition cost (WAC) is listed as $1,244 for a 200-unit vial, approximately $6.22 for a single unit.[50] For a single injection treatment ranging 2 to 20 units, drug costs of $200 or less, plus facility and doctor's costs can be assumed. Ultimately, cost effectiveness of botulinum toxin injection for epiphora would vary based on the number of treatments required by each patient.

Dosing of botulinum toxin A lacrimal gland injections across all studies ranged from 1.25 to 15 units per treatment. Most studies utilized a dose of 2.5 to 5 units. There was no correlation observed between the number of units used for initial injection and the percentage of repeat injections required for patients. Fortunately, risks of additional treatment when initial dosing was insufficient were shown to be minor and limited. An opportunity for future study may be comparing efficacy at different doses to determine optimal dosing guidelines for this indication.

Limitations of this review include the retrospective nature of many of the included studies. Most of the included studies consisted of non-randomized protocols without controls for comparison. The subject number within the studies was also limited with a range of 2–46 patients and a median of 15 patients. Comparison between the studies is also limited given the variations among providers in type of botulinum toxin utilized, dosing, injection technique, and follow up period. Similarly, outcomes reported in the studies vary between objective data including Schirmer and Munk scores, versus subjective, patient reported symptom improvement, making it difficult to draw comparisons between the included studies. Nonetheless, all studies reported an overall benefit in the injections' effectiveness in treating epiphora.

Further research could help solidify intraglandular botulinum toxin A injections as a leading option in management of epiphora. Physicians and patients would stand to benefit from a randomized control trial evaluating differences in surgical management versus minimally invasive, glandular botulinum toxin A injections. Finally, studies evaluating differences in dosing, injection technique, and dosing intervals could also help clinicians in establishing a routine treatment schedule.

Conclusion

In conclusion, glandular botulinum toxin A injection represents an emerging treatment modality for the management of epiphora. This low-cost and safe, in-office procedure can

provide an additional or adjunctive treatment option for many patients suffering from the effects of chronic epiphora.

Disclosure statement

Dr. Vinay Aakalu: In accordance with Taylor & Francis policy and my ethical obligation as a researcher, I am reporting that I am consultant to Horizon Pharmaceuticals. I have also received Grant Funding from the following:

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I have disclosed those interests fully to Taylor & Francis, and I have in place an approved plan for managing any potential conflicts arising from this involvement.

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Table 1.

Functional epiphora.

Author/Year	Study Type	# of Subjects	Indications	Injection Technique/ Location	Dosing	Results	Reported Side Effects
Girard et al. (2018)	Non-randomized, prosepective, intervention study	42 patients; 65 lacrimal glands; 18 males/24 females; Mean age 65 years	• Paroxysmal lacrimal hypersection (n = 56, 86%)• Aberrant 7th nerve regeneration (n = 2, 3%)• Facial palsies (n = 7, 11%)	Incobotulinum toxin A; transconjunctival direct injection into palpebral lobe of lacrimal gland	Mean 4.9 Units; Range 2–10 units; Re-injections (n = 39, 60%)	Munk Score mean reduction 2.68; Schirmer mean reduction of 9 mm; QoL questionnaire 88% (n = 37) satisfaction; epiphora resolution in 21% (n = 9) after first injection	• ptosis (n = 2, 3%)• diplopia (n = 6, 9%)• lacrimal gland hematoma (n = 2, 3%)
Shan et al. (2019)	Randomized, prospective, intervention study	15 patients; 4 males/11 females; mean age 38 years	• Submandibular gland transplantation c/b epiphora (n = 15, 100%)	Onabotulinum toxin A; Percutaneous injection into transplanted submandibular gland	3 groups of 5; 15, 20, & 25 Units; No re-injections reported	Schirmer mean reduction 64/73/78% respectively; VAS (visual analogue scale) Scores decreased in 20&25 Unit groups through 6 months	• None reported
Keegan et al. (2002)	Non-randomized, prospective, intervention study	4 patients; 3 males/1 female; age range 20–58	• Aberrant 7th nerve regeneration (n = 3, 75%)• Submandibular gland transplant (n = 1, 25%)	Abobotulinum toxin A; Transcutaneous lacrimal gland injection (n = 3, 75%); Subcutaneous injection near transplanted submandibular gland (n = 1, 25%)	20 Units in 3 divided doses; 1000–1200 units for submandibular injection; re-injections (n = 2, 50%)	Schirmer improvement (n = 3, 75%); subjective improvement (n = 3, 75%)	• ptosis (n = 2, 50%)• diplopia (n = 1, 25%)
Nava-Castañeda et al. (2006)	Non-randomized, prospective, intervention study	15 patients; 15 lacrimal glands; 8 males/7 females; mean age 63 years	• Gustatory epiphora (n = 15, 100%)	Onabotulinum toxin A; transconjunctival direct injection into palpebral lobe of lacrimal gland	2.5 Units; no re-injections reported	Schirmer test mean decrease 5.4 mm; statistically significant at 24 weeks in affected eyes	• ptosis (n = 2, 13%)
Whittaker et al. (2003)	Non-randomized, retrospective, intervention study	14 patients; 5 males/9 females; Mean age 60 years	• Functional epiphora (n = 14, 100%)	Onabotulinum toxin A; transconjunctival direct injection into palpebral lobe of lacrimal gland	2.5–5 Units; re-inections (n = 2, 14%)	Pt reported symptom improvement @ 1 week (n = 10, 71%); @ 13 weeks (n = 8, 73%); Schirmer test value improvement @ 1 week (n = 11, 79%); @ 13 weeks (n = 6, 55%)	• ptosis (n = 1, 7%)• diplopia (n = 1, 7%)
Hofmann (2000)	Non-randomized, retrospective, intervention study	• 2 patients	• Aberrant 7th nerve regeneration (n = 2, 100%)	Onabotulinum toxin A; transconjunctival direct injection into palpebral lobe of lacrimal gland	15 Units – 3 injections of 5 units each, 2 laterally subcutaneous and 1 transconjunctival glandular injection; re-injections (n = 2, 100%)	Pt reported symptom improvement; observed lack of gustatory epiphora	• None reported
Montoya et al. (2002)	Non-randomized, prospective, intervention study	• 4 patients; Mean age 57 years (range 35–75)	• Gustatory hyperlacrimation (n = 4, 100%)	Abobotulinum toxin A; transcutaneous (n = 3, 75%), transconjunctival (n = 1, 25%) direct injection into lacrimal gland	10 Units; re-injections (n = 3, 75%)	Pt reported symptom improvement (n = 4, 100%); Schirmer decrease @ 6 months (n = 4, 100%)	• ptosis (n = 1, 25%)• DES (n = 3, 75%)

Table 2.

Nonfunctional epiphora.

Author/Year	Study Type	# of Subjects	Indications	Injection Technique/ Location	Dosing	Results	Reported Side Effects
Girard et al. (2017)	Non-randomized, retrospective, intervention study	20 patients; 27 lacrimal glands; 6 males/14 females; mean age 67/63	• NLDO (n = 20, 100%)	Onabotulinum toxin A or Incobotulinum toxin A; transconjuntival direct injection to palepral lobe of lacrimal gland	Mean 5.2 Units; Range 2–10 Units; Re-injections (n = 14, 52%)	Munk Score Mean reduction 3.38; Schirmer's Mean reduction of 22 mm; QoL questionnaire 88% satisfaction; epiphora resolution (n = 9, 33%) after 1st injection	• ptosis (n = 8, 40%) • transient diplopia or esotropia (n = 3, 15%)
Ziahosseini et al. (2015)	Randomized, prospective, intervention study	17 patients; 22 lacrimal glands; 4 males/13 females; mean age 70.3	• Cannalicular obstruction (n = 10, 59%) • NLDO (n = 3, 18%) • Punctal Cautery (n = 4, 24%)	Onabotulinum toxin A: transconjunctival direct injection into palpebral lobe of lacrimal gland	Mean 3.5 injections/eye; Mean dose 2.5 units; Range 1.25–7.5 units/ injectionl; No re-injections reported	Munk Score Mean reduction 2.8; subjective epiphora resolution (n = 3, 18%); epiphora improvement (n = 15, 88%)	• upper eyelid hematoma (n = 1, 6%) • diplopia (n = 1, 6%)
Kaynak et al. (2016)	Non-randomized, prospective, comparative intervention study	38 patients; 18 (47%) conjunctivodacryocystorhinostomy; 20 (53%) Botulinum Toxin Injections; 8 male/12 female; mean age 49.7	• Proximal Lacrimal System Obstruction (n = 38, 100%)	Onabotulinum toxin A; transconjunctival direct injection into palpebral lobe of lacrimal gland	4 Units; re-injections (n = 2, 10%)	Munk Score Mean reduction 2.35; Schirmer 1 Test Mean decrease 2.2 mm @ 6 months *results for BTX-A group, no significant differences between groups	• ptosis (n = 5, 25%)
Eustis et al. (2014)	Non-randomized, retrospective, intervention study	• 3 children, 9 year old male, 16 year old female, 8 year old male	• Proximal ductal obstruction (n = 3, 100%)	Onabotulinum toxin A; transconjunctival direct injection into palpebral lobe of lacrimal gland; 2 (67%) under general anesthesia	5 Units; re-injections (n = 2, 67%)	Pt reported symptom relief (n = 2, 67%)	• papillary conjunctivitis (n = 1, 33%)

Table 3.

Mixed etiologies.

Author/ Year	Study Type	# of Subjects	Indications	Injection Technique/ Location	Dosing	Results	Reported Side Effects
Ahn et al. (2019)	Non-randomized, retrospective, intervention study	35 patients; 46 lacrimal glands; 20 males/15 females; median age 66 years;	• Proximal canalicular obstruction (n = 32, 69%) • Functional NLDO (n = 6, 13%)• Crocodile tearing (n = 4, 8%)• Inoperable condition (n = 4, 8%)	Onabotulinum toxin A; transconjunctival direct injection into palpebral lobe of lacrimal gland	2.5 Units; Mean 23 injections/eye (range 1–6); re-injections (n = 25, 54%)	Munk Score mean decrease 1.85 and 1.51 @ 1/3 months respectively; Schirmer 1 mean decrease 4.83 and 2.87 @ 1/3 months respectively	• ptosis (n = 7, 20%)• diplopia (n = 3, 8.5%)
Wojno et al. (2011)	Randomized, prospective, intervention study	46 patients; 22 males/24 females; Age Range 35–94	• NLDO (n = 27, 59%)• Gustatory epiphora (n = 19, 41%)	Onabotulinum toxin A; transconjunctival direct injection into palpebral lobe of lacrimal gland	2.5 Units; re-injections (n = 19, 41%)	Subjective improvement; complete improvement (n = 34, 74%), improved, but still tearing (n = 8, 17%), little to no improvement (n = 4, 9%)	• ptosis (n = 5, 11%)
Singh et al. (2019)	Retrospective interventional case series	31 patients, 37 eyes	Functional:• hypersecretion (n = 5, 71%)• crocodile tears (n = 1, 14%)• CN VII palsy (n = 1, 14%) Nonfunctional:• proximal canalicular obstruction (n = 12, 50%)• common canalicular obstruction (n = 6, 25%)• punctal stenosis (n = 3, 13%)• post-trauma NLDO (n = 1, 4%)• partial NLDO (n = 1, 4%) • uncategorized (n = 1, 4%)	Onabotulinum toxin A; transconjunctival direct injection into palpebral lobe of lacrimal gland	2.5 and 5 units, surgeon preference, median 4 units functional group: re-injections (n = 3, 43%) nonfunctional group: re-injections (n = 12, 50%)	Median reduction in Munk score: - 75% in functional group- 50% nonfunctional group Difference not statistically significant (p = .07)	Functional: • ptosis (n = 1, 14%) Nonfunctional: • ptosis (n = 2, 8%)
Lee et al. (2021)	Randomized, prospective, controlled trial	31 patients; 53 lacrimal glands; 17 males/14 females; mean age 71.5; Range 50–90	• Functional epiphora (n = 43, 81%)• Nonfunctional epiphora (n = 10, 19%)	Prabotulinum toxin A; transcutaneous (n = 25, 47%), transconjunctival (n = 28, 53%) direct injection into lacrimal gland	3 Units; re-injections (n = 14, 52%)	Schirmer's Mean reduction (p < .05)*; Tear Meniscus Height Reduction (p < .05)*; Indoor and Outdoor Munk Score Mean reduction (p < .05)*; (*through 24 weeks); Improvement in Glasgow Benefit Inventory QoL questionnaire; Duration of symptom relief 5.63±2.42 months	Transcutaneous Injection: • DES (n = 1, 4%)• ptosis (n = 2, 8%) Transconjunctival Injection:• diplopia (n = 1, 4%) • ptosis (n = 3, 11%)

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Table 4.

Results by Etiology.

Etiology	# of Studies	# of Subjects	Injection Technique/Location	gDosing	Results Reported	Reported Side Effects
Functional Epiphora	7	96 patients; 103 lacrimal glands; 16 submandibular gland transplants	• Transcutaneous lacrimal gland injection (n =6, 5%) • Transconjunctival lacrimal gland injection (n = 97, 82%) • Subcutaneous injection of transplanted submandibular gland (n = 16, 13%)	Range: 2.5–20 units*; re-injections (n = 48, 40%)*Not including submandibular gland injections	Objective: Munk Score mean decrease; Schirmer 1 mean decrease, VAS Score decreaseSubjective: QoL questionnaire; Patient reported symptom improvementDuration of Effect Reported: 4–6 months	• ptosis (n = 8, 7%) • diplopia (n = 8, 7%)• lacrimal gland hematoma (n = 2, 2%) • dry eye syndrome (n = 3, 3%)
Non-Functional Epiphora	4	78 patients; 90 lacrimal glands	• Transconjunctival lacrimal gland injection (n = 90, 100%)	Range: 1.25–10 units; Mean: 4.03 units; re-injections (n = 18, 20%)	Objective: Munk Score mean decrease; Schirmer 1 mean decreaseSubjective: QoL questionnaire; Patient reported symptom improvementDuration of Effect Reported: 3–12 months	• ptosis (n = 13, 17%) • esotropia (n = 2, 3%) • diplopia (n = 2, 3%) • upper lid hematoma (n = 1, 1%) • papillary conjunctivitis (n = 1, 1%)
Mixed Etiology Studies	4	143 patients; 182 lacrimal glands	• Transcutaneous lacrimal gland injection (n = 25, 14%) • Transconjunctival lacrimal gland injection (n = 157, 86%)	Range: 2.5–5 units; re-injections (n = 83, 46%)	Objective: Munk Score mean decrease; Schirmer 1 mean decrease; Tear meniscus height reductionSubjective: QoL questionnaire; Improvement in Glasgow Benefit Inventory; Patient reported symptom improvementDuration of Effect Reported: 3–5.5 months	• ptosis (n = 20, 14%)• DES (n = 1, 1%)• diplopia (n = 4, 3%)