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Botulinum Toxin-A Intraglandular Injection in Epiphora Management

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Abstract

This interventional study aimed to assess both the safety and efficacy of the Botulinum neurotoxin-A (BoNT-A) injection into the palpebral lobe of the lacrimal gland to manage epiphora symptoms. The study included 40 eyes of 30 patients, who came to the department of Ophthalmology, Al-Azhar University Hospital, complaining of epiphora due to lower lid laxity, obstruction of the lacrimal drainage apparatus, crocodile tears syndrome or malposition of the lower lid. Patients were injected with Botulinum neurotoxin-A (2.5 IU/0.1ml) into the palpebral part of the lacrimal gland. Shirmer-1 test, Munk score and Fluoresceine dye disappearance test (FDDT) were measured to evaluate the epiphora before the injection and on the scheduled follow-up visits on the first day, the first week, the first month, the third month, and the sixth month post-injection to assess the efficacy and safety and to record the complications and the recurrence rate. Improvement of epiphora was noticed in almost 67% of the patients after the first injection and 95% after the second injection with a highly significant decrease in the Schirmer's-1 test results, Munk score and Fluoresceine dye disappearance test in the study group after injection (P<0.001). Ptosis was the main complication in the study group with 3 patients affected which was transient and relieved within 8 weeks and one case of lacrimal gland hematoma. The Botulinum toxin injection in the palpebral part of the lacrimal gland can be effectively used to temporarily diminish excessive tearing with minimal side effects.

Keywords: Intraglandular injection, Botulinum neurotoxin-A, Epiphora, Munk score

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1. Introduction

Epiphora affects the quality of life and is inconvenient to the patients and their routine daily activities as a result of symptoms like blurred vision, eyelid skin excoriation, laxity of eyelids and dacryocystitis [1]. Epiphora could be either due to obstruction of the drainage system or functional causes as lower lid laxity, crocodile tears syndrome, and hypersecretion of the lacrimal gland [2]. According to the epiphora etiology, different treatments are available as, punctoplasty, balloon dacryoplasty, and conjunctivodacryocystorhinostomy [3]. For some patients, especially those who are elderly, have medical co-morbidities, have refractory epiphora that was not resolved with medical nor surgical treatment or have undergone previous surgery for the lacrimal drainage system, surgery may not be the best course of action [4] .

Botulinum neurotoxin-A (BoNT-A) is FDA-approved for dermatological, ophthalmological, and neurological medical purposes [5]. Its efficacy in treating epiphora is demonstrated in certain clinical studies as a promising cure for patients experiencing excess tearing or impairment of the lacrimal drainage pathway [6]. The injection of the BoNT-A in the lacrimal gland demonstrated a significant reduction in tear production by preventing acetylcholine from being released presynaptically into the cholinergic nerve fibers' neuromuscular end plates. [7]. On the other hand, the side effects of the BoNT-A are mild and temporary as ptosis, diplopia, lagophthalmos, and xerophthalmia [8].

Our study aimed to evaluate the safety and effectiveness of intraglandular injection of BoNT-A into the lacrimal gland's palpebral lobe for the management of either obstructive or functional epiphora. Additionally, the effect of repeated injections of BoNT-A was studied and its data was reported.

2. Materials and Methods

This prospective interventional clinical study was conducted at the department of Ophthalmology, Al-Azhar University Hospital and included 40 eyes of 30 patients who complained of epiphora during the period between September 2022 to August 2023. The protocol of the study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethical Board of Al-Azhar University. The full procedure was explained to the patients, and their informed consent was signed and recorded for their voluntary participation and publication approval.

The inclusion criteria of the included patients were epiphora patients grade 3 & 4 according to Munk score (Table 1), crocodile tears condition, functional epiphora caused by lower lid laxity or obstruction of the lacrimal drainage system with previously unsuccessful surgeries or patients refusing

any further surgery. Conversely, the exclusion criteria covered patients diagnosed with BoNT-A or albumin hypersensitivity, neuromuscular disorders, pregnant or lactating women, and dry eye or current ocular infection.

A full detailed history was obtained from every participant including medical and surgical history, allergies to BoNT-A, ocular inflammation/infection, past ocular surgeries or trauma. Following, full preoperative ophthalmological examination including; Best corrected visual acuity, intraocular pressure measured using Goldmann's applanation Tonometry (Keeler, UK), slit-lamp (Zeiss, SL 800) examination for the anterior segment for lid position examination, puncta position, patency, tear film, tear breakup time as well any inflammatory changes, diagnostic probing and syringing of the lacrimal drainage system was done, Schirmer-1 test, Munk score subjective questionnaire and fluorescein dye disappearance test.

In the fluorescein dye disappearance test (FDDT), the inferior fornix was stained with 2% fluorescein sodium dye, and the tear meniscus height was measured after 5 minutes with the remaining dye. According to MacEwen and Young modification of FDDT grading as specified by Zappia and Milder2 as grades 0 (conjunctival sac without fluorescence), 1 (thin fluorescein marginal tear strips only), 2 (in between grades 1 and 3), and 3 (bright and broad fluorescein strip) [9]. After applying local anesthetic drops, the Schirmer-1 test was conducted by placing a tiny filter paper strip within the inferior fornix, and then closing the eyes for 5 minutes. The filter paper was then taken out, and moisture content was measured [10]. The Munk rating system, the fluorescein dye disappearance test and the Schirmer-1 test were used to estimate the epiphora's intensity before BoNT-A injection and in the follow-up visits. All enrolled participants were requested to notify the duration of the effect and complications of the BoNT-A injections, from their perspective.

Botulinum toxin vial (Botox; Allergan; Irvine, CA, USA) contained 100 IU and was reconstituted with 4 ml of sterile, preservative-free normal saline to have a reconstituted concentration of 25 IU/ml. The BoNT-A injection was done in a surgery room after the patients' eyes were under topical anesthesia with 0.4% benoxinate hydrochloride. Patients were asked to tilt in a semi-lying position in a surgical armchair and look downward and medially to allow proper exposure of the palpebral lobe of the lacrimal gland and better control of the surgical injection. After that, the lateral aspect of the upper eyelid was gently everted to uncover the lacrimal gland. Following, an 0.1 ml (2.5 IU/0.1ml) of BoNT-A was injected by a 30-G syringe needle into the exposed palpebral lobe under direct visualization as shown in Fig.1. Antibiotics and corticosteroid eye-drops were prescribed four times per day for a week. Follow-up visits were scheduled to be conducted on the first day, one week, one month, three months and six months following the injection.

2.1. Statistical analysis

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). This data comprised any changes in Munk score, dye disappearance test and Schirmer's-1 test. Using the non-parametric Mann-Whitney U test, the preoperative and postoperative data for the study group were compared. P-values were considered statistically significant if they were less than 0.05.

3. Results

This clinical trial included 40 eyes of 30 patients, 11 males and 19 females. The mean age was 55.7, with a range of 29 to 73 years. Obstructive causes made up 52%, with nasolacrimal duct obstruction being the major cause of epiphora (21 eyes), while functional causes made up 48% (19 eyes). 1 month and 3 months following the injection of BoNT-A, the mean Munk score dramatically dropped from 3.725± 0.45 (range, 1-4) prior to injection to 1.58± 0.71 (range, 1-4; p 0.0001) and 1.85 ±0.735 (range, 1-4; p 0.0001), respectively (Fig. 2). Before injection, there were 11 eyes in grade III and 29 eyes in grade IV on Munk score. After one month, 22 eyes were in grade I, 13 were in grade II, and 5 were in grade III. While after 3 months, 14 eyes were in grade I, 18 were in grade II, and 8 were found to be in grade III. Two eyes in grade IV, eight eyes in grade III, 23 in grade II, and seven in grade I were present six months following injection. Comparing the results obtained before injection and after injection, the Munk score showed a highly statistically significant change (P 0.001). The mean Munk score reduction rate reduced to 50.67 ± 18.35% at 3-month post-injection. Six months after injection, there was a mean reduction rate of 45.25 ± 16.80%.

There was a significant reduction in the mean Schirmer-1 score as well. From 29.8 ± 4.22 mm before injection to 16.58 ± 4.37 mm ($p < 0.0001$) at 1 month and 18.08 ± 4.59 mm ($p < 0.0001$) at 3 months after injection, while after 6 months the mean Schirmer-1 score was 20.68 ± 1.97 mm (Fig. 3). The Schirmer-1 score's mean reduction rate at 3-months and 6-months post-injection was 39.93 ± 9.13% and 29.19 ± 12%, respectively. In the fluorescein dye disappearance test, the mean reduction rate was 55 ± 16.10% at one-month after injection and 48.33 ± 16.79% at three-month post-injection while the mean reduction rate at six-month was 38.33 ± 19.31% (Fig. 4). The forty eyes were included in Grade III before the BoNT-A injection in which 14 categorized as grade II and 26 as grade I at one-month post-injection and 22 was in grade II and 18 in grade I at three months post-injection. At six months post-injection, four eyes were in grade III, 26 in grade II, and 10 in grade I.

No discernible change occurred between the mean reduction rates of the Munk score, the Schirmer-1 test and the FDDT in terms of the efficacy and durability of effect of repeated injections (The first injection, n = 40 eyes; the second, n = 13 eyes). The 3-months after the first injection, the mean reduction rate of the Munk score was 48.47 ± 17.15%, while the mean reduction rate following re-injection was 51.92 ± 12.34% (P = 0.443) (Fig. 5). Comparably, following the initial injection, the mean reduction rate of the Schirmer-1 test was 38.13 ± 3.71%, while following the second injection it was 39.41 ± 3.27% with no statistical difference (P = 0.208) (Fig. 5). Additionally, the mean reduction rate of FDDT showed no statistical difference between the first injection (46.91±16.69%) and the second injection (51.28±17.29%; $P \leq 0.509$) (Fig. 5).

Postoperative complications occurred in 10% from the overall 40 injections, involving 4 patients, three of them complained of upper eyelid ptosis and one case had lacrimal gland hematoma. Within eight weeks, the ptosis spontaneously resolved in the three cases with no ocular

movement limitation detected. The patients followed Brimonidine twice daily for two weeks, which is an α2-adrenergic agonist eye drops that induce a 1 to 2 mm elevation of the upper part of the eyelid by contracting the Müller's muscle. [11].

4. Discussion

Keegan et al. published the initial research examining the impact of botulinum toxin in patients with epiphora, which indicated that one epiphora patient showed some subjective recovery in his state but that it was not clinically verifiable [12]. Whittaker et al. demonstrated in a study the efficacy of Botox in treating patients with functional epiphora. Using 2.5–5U of BoNT-A transconjunctival injections in the lacrimal gland's palpebral lobe, patients experienced symptomatic improvement [13]. Using the Munk and Schirmer scoring methods and the FDDT test, the main outcome of this study is that epiphora can be improved with BoNT-A intra-lacrimal gland injection, with no long-term side effects. Furthermore, we discovered that despite multiple injections, the injection's effect and its duration remained noticeably consistent.

For the Munk score, the statistically significant difference between the results before and after the injection procedure ($P < 0.001$); the mean reduction rate of 45.25% 6 months after injection, are consistent with a study conducted by Girard et al. in the study evaluating the effect of the Botulinum neurotoxin injection for the treatment of epiphora in nasolacrimal duct obstruction [14]. In line with the findings of the Munk score, Girard et al. reported that the Munk score was reduced by 87% following BoNT-A injection, with a marked improvement seen six months after the injection (3.88 ± 0.3 vs. 0.5 ± 0.8, $P < 0.0001$) [14]. Furthermore, Ziahosseini et al. reported that the mean Munk score (3.4, range 2-4) dramatically decreased to 1.6 (range 0-3, $P=0.0001$) when 17 patients (22 eyes) were injected with BoNT-A, average injections of 3.5 units [15]. Epiphora was improved by up to 60 to 90% reporting two cases of temporary bruising and diplopia (lasting 2 weeks) [15].

Concerning the Schrimer-1 results included in this study, six months after injection, it dropped to 20.68 ± 1.97 mm with a statistically significant difference ($P < 0.0001$) and a mean reduction rate of 29.19%. In accordance with our study, a pilot study examining some Lacrimal gland targeted therapies for refractory epiphora, Singh et al. reported that Schirmer-1 values showed a mean reduction of 5.25 mm (range, 2-8 mm) following intraglandular 2.5 units BoNT-A injection [16]. Elshaieb et al. also reported that the mean pre-injection Schirmer's test result was 30.1 ± 2.8 mm. At six months after injection, it shrank to 19.5 ± 8.5 mm with a statistically significant difference ($P < 0.0001$) [17]. These reported results are similar to a comparative study involving 20 eyes that had received Botox injections done by Kaynak et al. who documented both quantitative and qualitative assessments of epiphora. Before injection, the average Munk and Schirmer-1 scores were 3.95 and 12 mm, respectively. At one month after injection, they dropped to 1.05 mm and 5.4 mm, respectively, and at three months after injection, they reduced to 1.36 mm and 5.8mm, respectively [18].

In the FDDT test, there was a highly significant difference ($P<0.001$) between the results prior to injection in contrast to post-injection results with a mean reduction rate of 38.33% at 6 months post-injection in our study. These results are similarly reported in the study conducted by Elshaieb et al., in which the comparison of FDDT results before and after injection showed a highly significant difference ($P<0.001$). Following the first injection of BoNT-A, FDDT measurements fell in 60% of the subjects, and following the second injection, they decreased in 90% of the participants. [17]. It has been demonstrated that the dye disappearance test may be used to identify various levels of epiphora and assess the effectiveness of various treatment modalities [19]. As discussed by Roh et al., there was a significant statistical difference in FDDT results between pre-treatment and post-treatments in the studied groups, suggesting that FDDT measurements could be effectively remarkable in the diagnosis and postoperative assessment of nasolacrimal duct obstruction [19].

In our study, the efficacy of repeated injection was monitored with no statistically significant difference in the mean reduction rate of the Munk score, Schirmer-1 test and FDDT results after the second injection as compared to the first injection 3 months post-injection. According to Ahn et al., the efficacy and duration of the BoNT-A injection were consistent with repeated injections, and recurrent injections can be used to treat symptomatic epiphora instead of complex surgery. Repeated BoNT-A injections won't impair efficacy and can be used safely to treat epiphora, especially in patients with exposed lacrimal glands [3]. Another study validated the practice of repeatedly injecting BoNT-A into the eyebrows, claiming that performing this would delay the ptosis that naturally develops there and prevent the need for more invasive operations [20].

The reported side effect Ptosis, is documented as the most common side effect that occurred after BoNT-A injections. According to Lee et al., temporary ptosis was one of the most common adverse effects [21]. Only three individuals in this study (7.5%) had temporary ptosis that resolved within 8 weeks, and one had lacrimal gland hematoma (2.5%). On the other hand, two patients suffered mild stinging and dryness in the treated eye and one patient developed ptosis in the trial by Montoya et al. [22], whereas two patients experienced temporary ptosis and diplopia in the study by Whittaker et al. [13]. Ziahosseini et al. reported only temporary bruising and diplopia in two patients injected with BoNT-A [15].

Table 1. Munk score for epiphora grading [9]

Grade	Munk Score for Epiphora Grading
0	No epiphora
1	Epiphora need dabbing less than twice a day
2	Epiphora need dabbing 2-4 times a day
3	Epiphora need dabbing 5-10 times a day
4	Epiphora need dabbing more than 10 times a day or constant tearing

Figure 1. Using a 30-G needle, diluted BoNT-A is injected into the palpebral lobe of the lacrimal gland

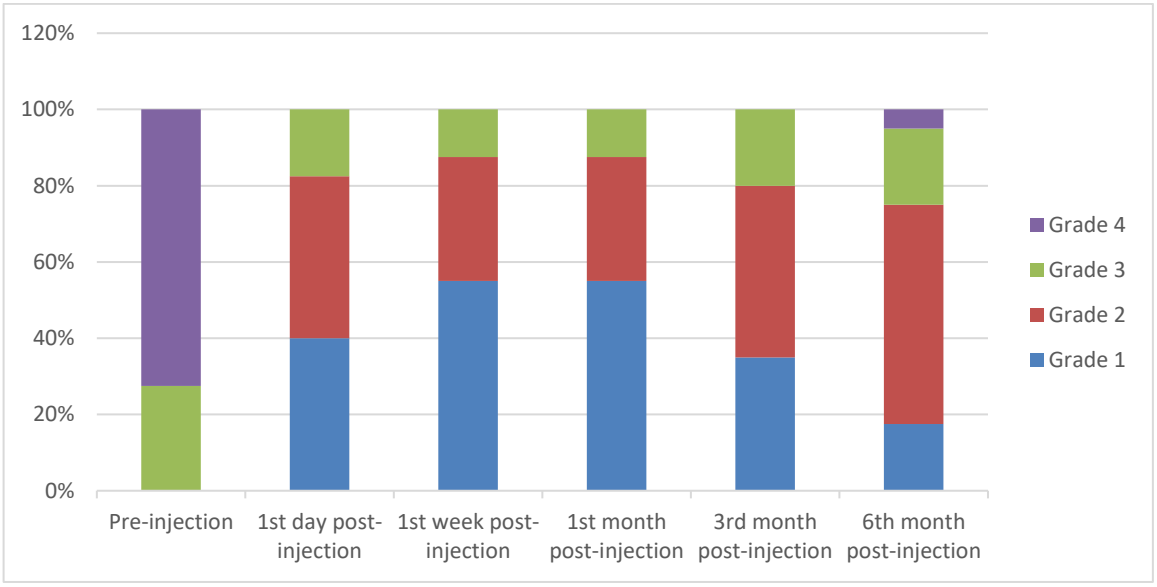

Figure 2. Comparison of Munk score results in the study population concerning before injection and follow-up assessment

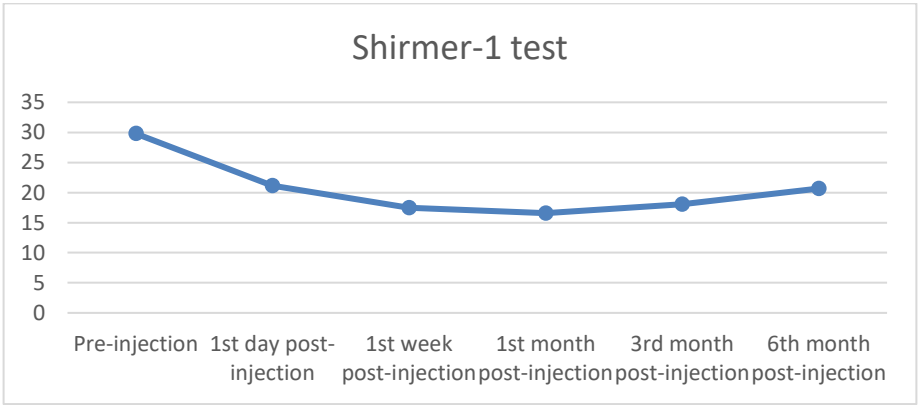

Figure 3. Schirmer-1 test mean in mm in the study population concerning before injection and follow-up assessment

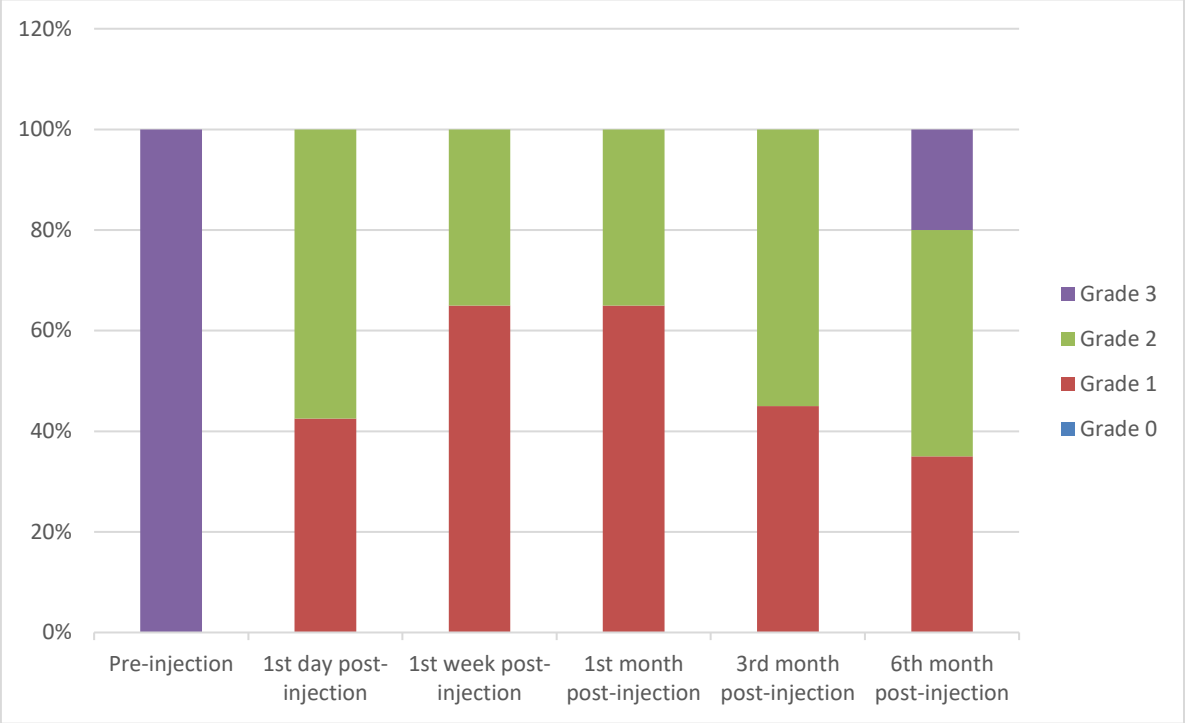

Figure 4. Comparison of FDDT results among study population concerning pre-injection and follow-up assessment

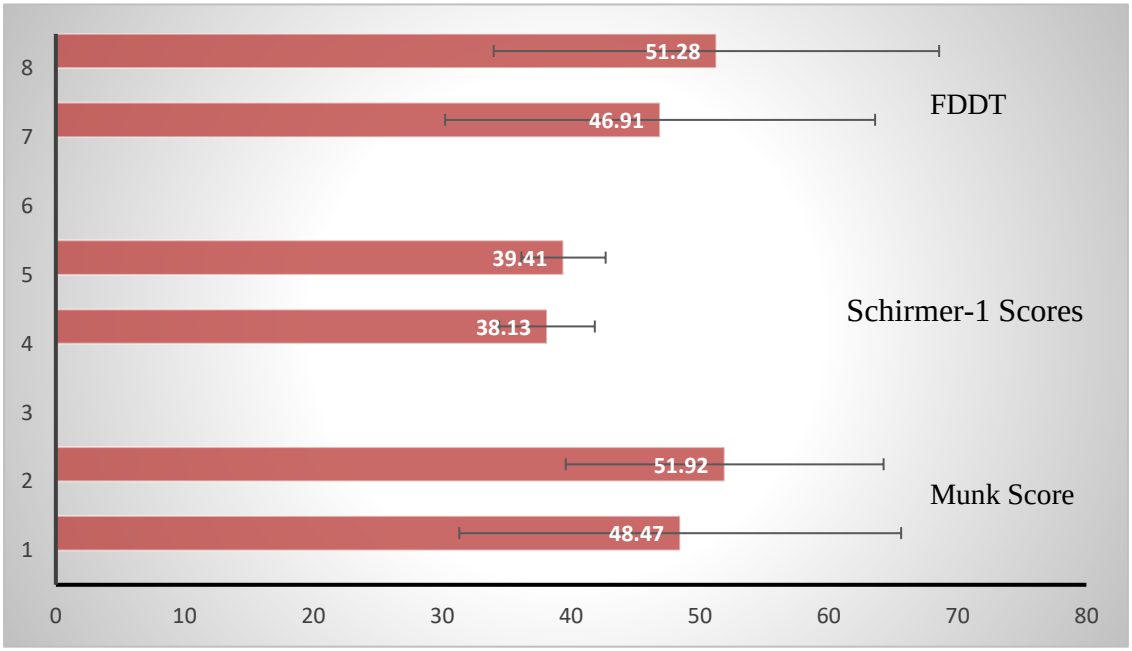

Figure 5. Comparison between mean reduction rates between first injection and second injection (re-injection)

4. Conclusions

Treatment of epiphora through the injection of BoNT-A in the lacrimal gland is thought to be an innovative therapeutic method. For a large number of patients experiencing the side effects of recurrent epiphora, this low-cost, safe, outpatient procedure can offer an alternative or supplemental therapeutic option according to the objective improvement of the results of this clinical experiment and prior researches. It should be taken into account for patients who do not tolerate topical medication, elderly patients, or patients in whom surgery may be risky. To reduce excessive tearing until a more effective long-term remedy can be found, BoNT-A treatment may be helpful.

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Disclosure statement

The authors declare no conflicts of interest.

Authors Contribution

All authors have contributed equally.

Ethical Approval Statement

The Research Ethics Committee (REC) for experimental and clinical studies of Al-Azhar University approved this research protocol.

Participation Consent

Informed consent was obtained from all individual participants included in the study.

Publication Consent

The authors affirm that human research participants provided informed consent for the publication of the images in the intended figures.

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