Transconjunctival botulinum toxin injection into the lacrimal gland in crocodile tears syndrome

Sabyasachi Pattanayak, Pramod Kumar Sharma¹, Swati Samikhya¹, Ipsita Khuntia¹, Kalyani Patra²

Purpose: To determine the efficacy and safety of botulinum toxin injection into the lacrimal gland as a symptomatic treatment of crocodile tear syndrome (CTS). Methods: Our study included six patients of unilateral gustatory hyper-lacrimation following either an episode of facial paralysis or post trauma or any related surgery that posed a risk of damaging the facial nerve. Detailed history regarding previous trauma, duration of facial paralysis, previous significant surgery, and duration of steroid use following facial paralysis was noted. Schirmer’s test was done at baseline and 3 months follow-up. Patients’ consent was taken prior to treatment with botulinum toxin injection in the lacrimal gland. Repeat injection of 5 U botulinum toxin (type A) was administered into the lacrimal gland of all patients transconjunctivally within an interval of 1 week. All patients were followed up with Schirmer’s test at 6 weeks and 3 months. Any complications during treatment were recorded. Results: All six patients showed complete or partial disappearance of reflex lacrimation while chewing following botulinum injection measured by a significant reduction in Schirmer’s value. When comparing Schirmer test values before (27.8 ± 3.58 mm) and after (11.6 ± 2.28 mm) BTX-A injection, the differences observed (P = 0.002) were statistically significant (P < 0.05). Only two patients developed mild transitory ptosis. No other complications were noted. Conclusion: Transconjunctival botulinum toxin injection into the lacrimal gland is an effective and safe method to decrease reflex lacrimation during eating or chewing in CTS or gustatory hyper-lacrimation syndrome.

Key words: Botulinum toxin, crocodile tears syndrome, gustatory hyper lacrimation syndrome

CTS is usually diagnosed clinically as a diagnosis of exclusion, and the differential diagnosis comprises lacrimal duct obstruction, chronic dacryocystitis, punctal stenosis, conjunctivitis, and foreign body in the conjunctiva. Patients with the previous incidence of Bell’s palsy may give a history of acute-onset symptoms of neck, mastoid, or ear pain; altered taste or facial sensation; and hyperacusis.[11]

As a symptomatically troublesome and difficult-to-manage condition, attempts have been made to reduce the symptoms of CTS by various methods such as intraorbital injection of alcohol or cocaine to destroy postganglionic fibers of the sphenopalatine ganglion, subtotal resection of the palpebral part of the lacrimal gland, sectioning of glossopharyngeal and facial nerves at different levels, and use of anticholinergic drugs.[3,10,12] Some of the treatments have resulted in total ablation of lacrimal secretion and some even threatening the sight.[10]

Boroojerdi et al.[13] reported the first successful treatment of crocodile tears by injection of botulinum toxin A directly into the lacrimal gland in 1998. Subsequent study reports showed...
complete or near complete resolution within a week with only minor and reversible complications with botulinum toxin.\textsuperscript{[13,14,15]} Recently, many reports are suggesting injection of botulinum toxin type A (BTX-A) into the lacrimal gland of CTS patients as an effective and safe method to ablate the symptoms by abolishing the reflex by chemodenervating the cholinergic neurons of the parasympathetic nervous system to the affected gland.\textsuperscript{[13,14,16,17]} Ptosis, lagophthalmos, entropion or entropion, functional epiphora, diplopia, and eyelid hematoma are the common complications encountered following botulinum injection.\textsuperscript{[18]}

The aim of our study is to determine the efficacy and safety of transconjunctival botulinum toxin injection into the lacrimal gland for symptomatic treatment of CTS and to study the complications resulting from it.

\section*{Methods}

The present study was a prospective interventional study in which after obtaining the approval of the institutional ethics committee, six patients clinically diagnosed as CTS without any contraindication for botulinum toxin injection and who gave the consent for the same were included. Detailed history of the present illness, including onset, duration, and progression of CTS, associated symptoms, and relevant past history, was obtained from each patient. A thorough slit-lamp examination was done in all six patients. Stimulation of gustatory reflex was done by asking the patients to chew a sweet-and-sour candy. Secretion of tear was documented by Schirmer’s test both prior to intervention and 3 months after injection in all patients. Schirmer’s value of more than 25 mm was noted in all the affected eyes with a history of lacrimation during eating or chewing. All patients were then prepared for transconjunctival injection after instilling topical proparacaine eyedrop, and the lids were double everted with the help of Desmarres’ lid retractor. Various published studies have reported short-term resolution of symptoms, either complete or near-complete, with 2.5–60 U of botulinum toxin A (Botox). However, higher doses have not been reported to have any additional benefit in terms of efficacy or duration.\textsuperscript{[13,19]} A dose of 5 U was decided based on the published literature on the onset and duration of effect, complication, and ease of preparation. Preparation of Botox of 5 U for injection is simple. We took 50 U Botox vial and mixed 1 mL of 9% preservative-free sodium chloride solution into the vial for reconstitution with gentle rotation of the vial. Then, 0.1 mL of reconstituted botulinum toxin containing 5 U (Botox® (OnabotulinumtoxinA, Allergan)) was injected directly into the palpebral lobe of the lacrimal gland seen by applying gentle pressure over the lateral third of orbit and lateral canthus. All patients were subjected to a 2\textsuperscript{nd} dose of 5 U of Botox transconjunctivally at the end of 1\textsuperscript{st} week of 1\textsuperscript{st} dose as it was reported that single dose of even 10 U is not effective in many cases.\textsuperscript{[19]} This site was approximately estimated to be the junction between the lateral third and medial two-thirds of superior orbital margin. All patients were asked for follow-up for the effect of treatment and severity and frequency of side effects at 1 week, 1 month, 3 months, and 6 months follow-up. Patients who showed waning of effect of botulinum toxin at the end of 3 month were given another dose of 5 U of botulinum toxin transconjunctival again. Dosage of all patients along with changes in reflex lacrimation, its duration, waning, 2\textsuperscript{nd} dosage, and side effects were documented in each visit.

\section*{Results}

The demographic profile, laterality of affection, etiology, and duration of the condition prior to the development of symptoms in all six patients included in the study are listed in Table 1. The mean age of the patients was 46.16 ± 15.91 and the range varied from 26 to 69. The male and female ratio was 4:2. The left eye was affected in four patients and the right eye in the other two. Etiologically, three patients had a history of facial trauma 2 years prior to the development of CTS, two patients were known cases of Bell’s palsy of more than 6 months’ duration, one was a diagnosed case of pleomorphic adenoma of the parotid gland and had undergone surgery 8 months prior to the development of symptoms suggesting CTS. The mean duration of facial palsy prior to the onset of symptoms was 19 ± 11.13 months with the range varying from 7 months to 36 months.

The relevant symptoms and signs of CTS patients, including onset, duration, progression, lid position, and associated symptoms, are tabulated in Table 2.

The detailed ophthalmic examination findings such as lid position, tear film break up time (TIBUT), Schirmer’s test findings prior to injection of Botox and 3 months post injection are tabulated in Table 3. All the patients had normal blink reflex, normal conjunctival and corneal epithelium, and normal corneal sensation.

After injecting 5 U of botulinum toxin transconjunctivally, only two out of six patients showed an improvement in lacrimation reflex following chewing. However, all patients were subjected to a 2\textsuperscript{nd} dose of 5 U of BTX type A transconjunctivally at the end of 1\textsuperscript{st} week of 1\textsuperscript{st} dose and all were observed to have partial or complete resolution of symptoms in the next week of 2\textsuperscript{nd} dose. It was seen that at the end of the 3\textsuperscript{rd} month, three patients had waning of effects with Schirmer’s test value of more than 12 mm and thus treated with a 3\textsuperscript{rd} dose of 5 U at the 3\textsuperscript{rd} month. One among them again showed reversal of symptoms at 3.5 months and two of them at 4 and 5 months. Thus, these three patients were given repeat transconjunctival injections at the end of 6 months. This is summarized in Table 4. The Schirmer’s test was recorded at the time of presentation and followed up after injecting the doses at 3 months as shown in the bar diagram in Fig. 1. It showed a significant decline in reflex tear production following gustatory stimulation which lasted from 3 months to 6 months. There was occurrence of mild and transient ptosis in one case which resolved spontaneously within 2 weeks and mild dryness of eyes in two cases.

\section*{Discussion}

Botulinum toxin (BTX) produced by autolysis of a gram-positive, anaerobic bacterium, \textit{Clostridium botulinum}, acts by blocking the neuromuscular transmission in motor and autonomic nerve terminals and by inhibiting the release of acetylcholine in the neuromuscular and cholinergic nerve junctions through chemo denervation.\textsuperscript{[19,20]} Boroojerdi et al. in 1998 first published the use of BTX A in the treatment of gustatory hyper lacrimation.\textsuperscript{[19]}

The technique and manner of injection vary between the transcuteaneous and transconjunctival approaches. In the transcuteaneous approach, the toxin is injected into the orbital lobe, whereas in the transconjunctival approach, it is injected under direct observation into the palpebral lobe.
of the lacrimal gland. Riemann et al. for the first time successfully treated a single case of CTS following idiopathic facial nerve palsy with BTX-A injection into the lacrimal gland through transconjunctival route. With this approach, the entire amount of BTX-A injected is delivered directly into the lacrimal gland requiring half the dose than used through transcutaneous route. The transconjunctival approach has the advantage of injection of relatively lower dose into the gland by direct visualization, thus resulting in fewer complications. In our study, all six cases were injected transconjunctivally with almost negligible discomfort and no complication. However, Lee et al. found no evidence that transconjunctival injections are more effective and safer than transcutaneous injections.

The exact dose of BTX-A to reach the maximum improvement is not well established. Hofmann presented two cases treated successfully with transcutaneous BTX-A injection 15 U of BOTOX®.

In our study, all the patients within 6 months follow-up experienced a significant decrease in lacrimation after the second dose of transconjunctival BTX-A injection into the lacrimal gland, demonstrated by a reduction in tearing by the Schirmer test in response to a taste stimulus and by a reduction in the frequency and severity of symptoms lasting from 3 months to 6 months. It was reported that the effect of Botulinum toxin usually peaks in the first week after the injection with a duration of effect persisting up to 3–6 months. Regarding complications, transient upper eyelid ptosis was the most frequent reported side effect. We also observed appearance of mild and transient ptosis in one case which resolved spontaneously within 2 weeks and mild dryness of eyes in two cases.

### Conclusion

In conclusion, we suggest that the use of two doses of BTX-A injection 5 U each at weekly intervals into the palpebral lobe of the lacrimal gland through the transconjunctival route is effective in bringing symptomatic relief to patients of CTS for almost 3–6 months. Though complications are rare with proper selection of doses and routes of administration, each patient should be followed up carefully for any possible side

### Table 1: Demographic profile of CTS patients

| Patient | Age in years | Gender | Laterality | Etiology | Duration prior to the onset |
|---------|--------------|--------|------------|----------|-----------------------------|
| 1       | 26           | Male   | Unilateral (LE) | Trauma     | 2 years                     |
| 2       | 37           | Male   | Unilateral (RE) | Trauma     | 3 years                     |
| 3       | 69           | Female | Unilateral (LE) | Trauma     | 2 years                     |
| 4       | 52           | Female | Unilateral (LE) | Bell’s palsy | 7 months               |
| 5       | 57           | Male   | Unilateral (RE) | Bell’s palsy | 15 months               |
| 6       | 36           | Male   | Unilateral (LE) | Post-op Pleomorphic adenoma | 8 months               |

### Table 2: Symptoms and signs of CTS patients

| Patients | Onset      | Duration | Progression | Lid position | Associated Symptoms                             |
|----------|------------|----------|-------------|--------------|-------------------------------------------------|
| 1        | Abrupt     | 3 months | Gradual     | Ptosis       | Ear pain, h/o epistaxis                         |
| 2        | Abrupt     | 1 year   | Gradual     | Lid lag      | Muscle twitching                                |
| 3        | Abrupt     | 5 months | Gradual     | Normal       | Decreased hearing, ear pain                     |
| 4        | Insidious  | 8 months | Gradual     | Normal       | Dribbling of saliva                             |
| 5        | Insidious  | 10 months| Gradual     | Normal       | Foreign body sensation (RE)                     |
| 6        | Insidious  | 6 months | Gradual     | Ptosis       | Facial muscle weakness                         |

### Table 3: Pre injection TBUT & Schirmer’s test findings before BOTOX injection and 3 months after 2nd dose BOTOX injection

| Patients | Pre-injection TBUT | Pre-injection Schirmer’s test | 3 months Post-injection Schirmer’s test |
|----------|--------------------|-------------------------------|----------------------------------------|
| 1        | 13 s               | 25 mm                         | 13                                     |
| 2        | 12 s               | 28 mm                         | 08                                     |
| 3        | 16 s               | 30 mm                         | 11                                     |
| 4        | 12 s               | 26 mm                         | 17                                     |
| 5        | 10 s               | 30 mm                         | 09                                     |
| 6        | 15 s               | 26 mm                         | 12                                     |
| Mean±SD  | 27.8±3.58          | 11.6±2.28                     |                                        |

![Figure 1](image-url): Bar diagram showing Schirmer test before and three months after 2nd dose of BOTOX injection.
Table 4: Summary of action of BOTOX dosage and duration of effect

| Patients | Onset of action after 2nd dose | Waning of action of BOTOX after 2nd dose (in month) | 3rd dosage after 3rd month | Reversal of symptoms (in months) | Next dose (at 6 months) | Side Effects |
|----------|-------------------------------|-----------------------------------------------|--------------------------|---------------------------------|------------------------|-------------|
| 1        | 1 week                        | 3 months                                     | 5 U                      | 4                               | 4th                    | Nil         |
| 2        | 2 weeks                       | 5 months                                     | -                        | 5                               | 3rd                    | Dryness of eye |
| 3        | 3 weeks                       | 6 months                                     | -                        | 6                               | 3rd                    | Nil         |
| 4        | 1 week                        | 3 months                                     | 5 U                      | 3.5                             | 4th                    | Ptosis       |
| 5        | 2 weeks                       | 3 months                                     | 5 U                      | 5                               | 4th                    | Dryness of eye |
| 6        | 2 weeks                       | 5 months                                     | -                        | 5                               | 3rd                    | Nil         |

Effects. A smaller number of cases was our major limitation; thus, a similar study in a larger number of cases is required to validate our conclusion.

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Conflicts of interest
There are no conflicts of interest.

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