Subconjunctival Botulinum Toxin Injection for Management of Upper and Lower Lid Retraction Associated with Thyroid Ophthalmopathy

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Abstract

Purpose: To evaluate the results and complications of subconjunctival botulinum toxin injections in the management of thyroid associated upper and lower lid retraction at Khatam-Al-Anbia eye hospital, Medical University of Mashhad.

Patients & Methods: In this prospective, non-comparative interventional case-series, 14 patients with lid retraction associated with thyroid eye disease were treated with one or more injections of Botulinum toxin into the proximal margin of the upper and lower tarsal plate, via a conjunctival approach. The goals of study were to reduce superior scleral show to less than 1 mm and decrease lower lid retraction. Main outcome measures were upper and lower lid response after Botulinum toxin injection, number of injections for controlling retraction during follow up and complications.

Results: Of 28 upper lids treated, 24 lids required only one treatment with achievement of less than 1 mm scleral show during follow up visits. Two lids required additional injection (in one patient for initially inadequate response and in another for recurrence during follow up).

Totally, we observed treatment failure (more than 1 mm scleral show after 3 upper lid injections) in two patients. Among twelve responsive patients, upper lid retraction was successfully controlled during follow up (Mean follow up was 7.6 months). No patient with initial satisfactory response became unresponsive during the study.

There was variability in the degree of reduction in lid retraction and duration of effect. It was also difficult to predict the time interval needed for re-treatment. The amount of lid lowering effect of injections varied among patients and lasted between 1 and more than 14 months (mean effect of each upper lid injection lasted 7.02 months). Mean reduction of palpebral fissure, levator function, superior scleral show and lower scleral show, were 3.28±1.80mm, 1.78±1.34mm, 2.46±1.07mm and 1.50±0.88±mm at the last visit respectively.

The procedure was well tolerated. No patient had diplopia or developed new motility problems, in particular hypotropia or superior rectus underaction in follow up visits. Two patients (3 eyes) experienced visually significant ptosis or chin up position lasting after 2 and 4 weeks. We experienced increasing corneal exposure and lagophthalmos in 16 of 21 eyes with lower lid treatment. In one of these patients, corneal ulcer developed.

Conclusion: Subconjunctival Botulinum A toxin injection provides an effective treatment for upper eyelid retraction associated with thyroid eye disease even in patient with long standing lid retraction. The treatment safely relieved symptoms and improved eye appearance as a temporary solution. Treatment of lower lid retraction was associated with high rate of lagophthalmos that led to corneal ulcer in one of our patient. By our experience, lower lid treatment is not recommended as routine in the case of lower lid retraction.

Key words: Upper Lid Retraction, Lower Lid Retraction, Thyroid Ophthalmopathy, Grave’s Ophthalmopathy, Subconjunctival, Botulinum Toxin, Dysport®.

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Introduction

The treatment of eyelid retraction is one of the challenging aspects in oculoplastics. Eyelid retraction often produces a look that is described as a stare with an accompanying illusion of exophthalmia. Retraction of the eyelids is a frequent accompanying feature of thyroid-associated ophthalmopathy. During early stages of the disease, lid retraction is secondary to a sympathomimetic response of the eyelid muscles. During later stages of the disease, there are a number of possible explanations. Lid retraction may be associated with proptosis or fibrosis in the superior rectus-levator palpebrae muscle complex or with contraction of the muscle complex countereacting a commonly existing fibrosis in the inferior rectus muscle.

The most severe consequences of lid retraction are derived from exposure of the cornea and the ocular tissue due to lagophthalmos. The severity of symptoms is related to the extent of corneal exposure, the ability of basic and reflex tearing to keep the cornea well lubricated, and the level of the patient's Bell's reflex. Because of visual threatening complication due to corneal exposure, treatment may be necessary in some patients. Conventional treatment is conservative or surgical. In conservative treatment, lubricating eye drops and ointments can be used for relief of symptoms in patients with lid retraction. For some patients this is not sufficient and they suffer from persistent symptoms of tearing, grittiness, photophobia and pain in addition to the staring eye appearance that maybe cosmetically unacceptable for the patient.

Persistent lid retraction may be adequately treated with eyelid surgery when the thyroid disease, eyelid retraction and the soft tissue disease are in a stable phase without significant soft tissue edema. During the active phase of the disease, surgical intervention is less effective, more unpredictable and may lead to complications. In addition, resolution may occur within one year of initiation of antithyroid treatment in about 50% of patients with eyelid retraction. Botulinum toxin type A, very potent neurotoxin acting at the motor end plate (neuromuscular junction) has many ophthalmic uses included in the management of idiopathic blepharospasm, strabismus, sixth nerve palsy, nystagmus, and entropion. A temporary ptosis is a well-recognized complication of strabismus and idiopathic blepharospasm treated with Botulinum toxin injections, possibly by diffusion of the toxin to the levator muscle. For patients with thyroid eye disease, Botulinum toxin injection has been used for treatment of strabismus, glabellar frown and refractory compressive optic neuropathy.

Scott et al suggested treatment of upper lid retraction resulting from Grave's ophthalmopathy as early as 1973 and reported three patients with thyroid eye disease and upper lid retraction treated with Botulinum toxin injection, demonstrating good results in two cases and temporary benefits in the third.

More recently, Jimmy et al reported eleven cases that were treated with subconjunctival Botulinum toxin injections and Shih and et al treated 15 cases with a single transcutaneous injection. We evaluated the benefits, safety and potential disadvantages of the treatment of thyroid associated eyelid retraction with subconjunctival Botulinum toxin injections into the upper and especially lower lid. It is first study that assessed the effect and complications of lower lid Botulinum injection.

Patients and Methods

In this prospective, interventional case series, 28 eyelids from 14 patients (ten female and four male) aged between 21 and 52 years with thyroid associated lid retraction were enrolled into the study from 2003 through 2005 (Table 1). The patients were euthyroid at the time of the study and had suffered from the thyroid associated bilateral lid retraction for duration of 3 months to five years (with mean of 26±17 months). No patients had history of ophthalmic surgery. Indications of treatment were cosmetic or exposure related symptoms including red eye, foreign body sensation and photophobia due to corneal exposure and dry eye (Table 1).

Prior to injection, a complete ophthalmic examination was performed, including visual acuity, measurements of vertical palpebral fissure and eyelid position in the primary position, levator function test, amount of Hertel's exophthalmometry, lagophthalmos,
ylation variables compared with protein.

LEAD® Technology, Inc. (Pro and post
possessed with SPSS software: Version 11.5
were completely stopped.

Exposure after lower lid injection, however,
showed no significant differences in protein
levels at the end of study, all other coclusions
were consistent with those of previous studies.

2. Materials and Methods

The dose administered depended on the
subject. The dose of each subject was applied
in the subcutaneous space at the lower lid
area, with the upper lid kept down. Prior to
the injection, a cotton tip applicator was
used to clean the subcutaneous space. The
subject was placed in a supine position. The
area was cleaned with alcohol, avoiding
infection. After the solution was administered,
the examination was repeated at one week, then
every 3 days and up to 12 months after
the injection.

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Table 2: The dose of Dysport® injections were adjusted with degree of retraction (scleral show) in primary position

<table>
<thead>
<tr>
<th>Scleral show</th>
<th>1 to 2 mm</th>
<th>2 to 3 mm</th>
<th>3 mm or more</th>
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<tbody>
<tr>
<td>Upper lid</td>
<td>10U²</td>
<td>15U²</td>
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<tr>
<td>Lower lid</td>
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Figure 1: Method of injections: For upper lid injection, with the patient looking down, upper eyelid was everted, two injections were applied, medially and laterally, into the subconjunctival space at the superior margin of the tarsal plate (injections were done superficially to avoid diffusion of toxin into orbicularis muscle). For lower lid injection, with the patient looking up, lower lid was everted, one injection was applied, centrally, into the subconjunctival space at the inferior margin of the tarsal plate.

Results

Fourteen patients (4 males and 10 females; mean age, 35.7 years) participated in this study. All the patients were euthyroid between 2-48 months (Mean=15±13 months). Onset of lid retraction was between 3 months to 5 years (Mean=26±17) [Table 1]. No patient had diplopia or motility problems before injections. The patients were followed up from 3 to 14 months (Mean=7.6 months) after treatment [Table 3].

Of 28 upper lids treated, 24 lids of required only one treatment with achievement of less than 1mm scleral show during follow up visits. Two lids required additional injection to satisfactory control of retraction (Patient #1 for initially inadequate response, re-treated 1 month after first injection (Figure 2), and patient #3 re-treated for recurrence during follow up).

Totally, we observed treatment failure (more than 1mm scleral show after 3 upper lid injections) in two patients (Patient #2 and #5) (Figure 3). Among twelve responsive patients, upper lid retraction successfully controlled during follow up. No patient with initial satisfactory response became unresponsive during study. There was variability in the degree of reduction in lid retraction. In addition, the amount of lid lowering effect of injections also varied between patients and lasted between 1 and more than 14 months (mean effect of each upper lid injection lasted 7.02 months). Prior to injection, the position of the treated upper eyelid was between 1 to 4 mm above the upper limbal margin. After injection, lowering of the eyelid or reduction of retraction occurred to varying degrees in the patients as summarized in Table 3.
Table 3: Patient lid position data before and after injections, complications and follow up time. The results varied between patients. 2 lids of two patients (#1 and 3) required additional injection to eliminate asymmetric lid position and achieve satisfactory lid position during follow up. Two lids were unresponsive after 3 injections. (Patient #2 and 5)

<table>
<thead>
<tr>
<th>Patient NO</th>
<th>Pre-injection visit</th>
<th>Site of injections</th>
<th>Additional injections</th>
<th>Complication / Duration of Complication</th>
<th>Last visit</th>
<th>FU</th>
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<tbody>
<tr>
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<td>PF (mm)</td>
<td>LF (mm)</td>
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<td>SS1 (mm)</td>
<td>SS2 (mm)</td>
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<td>R</td>
<td>15</td>
<td>15</td>
<td>7</td>
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<td>Both lids 1 times^ Lagophthalmos/ 6 months Lagophthalmos/ 1 months</td>
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<td>L</td>
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<td>7</td>
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<td>Both lids - Lagophthalmos/ 1 month</td>
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<td>R</td>
<td>13</td>
<td>16</td>
<td>6</td>
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<td>Upper lid - 2 time Lagophthalmos/ 1 month</td>
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<td>L*</td>
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<td>Upper lid - 2 time Lagophthalmos/ 1 month</td>
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<td>Both lids - Ptosis/ 2 week</td>
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In 11 cases (22 lids) treated for lower lid retraction, inferior scleral show was disappeared in 8 patients (16 lids) but as mention later, we did not re-treated unresponsive (except patient #1) or recurrent retraction. In patients with favorable response, lower lid retraction recurred only in 3 patients. In brief, favorable response observed in 63% of lids after one injection of Dysport® (10U) to inferior lid. Recurrence rate was low and equal to 18%.

Mean of palpebral fissure reduced from 15.21±1.44mm before injection to 12.21±1.52mm (P<0.00) at one month and 11.93±1.24mm (P<0.00) at the last visit. Mean of upper scleral show reduced from 2.7±0.71mm before injection to 0.36±0.78mm (P<0.00) at one month and 0.25±0.70mm (P<0.00) at the last following up. Mean of lower scleral show (in 16 cases with lower lid injection) reduced from 1.82±0.66mm before injection to 0.73±0.63mm (P<0.00) at one month and 0.32±0.56mm (P<0.00) at the last following up. In other word, Mean reduction of palpebral fissure, levator function, superior scleral show and lower scleral show, in order were 3.28±1.80mm, 1.78±1.34mm, 2.46±1.07mm and 1.50±0.80mm at the last visit. Table 4 summarized data that indicate treatment effects. All changes were statistically significant, according paired t-test (P<0.00).

Treatment was effective in all patients except two (Patient #2 and #5). The procedure was well tolerated. No patient developed eye deviation or diplopia after injections. In particular, hypotropia or superior rectus underaction did not detected in the follow up visits. Two patients (3 eyelids) experienced visually significant ptosis or chin up position lasting after 2 and 4 weeks (Figure 4). We experienced increasing corneal exposure and lagophthalmos in 16 of 21 eyes with lower lid treatment (Figure 2 and 3). Corneal exposure and lagophthalmos were not developed in patients without lower lid injection. Although lagophthalmos lead to corneal ulcer in one case (Patient #10), this complication resolved in other patients without any permanent sequel.

| Table 4: Mean values of palpebral fissure, levator function, upper scleral show and lower scleral show before and during follow up. All changes were statistically significant, according paired t-test (P<0.00) |
|---|---|---|---|---|
| Mean |
| Palpebral fissure | 15.21±1.44 | 12.21±1.52 | 11.93±1.24 | 3.28±1.80 |
| Levator function | 15.18±0.67 | 13.57±1.23 | 13.39±1.03 | 1.78±1.34 |
| Upper scleral show | 2.7±0.71 | 0.36±0.78 | 0.25±0.70 | 2.46±1.07 |
| Lower scleral show | 1.82±0.66 | 0.73±0.63 | 0.32±0.56 | 1.50±0.80 |
Figure 3: Patient #5: A: bilateral upper and lower lid retraction (pre-injection view). B: one week after bilateral upper and lower lid injections: dramatic response in right side, but there was no significant response in left upper lid. C: significant left lagophthalmos.

Figure 4: Patient #9: Bilateral ptosis 2 weeks after both upper lids injections.

Discussion
Several articles have been published on Botulinum toxin type A treatment for reduction of lid retraction in thyroid eye disease. The results of these reports vary significantly and we must consider some points in review of them. The inflammation and activity of thyroid ophthalmopathy and the amount of fibrotic process in the later stages both have dramatic effects on the result of Botulinum -therapy for lid retraction.

In this study in spite of overall favorite results, the amount of reduction of retraction with the same dose of Botulinum toxin type A varied between the patients, even bilaterally in the same patient (Figure 3). Explanations for these results include:

1. The anatomy of the lid retractors may be different between eyes. If Botulinum toxin did not reach to lid retractors, we could not expect palpebral change. In most of our patients (12 of 14) levator function changes didn’t exactly compatible with palpebral fissure height changes (they are not the same amount of reduction).

2. Although the same technique of injection was applied by the same person (Etezad M, the first author), subtle changes in the drug diffusion was unavoidable and it can lead to significant change in results because of neighboring of retractor and protractor. Paralysis of protractors (orbicularis oculi) is the important cause of lagophthalmos.

3. Degree of fibrosis, inflammation, edema and adhesions were not equal in all patients. In two patients
significant reduction of levator function didn't associate with reduction of palpebral fissure. Fibrosis could be the answer, especially, the duration of disease in these patients was more than the others.

4. It is difficult to measure eyelid position as a consequence of minute-to-minute variations in the patient's consciousness. So we can justify the measurements with multiple examinations.

We did not find any correlation between the amount of lid retraction and the effect of treatment. Severe lid retraction responded the same as milder forms by adjustment of the injection dose. The nine patients who had lid retraction for 2 years or more, responded well to treatment, with a satisfactory lid position at the last follow-up. Although, long history of lid retraction may increase the risk of fibrosis, our study showed that trying of Botulinum injection as a low risk treatment, is reasonable for long standing lid retraction. However, the responses in the two patients (#2 and #5) with more than 2 years (2 and 5 years) of thyroid disease appeared to be more resistant than the others (treatment failed in one of their lids).

The entire patients in our study were euthyroid; this may be effective to provide more successful results.

Several study evaluated the duration of effect of transcutaneous botulinum toxin injections. Adams et al[17] reported the time for complete recovery of the levator function after Botox® injection to be between three weeks and more than seven months (mean 8.1 weeks) on the non-TAO (Thyroid Associated Ophthalmopathy) patients. Biglan[18] reported full recovery after six months in TAO patients. Öszkan et al[19] observed a return of the eyelids to preinjection levels four to five months after the initial injection in TAO patients. We followed our patients until they needed re-treatment. The duration of the effect varied, lasting between 1 to more than 14 months. If patient response to first injection, we can expect average effect of 7.2 months for one injection. The temporary effect of injection has two advantages:

- The procedure was well tolerated and can be repeated easily.
- The complications such as ptosis are temporary too.
- Resolution of retraction may occur within one year of initiation of systemic antithyroid treatment in about 50% of patients with eyelid retraction [3], therefore, there is no need for long term effect (only one case of recurrence observed during 7.6 months follow up)

However, the degree of the lid retraction in thyroid eye disease may vary with time, and therefore in this study, the effects of treatment may be superimposed on the natural course of lid retraction. A randomized case-controlled study would be required to study this effect.

Favorable response observed in 63% of lids after one injection of Dysport® (10U) to inferior lid. Recurrence rate was low and equal to 18%. One can argue that lower lid retraction is consequence of exophthalmia. Interestingly in this study, all patients except one had Hertel exophthalmometry less than 22 mm. It showed that in addition to proptosis [1], the mechanisms similar to upper lid retraction are present in lower lid retraction.

The rate of complications of treatment was low and transient. No patient in this study developed diplopia but it should consider as a potential side effect. However, other study reported the low risk of inducing diplopia. Adams et al[17] noted a temporary superior rectus muscle weakness in 80% of the fifteen cases treated by transcutaneous injection into the levator muscle. Heyworth and Lee [20] reported permanent diplopia in three cases (out of 200 treated, hence 1.5%) after Botox® induction of protective ptosis. Mechanisms postulated for the permanent diplopia was not necessarily a non-reversible myopathic effect but more likely an occlusion induced breakdown of fusion or a constant muscle imbalance due to paralysis of the rectus superior muscle and co-contracture of the ipsilateral antagonist muscle. Latent deviations, which are very common among patients with thyroid eye disease, were considered a risk factor for irreversible eye muscle imbalance. In our study group none patient exhibited deterioration of superior rectus function. We cannot account for the reason for the low frequency of oculomotor problems in this high-risk patient group. Öszkan et al[19] hypothesize that TAO patients:
may possess a better barrier against the BTA
effect on the superior rectus secondary to
enlargement of the levator muscle and post-inflammatory adhesions to the
surrounding tissues. In addition, injection
using a subconjunctival approach has
advantage because more accurate and
reproducible placement of the Botulinum toxin
into the virtual space between levator and
Muller's muscles rather than of the relatively
blind placement transcmeos into the levator
region, which had been used in these studies.
Vision-impairing ptosis reported 0% to 40% in
different studies. In this study, the
prevention induced vision-impairing ptosis
observed in 2 patients (14%) (Figure 4). Uddin J
and Davies P used subconjunctival
approach and reported ptosis in 36% of
patients. The relative lower rate of ptosis
comparisons to other studies may due to dose-
adjustment according to amount of upper lid
retraction. Like other studies, we recommend
bilateral injection in the same patient at one
occasion for cosmetic purposes.
We did not find any other study that assessed
the effects and complications of lower lid
Botulinum injection. Although, single lower lid
injection is effective to eliminate lower lid
retraction, we do not recommend lower lid
injection as routine procedure because of high
rate (76%) of lagophthalmos and corneal
exposure. The side effects of lower lid
treatment, lagophthalmos and corneal
exposure may be due to crowded anatomic
space, less developed lower lid retractors and
easier diffusion of toxin anteriorly with
involvement of protractors (orbicularis oculi
muscles).
In brief, Botulinum toxin type A injection into
the upper eyelid retractors via conjunctiva is a
safe way to improve eye appearance and
reduce lid retraction for the patients with
thyroid eye disease especially in earlier
non-fibrotic stages of lid retraction. We believe
that injection using a subconjunctival
approach into the virtual space between
levator and Muller's muscles provide better
barrier against toxin diffusion than the
relatively blind transcutaneous method. In
addition, dose-adjustment according to
amount of upper lid retraction possibly avoid
under or over treatment. These may explain
higher rate of success and lower rate of
complications compare to other previous
studies.

Conclusion
Subconjunctival Botulinum A toxin injection
provides an effective treatment for upper
eyelid retraction associated with thyroid eye
disease especially in new onset lid retraction
and as a temporary solution. The treatment
safely relieved symptoms and improved eye
appearance.
Treatment of lower lid retraction associated
with high rate of lagophthalmos and corneal
exposure that led to corneal ulcer in one
patient. By our experience, lower lid treatment
is not recommended as routine in the case of
lower lid retraction.

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تزیروق زیر ملتحم‌های سم بوتولینوم A در درمان رترپکسیون پلك فوقانی
و تحتانی در پیماران مبتلا به افتالومیاتی نیروپلیدی

چکیده

هدف: بررسی تأثیر و عوارض زیر ملتحم‌های سم بوتولینوم A در درمان رترپکسیون پلك فوقانی و تحتانی در پیماران مبتلا به افتالومیاتی نیروپلیدی.

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مقدمه: در مدار کلی و در مواردی که درد زیادی را به رترپکسیون پلك فوقانی منجر می‌شود، درمان‌های غیر جراحی مانند استراکیز، آنتی‌بیوتیک‌ها و تزریق هیپنترکتورها ممکن است فعال نباشند. در این مقاله، به تزریق زیر ملتحم‌های سم بوتولینوم A در درمان رترپکسیون پلك فوقانی و تحتانی در پیماران مبتلا به افتالومیاتی نیروپلیدی و اثرات آن بر اسکلرال show، بخشیدن و حفظ قابلیت چشم‌پزشکی پیش‌بینی و تحلیل عوارض این تزریق پرداخته شده است.

مواد و روش‌ها: 14 پیمار مبتلا به رترپکسیون پلك فوقانی و تحتانی در زمان افتالومیاتی نیروپلیدی، تحت تزریق زیر ملتحم‌های سم بوتولینوم A در مراکز پزشکی و تحقیقاتی نموده تعداد تزریقهای مورد نیاز در مدت پیشگیری و عوارض مورد ارزیابی قرار گرفت. به کمتر از یک میلیمتر سبق در 3کیلولایر تزریق دیگر در مدت پیشگیری انجام شد. مجموعاً در 12 پیمار شکست درمایی (عدم باز پایه درمانی به سه زیرویی در هر یک از پلكهای فوقانی) مشاهده شد. در 12 پیمار یافته‌های مثبت کنترل شد. هیچ یک از پیمارانی که در ابتدا به درمان پاپس داده نبودند در مدت پیشگیری دچار شکست درمایی شدند.

نتیجه‌گیری: تزریق زیر ملتحم‌های سم بوتولینوم A برای درمان رترپکسیون پلك فوقانی و تحتانی در پیماران مبتلا به افتالومیاتی نیروپلیدی ممکن است به عنوان یک روش موثر و کم عوارض کسب شود. این تزریق ممکن است به عنوان یک روش موثر و کم عوارض کسب شود. در پیماران مبتلا به افتالومیاتی نیروپلیدی، تزریق زیر ملتحم‌های سم بوتولینوم A وعده‌های مثبتی را به خود برده و ضعف عضله ریناتور شکستگی و تشکیل نمود.

کلیات کلیدی: رترپکسیون پلك فوقانی، رترپکسیون پلك تحتانی، افتالومیاتی نیروپلیدی، افتالومیاتی بوتولینوم، تزریق زیر ملتحم‌های سم بوتولینوم A.