Review Article - Narrative Review

Taiwan J Ophthalmol 2024;14:548-553

Access this article online

Quick Response Code:

Website: http://journals.lww.com/TJOP

DOI: 10.4103/tjo.TJO-D-23-00043

Nonsurgical management of upper eyelid retraction in thyroid eye disease

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Abstract:

Upper eyelid retraction (UER) is the most common sign of thyroid eye disease (TED) and may result in lagophthalmos and exposure keratopathy. Measures to address UER are varied and include conservative treatment, surgical intervention, and injections of botulinum toxin, hyaluronic acid (HA) filler, and triamcinolone acetonide (TA). Our article will discuss the various nonsurgical aspects of managing TED-related UER, focusing on the injections of botulinum toxin, HA filler, and TA to the upper eyelid, which have all been reported to be effective in improving UER in both active and inactive states of TED. Individual response may vary, and repeated injections may be necessary.

Keywords:

Botulinum toxin injection, filler injection, periocular steroid injection, thyroid eye disease, upper eyelid retraction

Introduction

Upper eyelid retraction (UER) is a common clinical feature of thyroid eye disease (TED) and has been reported to be observed in about 90% of patients with TED.[1,2] Functional problems related to exposure of the ocular surface may arise, while some patients are most bothered by the cosmetic problems associated with UER.[3,4]

Measures to address UER include conservative treatment while waiting for spontaneous resolution, surgical intervention during the clinically inactive period,[5-16] and more recently, injections of botulinum toxin,[16-24] hyaluronic acid (HA) filler injection,[25,26] and triamcinolone acetonide (TA).[27-33] While surgical treatment remains an effective option, outcomes may be unpredictable, and reoperation rates are high.[34] In addition, there are some situations where surgery is inappropriate or contraindicated, where temporary or definitive measures are desired or required during the active phase of the disease, or where patients may prefer less invasive options.[34]

Our article will discuss the various nonsurgical aspects of managing TED-related UER, focusing on the injections of botulinum toxin, HA filler, and TA to the upper eyelid.

Upper Eyelid Retraction in Thyroid Eye Disease: Prevalence, Pathophysiology, and Natural History

Lid retraction is one of the most common signs of TED and a major diagnostic criterion for the disease.[35] It has been observed in more than 90% of the patients either unilaterally or bilaterally at some point during the course of the disease.[1]

Different mechanisms have been reported for UER due to TED. One mechanism is muscle hyperactivity in the active stage of the disease, where increased stimulation to the levator palpebrae superioris (LPS) – superior rectus muscle

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Submission: 28-03-2023
Accepted: 07-04-2023
Published: 23-05-2023

How to cite this article: Young SM, Kim YD, Woo KI. Nonsurgical management of upper eyelid retraction in thyroid eye disease. Taiwan J Ophthalmol 2024;14:548-53.

complex and the Müller's muscle to overcome the restriction of the inferior rectus muscle and to maintain the vertical eye alignment may lead to a UER.[36-40] Müller's muscle hyperactivity due to the sympathetic activity of thyroid hormones is another mechanism that leads to temporary lid retraction in patients with poor metabolic control in the early stages of the disease.[6,36] Reduced tone of the orbicularis oculi muscle with a reduced number of muscle fibers may also contribute to retraction by causing a relative levator muscle overaction.[41] In the inactive stage of TED, the fibrosis of the LPS and Müller's muscle following inflammation and the formation of cicatricial bands between LPS and the surrounding tissues is the main reason for retraction named under the cicatricial or restrictive theory.[42] Mechanical retraction of the eyelids secondary to extreme proptosis has also been reported as a contributing factor.[43]

The natural course of UER has not been well documented. In general, the natural history of TED itself has been poorly documented, especially in patients with moderate-to-severe disease, since these patients require specific disease-modifying therapies, which subsequently affect its outcome.[44] Much of what we know about the natural history of TED is based on old studies which mainly measured exophthalmos.[45-50] The most well described course of TED is that of the Rundle's curve. Described by Rundle decades ago, an initial progressive deterioration occurs for 6-24 months, reflecting the autoimmune process (dynamic active progressive phase), after which a plateau is reached. Thereafter a phase of spontaneous slow improvement (static phase) ensues, which may last for > 12 months and is characterized by regression of the inflammatory process and development of fibrosis.

Since Rundle's publication more than 60 years ago, there has been little on the description of the course of UER except for a recent study by Lee *et al*.,[51] which showed that TED-related UER spontaneously improves in approximately 70% of patients by 12 months and 75% of patients by 24 months. In addition, UER normalizes in approximately a third of patients by 12 months and half of the patients by 24 months. Certain factors such as the family history of TED, smoking history, gender, and age affect this likelihood.

Early Medical Treatment of Upper Eyelid Retraction in Thyroid Eye Disease

The first attempt to control UER in TED medically was during the 1960s, when it was demonstrated that topical administration of adrenergic blocking agents like guanethidine reduced retraction.[52] This treatment had limited success due to drug side effects such as vasodilatation, irritation, and ocular irritation and discomfort.[53] The drug, useful only in the mild forms of TED-related UER, was poorly tolerated and is no longer administered.[36]

Botulinum toxin injection

Botulinum toxin A (BTA) is a potent agent used for chemodenervation in TED, which causes paralysis of the LPS by inhibiting acetylcholine release from the motor end plates.[24,54] BTA has many ophthalmic uses included in the management of idiopathic blepharospasm,[55] strabismus,[56] sixth nerve palsy,[57,58] nystagmus,[59] and entropion.[60] Temporary ptosis is a well-recognized complication of strabismus and idiopathic blepharospasm treated with BTA injections, possibly by diffusion of the toxin to the levator muscle.[61] Botulinum toxin injections have also been injected into the upper lid through a percutaneous approach to lower the upper lid deliberately, creating a protective ptosis in the treatment of corneal disease.[62,63]

The use of BTA for the treatment of UER resulting from TED started as early as 1973 when Scott reported three patients with TED and UER treated with BTA, demonstrating good results in two cases and temporary benefits in the third.[64,65] Since then, BTA injection for weakening the LPS and inducing myogenic ptosis has been used as a nonsurgical approach in patients with UER due to TED. Ebner[18] reported the use of repeated single subcutaneous injection of botulinum toxin type A (BTTA) in six patients with dysthyroid eyelid retraction to induce upper lid lowering, with acceptable cosmetic results in five patients. Biglan[66] (two patients) and Ozkan *et al*.[20] (four patients) reported a total six of cases with dysthyroid UER that were treated with BTA injections with encouraging initial results. Injections were into the area of the levator complex, through the skin, without myographic control, as described by Adams *et al*.[63]

In contrast, Uddin and Davies[21] reported that their results from BTA injection using a subconjunctival approach were more effective than previously reported, which may be the result of the more accurate and reproducible placement of the BTA onto the levator and Muller's muscles rather than of the relatively blind placement percutaneously into the levator region, which had been used in previous studies.[18,20,66] Similarly, Morgenstern *et al*.[19] agree that the transconjunctival approach to injection may allow for more predictable results by increasing the effect on Muller's muscle and decreasing any undesirable weakening of the orbicularis muscle compared with a percutaneous approach. Another advantage with the transconjunctival approach purported by Uddin and Davies[21] is the reduced risk of motility problems in contrast to the percutaneous approach (Heyworth and Lee[67] reported persistent hypotropia when using the

percutaneous approach for the induction of protective ptosis). An explanation for the lack of superior rectus involvement may be that subconjunctival injections are in the region of the levator aponeurosis as it inserts onto the tarsal plate of the upper lid, which is anatomically distinct from the superior rectus; whereas when the percutaneous approach is used, the BTA is placed further back in the orbit where the levator muscle and superior rectus share a common sheath.

BTA seems to work in both the active and fibrotic phases of the disease. Morgenstern *et al*.[19] investigated the efficacy of BTA injection during the active inflammatory stage and suggested that BTA injection prevented fibrosis and allowed a more symmetrical and functional upper eyelid position without surgery. Costa *et al*.[23] compared the findings of patients in the inflammatory stage and those in the fibrotic stage after BTA injection, and found a higher average reduction of eyelid height in patients with fibrotic stage than in patients with a congestive stage at 2 weeks and 1 month after treatment. They also demonstrated that the BTA effect lasted longer in patients with fibrosis and explained it by the increased drug absorption due to increased vascular circulation in the congestive stage leading to a reduced local effect of BTA. Ozturk Karabulut *et al*.[24] included only patients in the fibrotic phase to avoid any misinterpretation of the findings related to fluctuations in eyelid position correlated to the disease activity and a possible spontaneous resolution.

Interestingly, recent studies identifying the effects of botulinum toxin on smooth muscle confirm that although botulinum toxin is more specific for cholinergic neuromuscular junctions found in the striated muscle, there is evidence to suggest a relaxing effect for smooth muscle.[68-70] Therefore, the eyelid-lowering effect may be primarily due to alteration in the Müller's muscle rather than the levator muscle.

In summary, chemodenervation with BTA injection may be an alternative adjunctive therapy in the treatment of inflammatory and fibrotic TED-related UER. Individual response to BTTA for treatment of eyelid retraction is variable, and side effects include temporary ptosis and diplopia.

Hyaluronic acid filler injection

The use of HA filler for UER has recently been gaining popularity.[71] HA fillers have many favorable characteristics that make it a popular injectable filler device. Its minimal immunogenicity and relative ease of use have helped HA become the most commonly used injectable filler today.[72] They have been recently expanded in their use from cosmetic soft tissue augmentation to more functional purposes, including the management of cicatricial ectropion, congenital eyelid malpositions, and paralytic lagophthalmos.[73-76] In addition, a few studies have shown HA to be useful in ameliorating both upper and lower eyelid retraction due to TED and other causes.[25,26,75,77]

The effect of HA fillers on UER is likely due to the mechanical effect of HA, similar to how it improves lower scleral show and provides elevation of the lower eyelid by adding volume and expanding the local tissue.[77] In the upper lid, HA was found in a variety of anatomical sites in the perilevator region after subconjunctival injection, mostly in the preaponeurotic space.[25] In this position, it can change shape with the movement of the eyelid and may decrease friction when interacting with the adjacent tissues or other HA aliquots. This bursa-like effect may be an important mechanism for the increased eyelid excursion and improved eyelid position after HA injection.[25]

In a study by Mancini *et al*.,[26] HA injection in the upper eyelid was found to improve asymmetry relating to relative UER of diverse etiology (three out of eight were due to TED). There was a statistically significant improvement in symmetry, which was sustained at 4–8-month follow-up. Of note, the average amount injected in the eyelid was 0.2 ml (range: 0.1–0.4 ml), lower than Young *et al*.'s[71] mean amount of 0.5 ml, which the latter postulated may be due to thinner Caucasian eyelids requiring less filler weight than the heavier and thicker East Asian eyelid. In contrast, Kohn *et al*.'s[25] study on HA filler for TED-related UER reported an average of 0.45 ml required (range: 0.2–0.7 ml), which is similar to Young *et al*.'s[71] study, suggesting that TED-related UER may require more filler than UER due to other mechanisms.

Young *et al*.'s[71] study confirms that the effects of HA in the treatment of UER are most evident immediately after the injection, as the greatest decrease in margin reflex distance 1 (MRD1) and upper scleral show occurred in the early period after injection.[78] In Kohn *et al*.'s[25] prospective pilot study, an average MRD1 reduction of 1 mm 1 month following HA injection was achieved, with the persistence of this effect for an average of 15 months. Compared to Kohn *et al*.'s[25] study, Young *et al*.[71] showed a greater mean decrease in MRD1 of approximately 2 mm after a single injection of HA filler.

Studies have found that the eyelid-lowering effect after HA injection was sustained for many months after injection, even up to 78 months.[25,71] This could be partially explained by the fact that HA filler lasts longer in the periorbital region, localization of the HA gel in the levator aponeurosis, as well as the natural history of TED-related UER, which has been shown to improve spontaneously with time.[44,71]

There are several reported advantages to HA fillers: they allow for precise placement and control, and they are usually reversible with hyaluronidase.[71] They also seem to have a long-lasting effect, at least in the upper lid. The prolonged retention beyond the manufacturer's claim may be attributed to the high deformation characteristic of the cross-linked HA fillers.[79] Their long-lasting effect may also be the reason for the persistent lumpiness in the upper lid in some patients, especially noticeable on downgaze.[71] This relatively more common, albeit minor, side effect of HA filler should be explained to patients before injection.

Triamcinolone injection

Glucocorticosteroid therapy is a well-established method for the treatment of TED due to its anti-inflammatory and immunosuppressive actions.[80] Triamcinolone is an intermediate-acting glucocorticoid. The addition of a fluorine group in the molecule increases the anti-inflammatory activity, which is five times more potent than an equal weight of hydrocortisone. Brand names of triamcinolone formulations include Aristospan, Clinacort, Kenalog-10, and Kenalog-40. TA is relatively insoluble and slowly absorbed. Its extended duration of action lasts for several weeks. Previous studies on TA injection have shown TA injections to be effective in reducing UER in TED.[27-33]

The proposed mechanisms of action of TA injection on TED-related UER include anti-inflammatory effect on the levator and Müller's muscle, steroid-induced myopathy, degenerative change in the levator muscle, detachment of the levator aponeurosis from the tarsal plate, or steroid-induced atrophy of the Müller's muscle.[81,82]

Young *et al*.[33] found that TA injection was effective in reducing eyelid retraction and inflammatory signs. The mean improvement in MRD1 from the initial to 1-month follow-up was 0.8 mm. This improvement was sustained with continued follow-up visits with an overall mean improvement of 2.1 mm in MRD1 from the initial to final follow-up. This is comparable with that reported by other studies, including Xu *et al*.,[28] who reported a mean MRD1 reduction of 2.19 mm over a follow-up of 6–27 months, and Lee *et al*.,[29] who reported a mean MRD1 reduction of 0.6–1.1 mm over a mean follow-up of 6 months. Some of these patients received multiple injections, signifying that repeated injections may be necessary for optimal control.

Some studies indicate that TA injection might be more beneficial for patients with UER in the congestive phase of TED.[27-32] Lee *et al*.[29] found more profound improvement in the active group (86.3%) compared with the inactive patients (25%). Young *et al*.[33] compared the effect of TA injection on both active and inactive groups and found similar success in the reduction of eyelid retraction.

One of the most common complications related to TA injection reported is intraocular pressure (IOP) elevation, with the prevalence ranging from 4% to 20%, reinforcing the importance of IOP monitoring at initial and follow-up visits for patients undergoing TA injection.[28-33] In all articles, IOP normalized with antiglaucoma medication, although the period of medication use varied from 1 to 12 months. No mention of permanent glaucomatous damage was reported in any of the studies. Other complications reported after TA injection are ptosis, menstrual cycle disturbances, and development of moon face, the latter both of which resolved 3–6 months after injection.[28,30,33]

Summary

There has been increasing use of nonsurgical methods to address UER, whether as an adjunct to other therapy or as a primary treatment to TED. These include injections of botulinum toxin, filler, and steroid. There are no studies comparing the various injection types. They all appear to be effective in improving UER in both active and inactive states of TED. Individual response may vary, and repeated injections may be necessary.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Yoon-Duck Kim, an editorial board member at *Taiwan Journal of Ophthalmology*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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