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CLINICAL STUDY

A single transcutaneous injection with Botox® for dysthyroid lid retraction

M-J Shih[1], S-L Liao[2] and H-Y Lu[1]

Abstract

Purpose **To evaluate the safety and efficacy of injections with botulinum toxin type A (BTTA, Botox®), given transcutaneously, in the treatment of upper lid retraction associated with thyroid eye disease (TED).**

Methods **A total of 15 patients (21 eyes) with a stable (TED) condition, and a euthyroid state, were enrolled into the study. There were 12 females and three males from ages 23 to 52 years. A single injection, at the centrally superior tarsal border transcutaneously, aiming at the levator aponeurosis and Müller muscle, was administered into each eyelid with 5–6 U of Botox®. All patients were followed regularly for 4–6 months. Any complications, such as ptosis, diplopia, pain, or lid ecchymosis were recorded.**

Results **All patients, except one, experienced much reduction of palpebral fissure. The mean difference of MRD_1 between pre- and postinjections of Botox® at the first week was −3.1 mm, and the effect remained, at least, for 2 months. There were temporary complications of ptosis in three patients and vertical diplopia in two patients, lasting 3–4 weeks.**

Conclusions **A single transcutaneous injection with Botox® for the treatment of thyroid lid retraction is safe and effective. Some minor complications may occur, such as ptosis and diplopia; however, it may offer an alternative and temporary method for patients with dysthyroid lid retraction, who are waiting for a staged operation of either an orbital decompression or a strabismus surgery or both.**

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[1]Department of Ophthalmology Shin-Kong Wu Ho-Su Memorial Hospital Taiwan

[2]Department of Ophthalmology National Taiwan University Hospital Taipei, Taiwan

Correspondence:
S-L Liao
Department of Ophthalmology
National Taiwan University Hospital
7 Chung-Shan S. Rd
Taipei, Taiwan
Tel: +886 23620555;
Fax: +886 23632430
E-mail: lang89@ha.mc.ntu.etu.tw

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Introduction

The clinical characteristics of thyroid eye disease (TED) include soft-tissue swelling, lid retraction, proptosis, restrictive myopathy, and compressive optic neuropathy. Among these manifestations, eyelid retraction in TED is the most common sign, where 25–50% of thyroid disease patients may have ocular complications. Of this group, 90% of these patients may have lid retraction at some point during their clinical course.[1] The mainstay for the management of upper lid retraction in TED is either by observation or surgical techniques. This depends on the severity of corneal involvement. Surgery by recession of the levator aponeurosis, Müller muscle or both[2] or Müllerectomy should be postponed for 6–12 months until the disease activity is stabilized. Another surgical deliberation is the management of lid retraction, where it should be deferred by an orbital decompression or a strabismus surgery.[3] Patients with an extreme degree of thyroid lid retraction may suffer from keratitis during this long period of exposure. Some nonsurgical alternatives to treat thyroid lid retraction have been postulated, such as, guanethidine, a topical adrenergic blocker.[4] These postulations were abandoned owing to the intolerable side effects. Chang *et al*[5] and Kung *et al*[6] reported the effects in the treatment of TED using somatostatin or prednisolone; however, the height of palpebral aperture did not dramatically decrease. Scott[7] first demonstrated the use of botulinum toxin type A (BTTA) for the treatment of thyroid lid retraction. This conjecture derives from the management of strabismus and blepharospasm, which is relevant to a possible ptosis complication.[8] Some authors[9, 10] reported the successful induction of nearly complete ptosis in patients with indolent corneal ulceration; however, a major side effect of weakness in the

superior rectus muscle was noted. Several reports[11–14] illustrated the effects of injections with BTTA in thyroid lid retraction; nevertheless, there were some variations between them, including the method of dispensation, optimal dosage, and rate of complications. We present our results of treatment with BTTA injections for thyroid lid retraction and compare the outcome with the previous literature.

Materials and methods

From February 2002 through January 2003, a total of 15 patients (21 eyes: 12 bilateral and nine unilateral) with thyroid lid retraction, who were confirmed to be in a stable TED state, were objectively evaluated using a marginal reflex distance (MRD), exophthalmometry, and given a clinical activity score (CAS).[3] The patients, who were enrolled into this study, were also evaluated to be in a euthyroid state for, at least, 6 months by T3, T4 and TSH serological testing. There were 12 female and three male, patients, whose ages were from 23 to 52 years. We objectively measured the degree of upper lid retraction by documenting the distance from the corneal light reflex to the upper lid margin (MRD_1) in the primary position. The extraocular movement was also checked before and after injections of BTTA. All the patients were informed about the benefits and possible side effects of injection with BTTA (Botox, Allergan, Inc., Irvine, CA, USA). Informed consent was obtained.

We reconstituted the Botox® solution using 1 cm^3 unpreserved normal saline, yielding a concentration solution of 1 U/0.01 cm^3. Using a 0.3 or 0.5 cm^3. commercially manufactured insulin syringe, a single transcutaneous injection at the centrally superior tarsal border, aiming at the complex of levator aponeurosis and Müller muscle under the protection using an eye shield, was administered into each eyelid with 5–6 U (0.05–0.06 cm^3, 5–6 U as shown in the scale of the insulin syringe) (Figure 1). There was no supplement of local anaesthesia. After injections of Botox®, all the patients were regularly followed up from 4 to 6 months. Any side effects, including ptosis, diplopia, pain, ecchymosis, or ocular discomfort, were recorded.

Figure 1 Under protection using an eye shield, a single transcutaneous injection at the centrally superior tarsal border was administered into each eyelid, aiming at the complex of levator aponeurosis and Müller muscle.

Results

Most patients, except one, experienced much improvement of the upper eyelid retraction (Figure 2). The mean difference of MRD_1 between pre- and postinjection of Botox® at the first week was –3.1 mm (range, 0 to −8 mm) after a single dose injection (Table 1). An additional 4 U (0.04 cm^3) of Botox® was administered to the eyelid with a meagre response a week after, and the patient was satisfied with the end result (Table 1, patient 10, left eye). All the patients achieved maximal improvement of lid retraction within 1 week, which

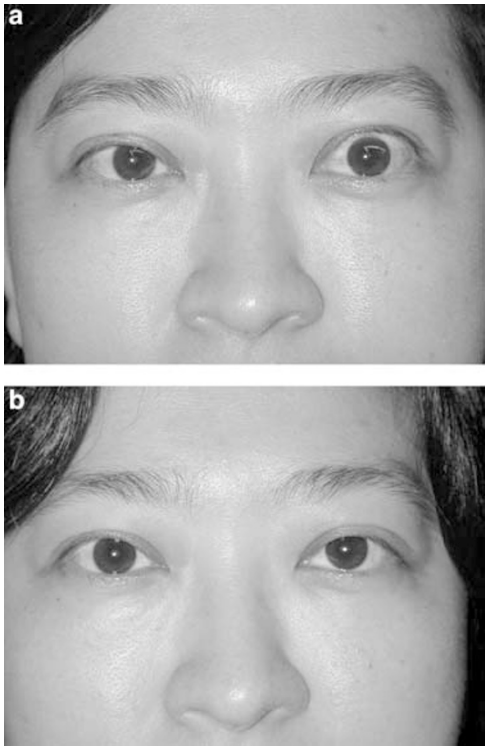

Figure 2 Much improvement of palpebral fissure was demonstrated in the left eye between (a) preinjection and (b) postinjection of Botox®.

Table 1 Results of all patients, including pre-, postinjection of Botox® in MRD_1, differences of MRD_1, dosage of Botox®, and complications

Case	*Side*	*MRD_1 (preinjection, mm)*	*MRD_1 (postinjection, mm)*	*Differences of MRD_1 (mm)*	*Dosage (U)*	*Ptosis*	*Diplopia*
1	R	8	5	−3	5		
	L	8	6	−2	5		
2	R	7	—[a]	—[a]	5	Complete for 1 month	
3	L	8	6	−2	5		
4	L	7	4	−3	5		
5	R	9	4	−5	6		
6	R	7	4	−3	6		
7	R	7	4	−3	5		(+)[c]
8	L	7	0	−7	6	Partial for 20 days	(+)[c]
9	R	7	3	−4	6		
	L	7	5	−2	6		
10	R	8	5	−3	5		
	L[b]	9	9	0	5+4		
11	R	8	6	−2	6		
	L	8	5	−3	6		
12	R	8	0	−8	5	Partial for 3 weeks	
	L	8	4	−4	5		
13	L	7	4	−3	5		
14	L	7	4	−3	5		
15	R	8	5	−3	5		
	L	7	5	−2	5		

[a]Complete ptosis.
[b]Additional 4 U of Botox® were administered to the left eye of Patient 10 owing to the meagre response.
[c]Two patients (Nos. 7 and 8) with transient vertical diplopia, which resolved within 20 days.

Figure 3 The same patient suffered from an incomplete ptosis in the left eye noted at the first follow-up postinjection of Botox®; however, the condition resolved completely and spontaneously, shown in Figure 2b, within 1 month.

remained at least for 8 weeks. There were three patients with complications of ptosis, one complete and two incomplete; nonetheless, these disappeared spontaneously within 1 month (Figure 3). Two patients suffered from transient vertical diplopia for 20 days after the injection of Botox®. We noted that there are some variations of response to Botox® injection in patients with a similar degree of lid retraction. There were no patients complaining of pain or lid ecchymosis after injection. After a regular monthly follow-up, all the patients recovered to the pretreated level of lid retraction before the fifth month postinjection of Botox®.

Discussion

We report the effects of Botox® injection transcutaneously with a single dose for patients with dysthyroid lid retraction, who remained in a stable ophthalmic condition and a systemically euthyroid state. There were fewer complications of ptosis and vertical diplopia in this study compared to those in other studies.[11–14] Details are shown in Table 2. From previous studies, we noted more patients with complications of ptosis or vertical diplopia with injections of Botox® underneath the superior orbital rim, which is anatomically located near the levator palpebrae superioris, and the common sheath of the levator palpebrae superioris and the superior rectus muscle. To avoid these complications from occurring, it is suggested that the site of injection should be in close proximity to the insertion of the levator aponeurosis and Müller muscle.

Although the response of patients with thyroid lid retraction to Botox® injection varies, we believe that a single dose of 5 U of Botox® solution is enough for most patients with a moderate-to-severe degree of lid retraction. Several repeated injections of Botox® in

Table 2 Comparison of results of several reports using BTTA in the treatment of thyroid lid retraction

Authors	*Number of eyes*	*Route of injections*	*Dosage (U)*	*Duration (months)*	*Side effects (number of complications)*
Ebner (1993)	7	Transcutaneous, at the superior tarsal border	2.5–7.5	1–8	Ptosis (3)
Biglan (1994)	4	Transcutaneous, aiming at the levator palpebrae superioris	5	3–4	Ptosis (1)
Ozkan et al (1997)	8	Transcutaneous, beneath the orbital roof	2.5–7.5	3–4	Ptosis (5)
Uddin et al (2002)	16	Subconjunctival, two points of superior tarsal border	10–15[a]	1–40	Ptosis (4) Diplopia (3)
Present studies	21	Transcutaneous, at the centrally superior tarsal border	5–6	2–4	Ptosis (3) Diplopia (2)

[a]Several repeated injections were needed.

meagre response of patients, in previous reports, may contribute to the site of injection rather superficially. Either transcutaneous or subconjunctival injection[14] of Botox® can be performed; however, we deem that the eversion of the upper eyelid may produce more discomfort for patients. As ophthalmopathy can be aggravated by an unstable thyroid state, prevention or correction of both hyper- and hypothyroidism is essential. This is the reason for our choice of patients with lid retraction in a euthyroid state instead of patients in a systemically acute inflammatory stage. Similarly, we also did not include patients with an unstable ophthalmic condition because during the clinical course of TED, fluctuation of disease activity is more common in an acute stage. Premature injection of Botox® may result in more arbitrary results, and a spontaneous resolution in lid retraction may also be masked by the injection of Botox®. The possible mechanism of thyroid lid retraction is a combination of early inflammatory and late fibrotic factors. We do not think that there is any permanent effect with the administration of Botox® to a thyroid lid retraction, at an ophthalmically acute inflammatory stage, because it does not change the environment of inflammation.

The effects of Botox® are temporary and the duration is about 2–4 months, as we learn in our study. Although the pharmacological mechanism of Botox® is the inhibition of the presynaptic release of acetylcholine at the neuromuscular junction, we found that there is still a response upon injection of Botox® to the levator aponeurosis, but not to the muscle itself. This may produce an optimal palpebral height with no obvious complication of ptosis.

Conventionally, patients with thyroid lid retraction require a waiting period before lid surgery correction. This waiting period may include either an orbital decompression or a strabismus surgery, or both. Therefore, there is a long period of time for them with a disfiguring lid appearance. Although there are various responses between inter- or intra-patients after injection, it may offer an alternate method for patients during a staged operation because the administration of Botox® to thyroid lid retraction is rather safe and effective with little complication.

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