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Clinical short communication

Apraclonidine in the treatment of ptosis

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ABSTRACT

Transient ptosis is a known complication of botulinum toxin (BoNT) injection due to inadvertent migration of toxin into the levator palpebrae superioris muscle. Currently there is no treatment available for BoNT induced ptosis. Apraclonidine hydrochloride is a topical ophthalmic solution with selective alpha-2 and weak alpha-1 receptor agonist activity that has the ability to elevate the eye lid. Apraclonidine has been used as a diagnostic test in Horner's syndrome. We evaluated the effects apraclonidine in a cohort of BoNT induced ptosis and a patient with Horner syndrome. Each patient was administered 2 drops of apraclonidine 0.5% solution to the eye with the ptosis and was re-examined 20–30 min later. All 6 patients showed improvement in ptosis. There was also improvement in ptosis in a patient with Horner's syndrome. Apraclonidine is not only useful as a diagnostic test in Horner's syndrome, but may be an effective and safe treatment for BoNT-induced ptosis.

1. Introduction

Ptosis is a manifestation of a variety of neurological and medical conditions. Transient ptosis is also a known complication of botulinum toxin (BoNT) injection used to treat blepharospasm due to inadvertent migration of toxin into the levator palpebrae superioris muscle. Apraclonidine hydrochloride is a topical ophthalmic solution with selective alpha-2 and weak alpha-1 receptor agonist activity and an elimination half life of 8 h. Apraclonidine 0.5% is used as a short-term adjunctive therapy in patients with glaucoma who are already taking maximally tolerated medical therapy that requires additional intra ocular pressure reduction [1,2]. Apraclonidine 1% solution is currently approved for the prevention and treatment of post-operative elevation in intraocular pressure following procedures such as argon laser trabeculoplasty and argon laser iridotomy.

In addition to reducing intraocular pressure, apraclonidine has the ability to elevate the eyelid due to its effect on the superior tarsal or Müller muscle which are smooth muscles innervated by sympathetic nerves. Although formal studies are lacking, this unique action may have a utility in clinical practice to treat ptosis following BoNT injection. Additionally, apraclonidine dilates a miotic pupil in the setting of sympathetic denervation and has been proposed as a diagnostic test in Horner's syndrome [3]. We describe the results of a cohort of patients with BoNT-induced ptosis and their response to apraclonidine.

2. Methods

The study was conducted at the Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, Texas. Patients with ptosis following BoNT injection and a single patient with suspected Horner's syndrome were included in the study. Each patient was administered 2 drops of apraclonidine 0.5% solution to the eye with the ptosis and was re-examined 20–30 min later. All patients were videotaped before and after the administration of apraclonidine. Video recordings, obtained after a signed consent form (approved by the Institutional Research Board for Human Research, Baylor College of Medicine), were randomized and rated by a neurologist "blinded" to which video segment was before or after the administration of apraclonidine. The degree of ptosis prior to administration was rated 1 = mild eye lid droop < 25% of the palprebal fissure; 2 = moderate eye lid droop 26–50% of the palprebal fissure; 3 = severe eye lid droop >50% of palprebal fissure; 4 = complete (100%) ptosis. The degree of improvement following apraclonidine was rated as 0 = no improvement; 1 = mild improvement, ≤25% improvement in ptosis; 2 = moderate improvement, 26–50% improvement in ptosis; 3 = marked improvement, ≥50% improvement in ptosis; 4 = complete resolution.

3. Results

Six patients (4 female) with BoNT-induced ptosis with a mean age of 53 years (range: 17–73 years) were included in the study (Table 1). All 6

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Table 1
Demographic data of patients with Onabotulinum toxin A (BOTOX) induced ptosis and Horner's syndrome.

Patient	Age/sex	Diagnosis	Clinical information	Severity of ptosis prior to apraclonidine	Degree of improvement after 0.5% apraclonidine
1	70 Male	BoNT-induced ptosis	Indication for BoNT injection: blepharospasm. He was injected 50 units to each corrugator, 50 units to each upper pretarsal orbicularis oculi, 15 units to each lower pretarsal orbicularis oculi muscles. Developed left eye ptosis.	1 = Mild	3 = Marked
2	71 Female	BoNT-induced ptosis	Indication for BoNT injection: cranio-cervical dystonia. She was injected 20 units to each brow area. Developed left eye ptosis.	2 = Moderate	3 = Marked
3	73 Female	BoNT-induced ptosis	Indication for BoNT injection: blepharospasm. She was injected 30 units to each upper pretarsal orbicularis oculi (lateral), 10 units to each lower pretarsal orbicularis oculi muscles. Developed left eye ptosis.	1 = Mild	4 = Complete
4	17 Female	BoNT-induced ptosis	Indication for BoNT injection: eye blinking tics in Tourette syndrome. She was injected 10 units to each upper pretarsal orbicularis oculi muscles. Developed right eye ptosis.	3 = Severe	3 = Marked
5	38 Male	BoNT-induced ptosis	Indication for BoNT injection: eye blinking tics in Tourette syndrome. He was injected 10 units to each upper pretarsal orbicularis oculi muscles. Developed right eye ptosis	1 = Mild	4 = Complete
6	47 Female	BoNT-induced ptosis	Indication for BoNT injection: left sided hemi-facial spasm. She was injected 20 units to the left brow area, 25 units to the upper pretarsal orbicularis oculi, 20 units to the lower pretarsal orbicularis oculi muscles. Developed left eye ptosis.	2 = Moderate	3 = Marked
7	53 Female	Horner's syndrome	Presented with drooping of the right eyelid for over 6 months duration. Examination showed right partial ptosis, right miosis and the clinical diagnosis was right Horner's syndrome.	1 = Mild	4 = Complete

BoNT = botulinum toxin.

patients showed improvement in ptosis. There were 3 patients with mild ptosis: one showed marked improvement and 2 showed complete or near complete improvement in ptosis. There were 2 patients with moderate ptosis: both showed marked improvement in ptosis. There was one patient with severe ptosis who showed marked improvement in ptosis. There were no adverse effects. Patient 7 (Fig. 1, D1, Table 1) with partial ptosis and miotic pupil showed complete resolution of partial ptosis and dilatation of the pupil 20 min after application of apraclonidine which helped to confirm the diagnosis of Horner's syndrome. Despite extensive diagnostic evaluation, no etiology of her Horner's syndrome was found. She had used apraclonidine once or twice a day intermittently to control her ptosis for the next 2 months without any adverse effect.

4. Discussion

Apraclonidine effectively improved ptosis in all six patients with BoNT-induced ptosis and it also improved partial ptosis in the patient with Horner's syndrome (Table 1 and Fig. 1). Elevation of the eyelid normally results from a combined action of two muscles namely, *levator palpebrae superioris* and *superior tarsal or Müller muscle*. *Levator palpebrae superioris* is a skeletal muscle innervated by the oculomotor nerve which elevates and retracts the upper eyelid. On the other hand *superior tarsal muscle* is a smooth muscle innervated by sympathetic nerve and its primary action is to keep the upper eyelid raised after the *levator palpebrae superioris* has raised the upper eyelid. Apraclonidine likely reversed the ptosis by stimulating contraction of the *superior tarsal muscle* elevating the upper eyelid by 1–3 mm due to its alpha-2 agonist action [4,5]. In Horner's syndrome, the resolution of ptosis by apraclonidine may be facilitated by denervation hypersensitivity of alpha-2 receptors in the *superior tarsal muscle* [6,7].

Transient ptosis, due to inadvertent migration of toxin into the levator palpebrae muscle, is a known complication of BoNT injection into orbicularis oculi muscle in patients with blepharospasm. Upper lid ptosis typically occurs in <25% of all patients but may be observed up to half of all patients during their course of BoNT treatment for blepharospasm [8–10]. The risk of ptosis can be minimized by injecting lateral and medial to the mid-pupillary line, with the needle pointing away from the midline to prevent the toxin from diffusing into the *levator superioris muscle* [11,12].

Currently there is no treatment available for BoNT-induced ptosis and typically the patient has to wait several weeks, before the effects of the toxin wear off for the ptosis to spontaneously improve or use "eyelid crutches" to elevate the upper eyelid [13,14]. Apraclonidine has been reported to be used in the cosmetic industry for BoNT induced ptosis, but except for a few case reports it has not been assessed in formal clinical trials [11,15]. The use of apraclonidine in blepharospasm was recently reported [16].

Horner's syndrome occurs as a result of interruption of the sympathetic innervation to the eye and typically presents with miosis, partial ptosis and facial anhydrosis on the affected side [17]. The diagnosis of Horner's syndrome is based on clinical features, pupil dynamics and pharmacological testing. Topical 5% or 10% cocaine solution has been the standard medication used for the pharmacologic diagnosis of Horner's syndrome. However, cocaine is expensive and is not readily available since it is a controlled substance. Apraclonidine has been proposed as a diagnostic test for Horner's syndrome [1]. This alpha agonist dilates the pupil in Horner's syndrome, by acting on alpha-1 receptors in the pupil dilator muscle that are hypersensitive due to denervation. In addition, in Horner's syndrome, there is an absence of presynaptic alpha-2 receptor activity, which normally down regulates the release of norepinephrine into the synaptic junction and this decelerates alpha-1 stimulated mydriasis [3]. Previous studies have shown that the miotic pupil on the Horner's side typically dilates and becomes larger than the healthy side, although this was not noticed in our patient with Horner's syndrome. The advantage of apraclonidine over alpha-1 mydriatics, like epinephrine and phenylephrine, used in the past to diagnose Horner's syndrome, is that in apraclonidine the alpha-1 activity is relatively weak and does not dilate the normal pupil [2]. It is not well established whether all interruptions of sympathetic outflow cause alpha-1 supersensitivity at the iris dilator muscle, required for apraclonidine to have its mydriatic effect. It is also not known how long it takes for significant supersensitivity to develop [2].

Our patients did not experience any side effects related to apraclonidine. The most commonly reported side effects leading to discontinuation of apraclonidine in some cases included (in decreasing