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REVIEW ARTICLES

Botulinum toxin–induced blepharoptosis: Anatomy, etiology, prevention, and therapeutic options

Mark S. Nestor MD, PhD[1,2,3] | Haowei Han DO[1] | Anita Gade DO[1] | Daniel Fischer DO, MA[1] | Yves Saban MD, PhM[4,5,6] | Roberto Polselli MD[7]

[1]Center for Clinical and Cosmetic Research, Aventura, Florida, USA

[2]Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, Florida, USA

[3]Division of Plastic Surgery, Department of Surgery, University of Miami Miller School of Medicine, Miami, Florida, USA

[4]Facial Plastic and Maxillofacial Surgery, Facial Anatomist, Nice, France

[5]European Academy of Facial Plastic Surgery (EAFPS), Lübeck, France

[6]Rhinoplasty Focus Group, Chennai, India

[7]Ear Nose Throat, Facial Plastic Surgery, Private Practice in Marina di Carrara, Marina di Carrara, Italy

Correspondence
Mark S. Nestor, Center for Clinical and Cosmetic Research, 2925 Aventura Blvd., Suite 205, Aventura, FL 33180, USA.
Email: nestormd@admcorp.com

Abstract

Background: Botulinum toxin A (BoNT-A) has grown tremendously in aesthetic dermatology since 2002 when the United States Food and Drug Administration (FDA) first approved its use for treating moderate-to-severe glabellar lines. Blepharoptosis, due to local spread of toxin, is a reported side effect of BoNT-A which, although rare, more frequently occurs among inexperienced practitioners.

Objectives: The purpose of this review is to highlight the causes and management of eyelid ptosis secondary to BoNT-A administration including new anatomic pathways for BoNT-A spread from the brow area to the levator palpebrae superioris muscle.

Methods: A literature search was conducted using electronic databases (PubMed, Science Direct, MEDLINE, Embase, CINAHL, EBSCO) regarding eyelid anatomy and the underlying pathogenesis, presentation, prevention, and treatment of eyelid ptosis secondary to BoNT-A. Anatomic dissection has been performed to assess the role of neurovascular pedicles and supraorbital foramen anatomic variations.

Results: Blepharoptosis occurs due to weakness of the levator palpebrae superioris muscle. Mean onset is 3–14 days after injection and eventually self-resolves after the paralytic effect of BoNT-A wanes. Administration of medications, such as oxymetazoline hydrochloride or apraclonidine hydrochloride eye drops, anticholinesterase agents, or transdermal BoNT-A injections to the pre-tarsal orbicularis, can at least partially reverse eyelid ptosis. Anatomic study shows that a supraorbital foramen may be present in some patients and constitutes a shortcut from the brow area directly into the orbital roof, following the supraorbital neurovascular pedicle.

Conclusion: Providers should understand the anatomy and be aware of the causes and treatment for blepharoptosis when injecting BoNT-A for the reduction of facial wrinkles. Thorough anatomic knowledge of the supraorbital area and orbital roof is paramount to preventing incorrect injection into "danger zones," which increase the risk of eyelid ptosis.

KEYWORDS
anatomy, blepharoptosis, botulinum toxin, eyelid, ptosis, review

1 | INTRODUCTION

Botulinum toxin is an injectable neuromodulator derived from the anaerobic, spore-forming, gram-positive bacillus bacterium, *Clostridium botulinum*. It works by inhibiting acetylcholine release from peripheral nerves at the neuromuscular junction.[1] Injection of a small amount of botulinum toxin into a specific region paralyzes the targeted or nearby muscles, resulting in improvement in facial lines and a more youthful appearance.[2] So far, eight distinct serotypes (type A–H) of *C. botulinum* have been identified of which serotypes A and B are approved for clinical use. The United States Food Drug and Administration (FDA) first approved the use of botulinum neurotoxin for the treatment of blepharospasm, hemifacial spasm, and strabismus in 1989.[3] In 2002, the U.S. FDA announced the approval of the use of botulinum neurotoxin for the treatment of glabellar lines (frown lines between the eyebrows).[2] Since its discovery, botulinum toxin has evolved from a poison to a versatile tool in managing a myriad of clinical and cosmetic conditions.[4]

Currently, the U.S. FDA has licensed four commercially available brands of Botulinum neurotoxin type A (BoNT-A): OnabotulinumtoxinA (Botox), AbobotulinumtoxinA (Dysport), IncobotulinumtoxinA (Xeomin), and PrabotulinumtoxinA (Jeuveau). While Dysport, Xeomin, and Jeuveau are approved for the treatment of glabellar lines, Botox is approved for the additional management of lateral canthal lines (LCL) and forehead frontalis lines (Figure 1).[5] Off-label BoNT-A cosmetic indications include treatment of bunny lines, perioral lines, mental crease and dimpled chin, mouth frown, platysmal bands, and horizontal neck lines.[6]

Possible side effects of BoNT-A at the injection sites include bleeding, bruising, swelling, erythema, and pain which can be minimized by using thinner needles and diluting BoNT-A with saline. Systemic effects like headaches may also occur, but typically resolve after 2–4 weeks. The headache can be treated using systemic analgesics. Other side effects induced by local spread of botox include ectropion when treating regions near the lower eyelid, strabismus when treating crow's feet or bunny lines, and most commonly, blepharoptosis after glabella injection.[7]

2 | BLEPHAROPTOSIS

Blepharoptosis (eyelid ptosis) occurs when the levator palpebrae superioris (LPS) muscle is weakened in the superior intraorbital compartment due to BoNT-A. These two areas, superficial frontal (third facial anatomic layer) and deep intraorbital (deep to the facial fifth layer), are separated by the fibrous orbital septum insertions on the superior orbital ridge. The orbital septum constitutes a true anatomic barrier presenting a few weak points that could allow for unintended spread of toxin: the superior neurovascular pedicles (ie, supratrochlear, supraorbital and lacrimal pedicles; Figures 2 and 3).

Blepharoptosis, or eyelid ptosis, is one of the most common significant potential side effects of BoNT-A injection and is defined as drooping of the upper eyelid. Blepharoptosis can lead to decreased or occluded vision, thus interfering with daily function.[8] Although the exact definition varies slightly among the literature, it is generally accepted that an eyelid positioned 1.5–2.0 mm below the limbus, the border at which the cornea and sclera meet, is considered to have undergone ptosis.[9] It has also been defined as an upper marginal reflex distance (MRD) below 2 mm or an asymmetry of more than 2 mm between the two eyes.

Blepharoptosis overall is multifactorial in etiology and can be congenital or acquired (ie, Horner's syndrome and myasthenia gravis). It also occurs due to weakness of the levator palpebrae superioris muscle which can be induced via BoNT-A cosmetic injections. There are five classifications of ptosis: neurogenic, myogenic, aponeurotic, mechanical, and traumatic.[10,11] Ptosis induced by BoNT-A is classified as myogenic as it is due to impairment of transmission of electrical impulses at the neuromuscular junction.

Eyelid ptosis has been documented as an adverse event in numerous BoNT-A clinical trials, with variable incidence in the treatment groups. Importantly, eyelid ptosis did not occur in any placebo groups, illustrating that it is directly attributable to botulinum toxin injection (Table 1). In a multicenter United States FDA study conducted by Allergan, the incidence of BoNT-A-induced blepharoptosis was estimated to be 5.4% among inexperienced injectors and <1% among experienced injectors.[8,12] Cavallini et al[4,13,14,15,16] reviewed 35 articles, with over 8000 patients, concluding the rate of blepharoptosis to be about 2.5%. Incidence appears to have decreased over the years as practitioners become more experienced with BoNT-A administration. To our knowledge, only a few case reports and case series exist detailing this adverse event. Total number of studied patients and blepharoptosis episodes are summarized in Table 1.[12,17-29] Even with spontaneous resolution, patients report a lot of aesthetic and visual discomfort due to the decrease in the eyelid opening, making the waiting period for resolution extremely uncomfortable.

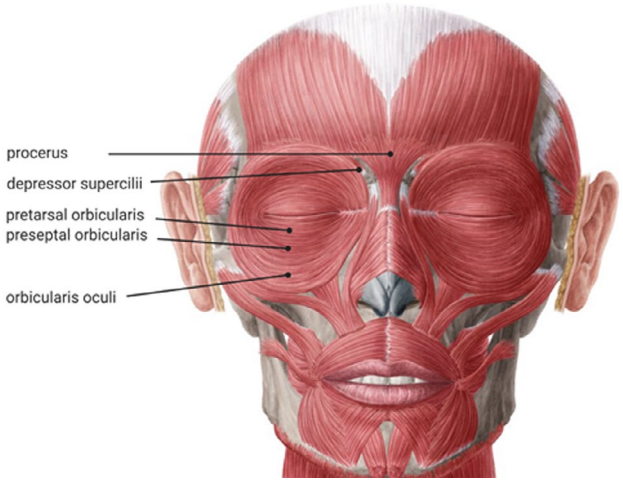

FIGURE 1 Facial muscle anatomy

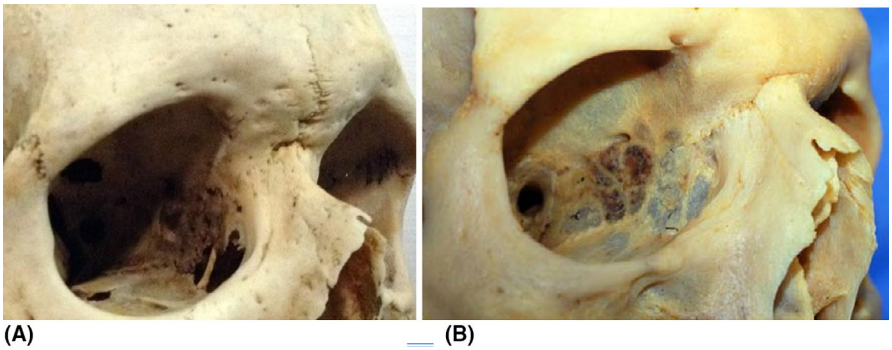

FIGURE 2 Anatomic skull specimen showing anatomic variations of the supraorbital pedicle: supraorbital foramen (A) or supraorbital notch (B)

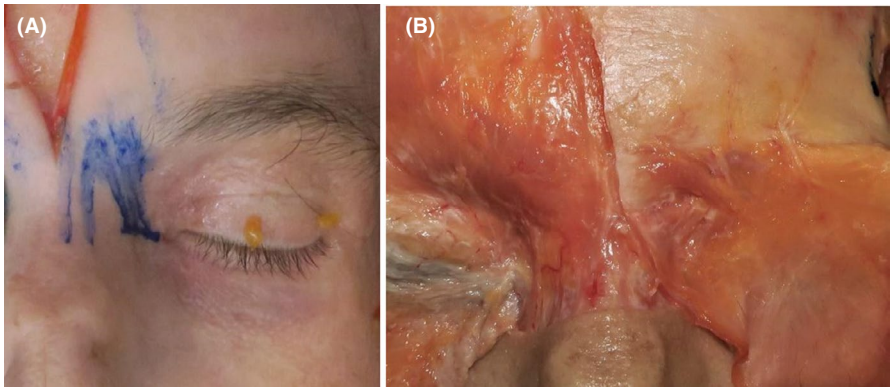

FIGURE 3 (A, B) Anatomic dissection of the superior periorbital area. Anatomic location of the brow above the superior orbital ridge is seen here (Figure 3A). Skin elevation of the supraperiosteal layer (Figure 3B) with the forehead flap pulled downward, showing the bony insertion of the head of the Corrugator Supercilii muscle on the glabella, just below the superciliaris bony eminence of the frontal bone. This bony eminence is always palpable and constitutes an important landmark for the injection of BoNT-A in the proper place that is between the supero-medial orbital angle and the frontal eminence. Lateral to the corrugator muscle insertion, two neurovascular pedicles are visible: medially the supratrochlear and laterally the supraorbital. In this case, the supraorbital neurovascular pedicle is passing through frontal bony foramen. As shown here, a BoNT-A injection performed close to the mid-brow area may provide toxin direct access through the supraorbital foramen to the intraorbital bony roof

3 | ANATOMIC STUDY OF THE UPPER EYELID AND SURROUNDING STRUCTURES

Blepharoptosis is classically attributed to the spreading of botulinum toxin through the fascia of the orbital septum to the levator palpebrae superioris muscle in the upper eyelid often due to the application of botulinum toxin outside the safe zone or to marked dispersion of the toxin from excessive manipulation of the region. However, further anatomic investigations by Saban and Polselli[31] suggest that there is more than a single mechanism of spread of the neurotoxin from the superficial brow area to the deep intraorbital anatomic content. It is still unclear whether spread of toxin through the orbital septum is the only way that BoNT-A is able to access the LPS muscle or whether the toxin is able to cross through a fibrous barrier within the orbital septum. If neurovascular pedicles are responsible for the intraorbital spread of BoNT-A, then the area around the supratrochlear pedicle may be a possible danger zone. Although this zone has classically been considered limited to the middle supraorbital area, it may actually constitute a larger region than previously thought (Figures 2–5).

Upper eyelid elevation is largely controlled by two muscles: the levator palpebrae superioris muscle and superior tarsal muscle (STM), or Müller's muscle (Figure 6; Table 2).[32] The LPS is triangular in shape, measuring approximately 40 mm in total length, and extends along the roof of the orbit from the orbital apex to the superior eyelid.[32,33] It is also the major antagonistic muscle of the orbicularis oculi that controls eyelid closure.[32] It originates at the undersurface of the lesser wing of the sphenoid at the orbital apex, the posterior part of the orbit where all four orbital walls converge and form the optic canal.[32,34] The superior branch of cranial nerve III, or the oculomotor nerve, innervates the LPS and therefore can be inactivated by BoNT-A.[32,35] The LPS inserts at the superior tarsal plate and skin of the upper eyelid at the orbital septum, a region of thin fibrous tissue that separates the intraorbital fat from eyelid fat and the orbicularis oculi muscle (Figures 7-10).[36] Because the LPS is composed of both skeletal and smooth muscle, it is under both voluntary and involuntary control. When contracted, it can lift the eyelid by anywhere between 12 and 20 mm.[37]

Located just deep to the LPS and on the under surface of the upper lid conjunctiva, the Müller's muscle-STM is an involuntarily

TABLE 1 Existing literature on cosmetic botulinum toxin–induced blepharoptosis.[4,12,14-30]

Author's Name	Type of research	# of patients in the study
Carruthers et al. 2002	Multicenter, double-blind, randomized, placebo-controlled trial	203 BoNT-A, 61 placebo (5.4% with mild blepharoptosis in BoNT-A group only)
Carruthers et al. 2003	Double-blind, randomized, placebo-controlled trial	202 BoNT-A, 71 placebo (1.0% with blepharoptosis in BoNT-A group only)
Rzany et al. 2006	Multicenter, double-blind, placebo-controlled, randomized trial	146 BoNT-A and 75 placebo (1.4% with blepharoptosis)
Rzany et al. 2007	Retrospective, cross-sectional patient chart review	945 BoNT-A (0.51% with blepharoptosis)
Monheit et al. 2007	Randomized, double-blind, placebo-controlled trial	279 BoNT-A and 94 placebo (0.8% with ptosis)
Harii et al. 2008	Double-blind, randomized, placebo-controlled trial	91 BoNT-A, 49 placebo (2.2% with blepharoptosis in BoNT-A group only)
Kawashima et al. 2009	Multicenter, randomized, open-label trial	363 BoNT-A (3.3%–4.4% with blepharoptosis)
Brandt et al. 2009	Randomized, placebo-controlled trial	105 BoNT-A and 53 placebo (3% with ptosis in BoNT-A group only)
Cohen et al. 2009	Open-label phase III trial	1415 BoNT-A (1% with blepharoptosis in fixed group, 2% with blepharoptosis in variable group)
Rubin et al. 2009	Open-label, followed by multicenter, randomized, placebo-controlled, double-blind trial	311 BoNT-A and 155 placebo (3.2% with blepharoptosis in BoNT-A group only)
Kane et al. 2009	Randomized, double-blind, placebo-controlled, phase III trial	544 BoNT-A and 272 placebo (2% with blepharoptosis in BoNT-A group only)
Moy et al. 2009	Open-label phase III trial	1200 BoNT-A (4% with blepharoptosis)
Ascher et al. 2009	Multicenter, randomized, double-blind, placebo-controlled, dose-ranging trial	164 BoNT-A and 54 placebo (0.6% with blepharoptosis in BoNT-A group only)
Wu et al. 2010	Double-blind, randomized, placebo-controlled trial	170 BoNT-A, 57 placebo (0.6% with ptosis in BoNT-A group only)
Karami et al. 2007	Case report	1
Akkaya et al. 2015	Case report	1
Steinsapir et al. 2015	Retrospective case review series	7

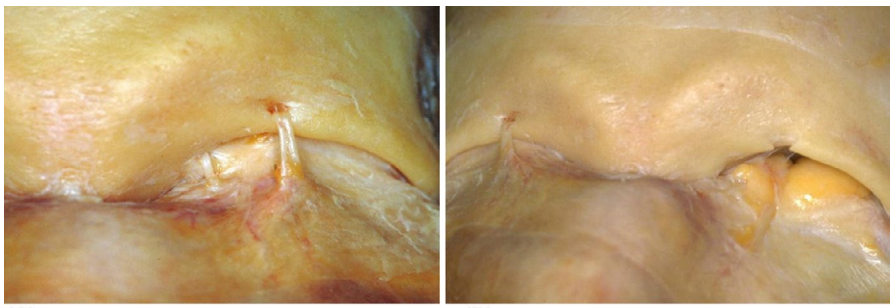

FIGURE 4 (A, B) Anatomic dissection of the superior periorbital area (Part II). After sub-periosteal elevation, the frontal flap is pulled downward, showing the supraorbital pedicles and the superior orbital ridge. It is important to note how the supraorbital pedicle can exit the orbit through two different pathways: the supraorbital foramen on the left side (A) and the supraorbital notch on the opposite side (B). Hence, the spread of BoNT-A may be different in the same patient depending on this anatomic bony variation: longer distance on the "notch side" and shortcut on the "foramen side." This demonstrates significant differences in intraorbital spread of toxin depending on anatomic variation

activated adrenergic muscle about 12 mm in average length.[16] Although the muscle does contribute to lid elevation, it acts largely as an assisting force to the LPS.[38] The STM originates at the muscle belly of the LPS and inserts on the superior tarsal plate of the upper eyelid.[38] The STM contains smooth muscle fibers and receives innervation from the superior sympathetic cervical ganglion which places it largely under involuntary control.[38] Damage to the cervical ganglion that feed impulses to this muscle would result in mild ptosis as seen in Horner's syndrome.[38]

The primary function of the STM is to maintain elevation of the upper eyelid.[38] The STM assists in elevating the upper eyelid up to an additional 2.5 mm after the LPS-initiated elevation due to

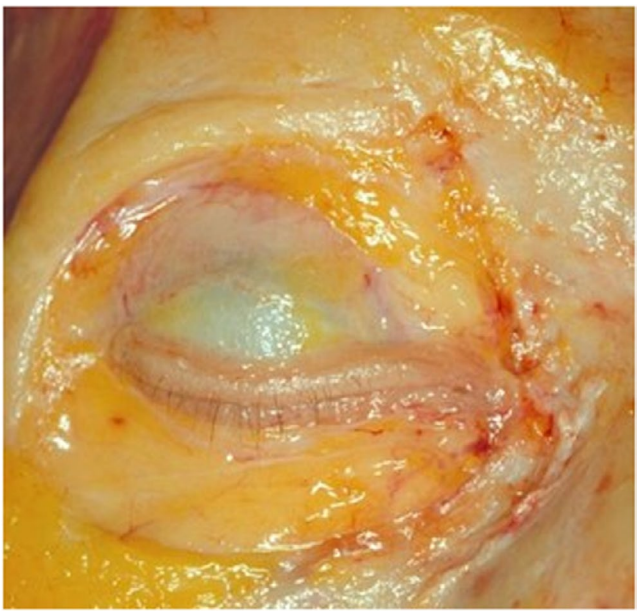

FIGURE 5 Orbital septum anatomy. Left side, front view. The skin and orbicularis oculi muscle have been resected to show the underlying orbital septum; the neurovascular pedicles have been resected together with the periorbital soft tissues. The superior orbital septum is attached onto the orbital ridge following a continuous fibrous junction. The supratrochlear, supraorbital, and lacrimal pedicles are the only passages allowing for toxin spread from the brow area to the intraorbital content. The biggest neurovascular pedicle is the supraorbital pedicle which connects to the LPS muscle

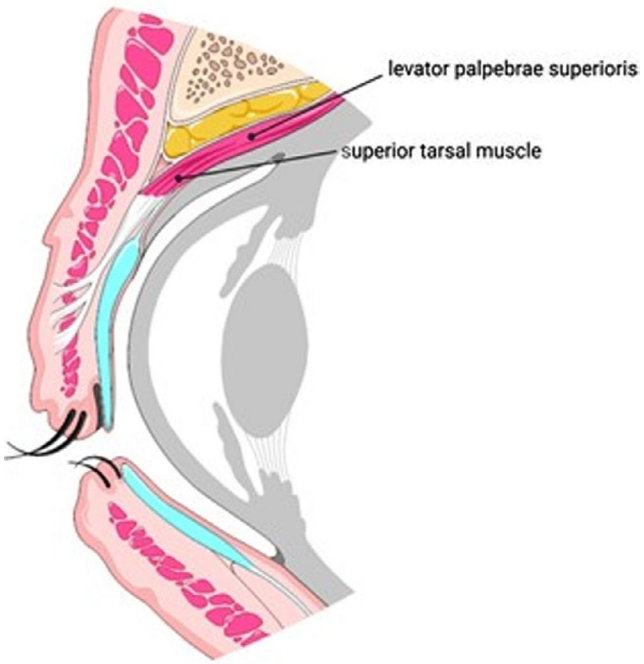

FIGURE 6 Eyelid anatomy

sympathetic nervous system response.[39,40] This adrenergic innervation is responsive to apraclonidine ophthalmic drop stimulation. Anticholinesterase or alpha-adrenergic eye drops improve cholinergic transmission indirectly by inhibiting the destruction of acetylcholine, a fundamental chemical mediator in the transmission of nerve impulses, increasing or prolonging their effects. They cause the Müller's muscle to contract leading to eyelid retraction of 1–2 mm.

The upper lid margin normally hangs about 1–2 mm below the upper limbus, the point at which the cornea and sclera meet, which helps to measure degree of lid lag.[41] The palpebral fissure height (PFH) is also important to note for the same reason. The PFH is the distance from the upper eyelid margin to lower eyelid margin at the mid-pupillary line in millimeters. The PFH varies between individuals and, however, seems to average around 11–12 mm with a variation of about 2 mm.[42] No significant differences in the PFH have been observed with age; however, differences have been noted with regard to genetics and ethnicity.[43,44]

4 | MECHANISM OF ACTION AND RISK FACTORS

The underlying mechanism for BoNT-A-induced ptosis is based on molecular effect on nerve terminals of the muscles which the practitioner does not intend to target. In the case of treating lateral canthal lines, the targeted muscles are the lateral aspects of the orbicularis oculi. The only difference between a patient that develops BoNT-A-induced lid ptosis versus one that does not is that the patient receiving a therapeutic effect has toxin bound only to the nerve endings of the intended targeted muscle. In contrast, the patient with eyelid ptosis has toxin bound to nerve endings of an unintended targeted muscle as well. With regard to eyelid ptosis, the unintended targeted muscle is the LPS, as the STM adrenergic muscle is not as accessible by BoNT-A.

Botulinum toxin A works by binding to transport proteins in nerve cells and blocking the release of acetylcholine from nerve endings; this neurotransmitter is responsible for muscle contraction. In blocking this effect, BoNT-A reduces the capacity of a muscle to generate a contraction and maintain tension.[16] Unfortunately, there are no means to ensure that BoNT-A will bind only to the muscles that an administrator intends to target. The degree to which injected toxin may overflow from a targeted region to an unintended targeted region is largely determined by the active physical distribution of toxin suspension or spread.[5] This is dependent on factors such as site of injection (muscle mass), reconstitution volume, injection volume, depth, speed of injection, and needle gauge, which comprise injection technique.[5] The lower the spread of toxin, the higher the accuracy in treating intended targets and the lower the chance of eliciting side effects such as ptosis.[5]

Development of ptosis occurs more frequently with injection of BoNT-A by inexperienced practitioners who may exhibit inappropriate technique, miss the intended target when injecting toxin, or administer too large a volume, which may lead to excessive spread of toxin to unintended muscle targets. It is classically suggested

TABLE 2 Characteristics of the lid retractors[32,38]

Muscle name	Nerve innervation	Blood supply	Origin	Insertion	Muscle Fiber	Function
Levator palpebrae superioris	Superior branch of oculomotor nerve (somatic nervous system), Cholinergic innervation	Branch of the ophthalmic artery	The periosteum of the lesser wing of the sphenoid bone	Anteriorly into the upper eyelid skin, inferiorly on the anterior surface of the upper tarsal plate	Skeleton muscle	Elevation and retraction of the upper eyelid
Superior tarsal muscle	Postganglionic sympathetic fibers originating from the superior sympathetic cervical ganglion (sympathetic nerve system), Adrenergic innervation		Underneath the levator palpebrae superioris muscle	Superior tarsal plate of the upper eyelid	Smooth muscle	Maintain the elevation of the upper eyelid

FIGURE 7 Orbital roof, superior view. The forceps are medially pulling on the LPS muscle. Whitnall's ligament is shown as a white transversal structure that corresponds to the junction between the LPS muscle and its aponeurosis. The rectus superior muscle is visible just underneath the LPS muscle

FIGURE 8 Measurement of marginal reflex distance 1 (red), marginal reflex distance 2 (blue), and palpebral fissure (green)

that if BoNT-A is inadvertently injected into the lower frontalis or orbicularis oculi muscles located medially to the mid-pupillary line, ptosis may result. The underlying mechanism involves toxin spreading through the orbital septum and binding to receptors on nerve terminals in the levator palpebrae superioris muscle, as it traverses either the pre-periosteal plane or the tributaries of the superior ophthalmic vein.[8]

Anatomic variation can also alter the propensity for developing blepharoptosis. Variations in the exit point of the supraorbital neurovascular pedicle are one example. While this pedicle exits a supraorbital notch at the inner surface of the superior orbital rim in about 74% of patients, it exits a supraorbital foramen on the outer surface of the superior orbital bone in the remaining 26% (Figure 4).[45] Since the latter pathway makes the supraorbital nerve more superficially exposed and provides a shorter route for the nerve (and BoNT-A) to travel before innervating the LPS,

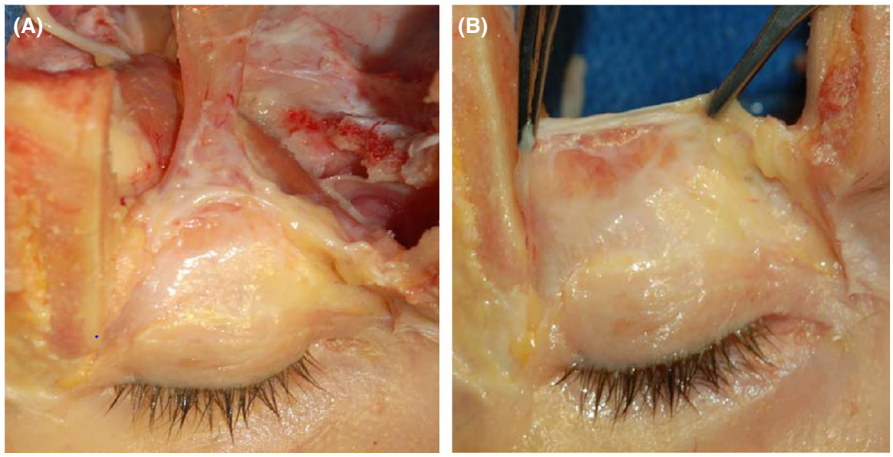

FIGURE 9 (A, B) Anatomic dissection of left orbit. The superior bony framework has been resected together with the orbital septum and the fat compartments to show the LPS muscle, Whitnall's ligament, and the LPS aponeurosis that extends from Whitnall's ligament to the upper lid tarsus and skin close to the eyelashes. LPS muscle has been released from its posterior insertion and is pulled upward and spreads transversally into a fan shape. In Figure 8B, magnified on the LPS aponeurosis, Whitnall's ligament is pulled with two forceps. By transparency through the LPS aponeurosis, Müller's STM is showing an orange color with longitudinal muscular fibers

this may make patients with this variant more prone to developing blepharoptosis. Differences in the observed frequencies of these notches and foramen have been noted in certain populations. Anatomic dissections have indicated supraorbital notches to be more frequent among European populations from warmer climates and supraorbital foramen more frequent among European populations from colder climates.[46]

Patient-dependent risk factors include younger age, outdoor work life, sun damage, loss of skin elasticity, and thicker skin (Table 3).[8,47] Medical-dependent risk factors include prior facial surgical procedures, neurological conditions such as multiple sclerosis or myasthenia gravis, and prior history of Bell's palsy or other induced eyelid ptosis.[8] Risk of developing ptosis can also occur based on product dilution and product quality. Toxins with a higher molecular potency can be expected to lower the threshold for developing ptosis. Finally, injection technique is likely the most important factor in patients developing ptosis. This includes placement and administration of BoNT-A injection and dosing.[8]

5 | CLINICAL EXAMINATION

Although eyelid ptosis affects approximately 2.5% of patients receiving BoNT-A, there are few case reports in the literature. The symptom onset is about 3–14 days post-injection and may be unilateral or bilateral, typically resolving within 3–4 weeks. Ptosis may be mild and unnoticable, but the patient will likely report a heavy feeling in their eyebrow or eyelid and may not be able to fully open the affected eye. The heaviness around the eye usually worsens throughout the day of onset. In rare cases, the ptosis can be severe and may occlude vision.[8] Co-occurrence of mydriasis and ptosis has also been reported.[14] The total reversal of ptosis has been reported to take up to 3 months.[48] Steinsapir et al[15] reported seven cases with persistent ptosis after cosmetic BoNT-A injection which lasted about 6–13 weeks. Racette et al[49] documented a patient with cervical dystonia, previously treated with BoNT-A, who developed bilateral ptosis after BoNT-B injection; it is possible that the accommodation reflex was affected by BoNT administration. Crist reported a 57-year-old woman with a history of Bell's palsy who developed ptosis after Botox treatment to her forehead wrinkles. Additionally, the patient had to elevate her eyelid while driving and she experienced diminished depth perception.[50]

Clinical examination should begin with the patient's head in a chin-up position so that the examiner can objectively observe and measure palpebral fissure height (PFH). PFH is measured at the mid-pupillary line and graded on a scale as follows: mild (1–2 mm), moderate (3–4 mm), or severe (> 4 mm).[51] Eyelid position should be noted after measurement of PFH. Patients should be asked to relax their eyebrows, avoid any attempt to voluntarily raise the eyelids, and stare straight forward. This gives the examiner a neutral gaze to evaluate and to make objective measurements.

Other tools to measure the severity of ptosis include the marginal reflex distance 1 (MRD-1) and marginal reflex distance 2 (MRD-2) which is measured as the vertical distance between corneal eye reflex to the upper and lower eyelid, respectively.[52] The normal range for MRD-1 is 4.0–4.5 mm. Typically, eyelid asymmetry is measured when the relative difference in MRD-1 between both eyelids is 1 mm or greater. Levator function measures the distance of the upper eyelid margin from maximal downgaze to upgaze, while the frontalis muscle is held still by the clinician (normal is 14 mm or more). The palpebral fissure is the distance between the upper and lower lid margin, while the patient is in primary gaze (normal range: 7–12 mm; Figure 9).[53]

At first glance, the affected eyelid may seem to exhibit a greater severity of ptosis than an objective measurement would reveal because the contralateral eyelid could appear retracted. This occurs in

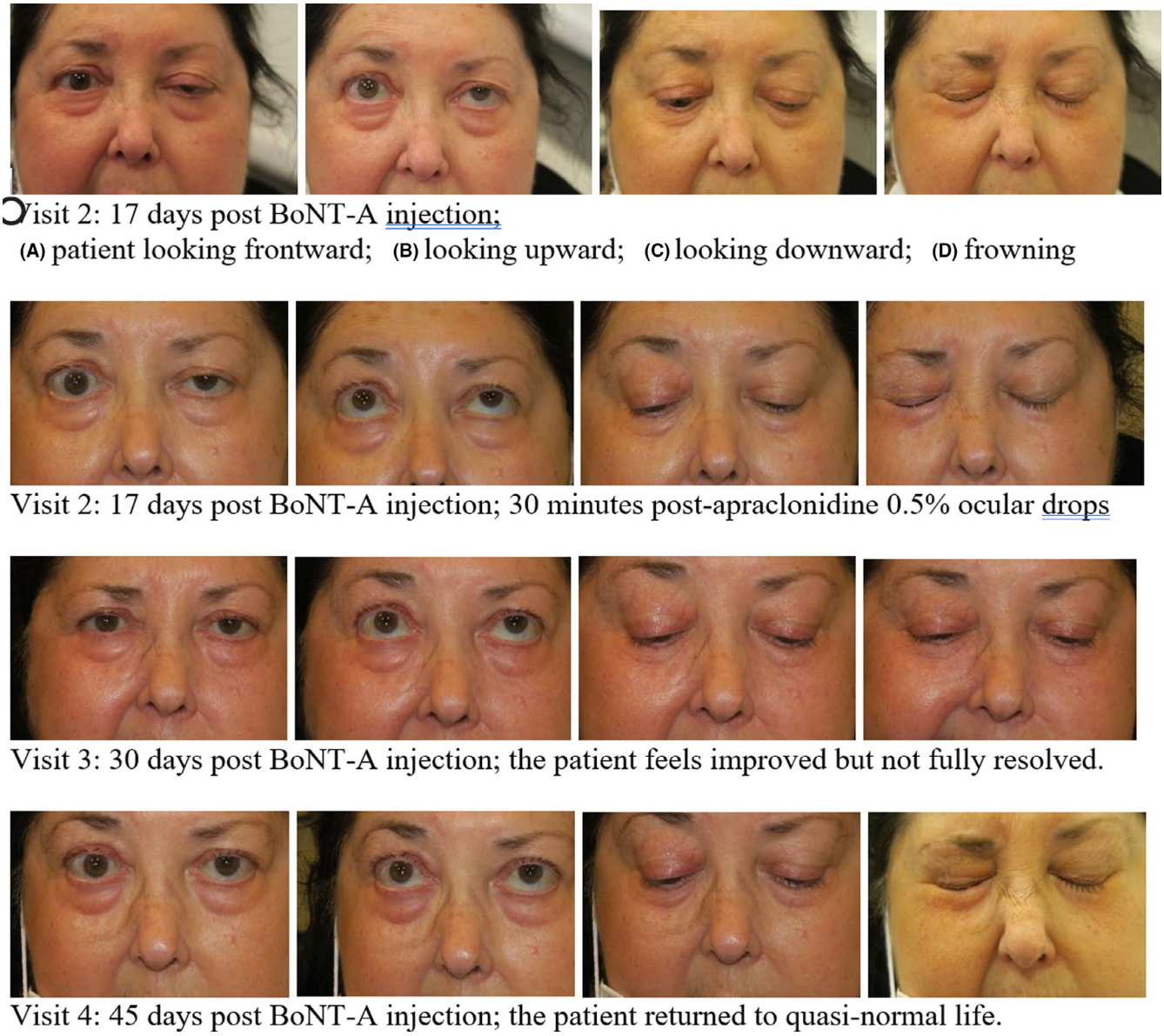

FIGURE 10 Patient presenting with eyelid ptosis after BoNT-A injection for left hemifacial spasm. Visit 2: 17 days post-BoNT-A injection; (A) patient looking frontward; (B) looking upward; (C) looking downward; and (D) frowning. Visit 2: 17 days post-BoNT-A injection; 30 min post-apraclonidine 0.5% ocular drops. Visit 3: 30 days post-BoNT-A injection; the patient feels improved but not fully resolved. Visit 4: 45 days post-BoNT-A injection; the patient returned to quasi-normal life

TABLE 3 Risk factors of botulinum toxin–induced blepharoptosis[8,47]

Patient Factors	Younger age, excessive time outdoors, heavy brow, short brow, excessive sun exposure, loss of skin elasticity, thicker/heavier skin, increased frontalis muscle activity Anatomic variation: supraorbital foramen
Product Factors	Poor dilution, lower quality
Treatment Factors	Inappropriate injection technique or injection placement, excessive unit dosage or volume
Underlying Medical Conditions	Previous facial surgery, neurological diseases (ie, myasthenia gravis, multiple sclerosis), previous history of ptosis or Bell's palsy

about 10%–20% of cases of unilateral ptosis and can be explained by the fact that both LPS muscles are innervated by a single midline brainstem nucleus that provides equal bilateral central output.[54] In unilateral ptosis, a patient attempts to overcome the lid lag through excessive stimulation of the LPS of the affected eye which may induce retraction of the contralateral eye. This is known as Hering's law.[55] This explains why it may be useful to take measurements of not only the affected eyelid, but the unaffected eyelid as well, in

order to adjust for contralateral eyelid retraction when determining lid lag severity. Objective measurements may also be helpful in the case of bilateral ptosis which, if asymmetric, can make the less affected eyelid appear normal. This is important when it comes to treatment, as objective measurements may tell us whether a patient should receive treatment to one eye or both. One way to check for bilateral ptosis is to manually elevate the eyelid that exhibits the most obvious degree of ptosis and watch for a corresponding fall of the contralateral eyelid. This reflex is again explained by Hering's law.[56] As excessive stimulation of the ptotic eyelid is decreased with its manual elevation, the contralateral lid experiences the same decrease in stimulation and reflexively lessens its degree of retraction.

Practitioners should also take note of surrounding extraocular muscle function since they share the same cranial nerve innervation as the lid elevators. Weakness in the ability of a patient to look up, down, or medially could indicate inappropriate spread of toxin to other muscles and greater dispersion along cranial nerve III.

6 | MINIMIZING RISK

In general, practitioners can and should take certain precautions to minimize the risk of eyelid ptosis or any other type of ptosis when administering botulinum toxin for aesthetic purposes. As always, a comprehensive medical history should be obtained to account for any pre-existing conditions such as myasthenia gravis, amyotrophic lateral sclerosis, or pharmaceutical drugs such as aminoglycosides, warfarin, and Alzheimer's medications that may impact the performance or efficacy of BoNT-A. Patients should be asked about prior administration of BoNT-A and any side effects they have experienced in the past, if any. Patients should always be informed that while the incidence of eyelid ptosis is uncommon, it is still a possibility. They should also be educated on proper post-injection behaviors, such as avoiding massaging the treated areas or lying flat, certain physical exercises, for 3–4 h post-treatment so as to avoid greater spread of toxin.[57,58]

Practitioners should also take into account a patient's individual anatomy and musculature that may influence treatment location and technique. Initial anatomic brow or eyelid positioning prior to treatment should be noted as well in order to obtain an objective baseline to compare to after treatment. Pre-treatment photographs are an essential tool in obtaining an objective baseline. This is particularly important in patients with eyelid or brow asymmetry as it is estimated that about 90% of the population exhibit asymmetry of the brow.[59]

King et al[8] provide four main recommendations for minimizing the risk of eyelid ptosis with botulinum toxin use:

1. When treating the glabella, inject 1 cm above the brow.
2. Apply digital pressure over the supraorbital rim with the non-injecting hand while injecting the corrugator supercilii.
3. Point the needle superiorly away from the orbit when injecting around the glabellar complex.
4. Do not inject medial to the mid-pupillary line and remain at least 1 cm away from the orbit margin when injecting inferior to the eye during the treatment of crow's feet. Do not inject directly below the eye if a patient exhibits significant scleral show, has had prior frontal surgery (ie, elevation of the forehead flap to the supraorbital rim during orbital decompression or forehead endoscopic lifting), or has a negative eyelid retraction test (delay in skin below the eye returning to its normal position after being manually pulled down).[60]

Ramey et al. further suggested to point the needle superficially, using appropriate low volume. Deep injections with possible involvement of the supraorbital nerve or branches of the superior ophthalmic vein should be avoided.[61]

Halamkarpour et al. administered BoNT-A (Dysport; Ipsen) to fifteen patients with history of ptosis following BoNT-A injection. 10 U into the procerus muscle and 20 U into the superior middle aspect of each corrugator muscle, instead of injecting into the belly of the corrugator muscles. Excellent response was seen in 10 patients. Outcomes were further improved by injecting 5 U of BoNT-A (Dysport; Ipsen) into the contractible corrugator in patients with good response and 5 U in each corrugator (total of 10 U) in patients with moderate response.[62]

Brown et al. demonstrated a technique of using 1% lidocaine injections to predict BoNT-A treatment outcomes. A 0.1 ml (five equivalent units) of 1% lidocaine was injected × five sites in the glabella and 0.05 ml (2.5 equivalent units) was injected × three sites in the frontalis.[63] After 10 min, improvement in glabellar and frontalis rhytids was observed with “spocking” of the lateral brows. The practitioners subsequently administered an additional 0.05 ml (2.5 equivalent units) of 1% lidocaine more laterally for release of the contracted frontalis with resolution of brow spocking and determined the optimal placement of BoNT-A.[63]

7 | MANAGEMENT

Multiple medical treatments exist for management of eyelid ptosis:

7.1 | Oxymetazoline hydrochloride ophthalmic drops

Oxymetazoline HCl 0.1% (Upneeq, Osmotica Pharmaceuticals) is currently the only FDA-approved pharmacologic treatment for acquired blepharoptosis in adults. Oxymetazoline was indicated for the treatment of nasal congestion over 50 years ago and functions as a potent α1 and α2-adrenergic agonist by stimulating the STM to elevate the eyelid.[64] At low concentrations, it can be applied as a topical nasal decongestant, and ocular administration of less than 0.025% oxymetazoline has been shown to reduce hyperemia.[65] Common side effects include punctate keratitis, conjunctival hyperemia, dry eye, blurry vision, eye irritation, and headache.

In two key randomized, double-masked, placebo-controlled, phase III trials, Oxymetazoline HCl 0.1% demonstrated a statistically significant improvement in superior visual field and eyelid elevation among subjects with acquired blepharoptosis as measured by the Leicester Peripheral Field Test (LPFT) and Marginal Reflex Distance Test (MRD-1), respectively.[65,66] Trial 1 consisted of 94 patients treated with Oxymetazoline HCl 0.1% and 46 patients treated with placebo, while Trial 2 consisted of 109 patients treated with Oxymetazoline HCl 0.1% and 55 patients treated with placebo. All subjects in both trials received treatment once daily to each eye for 6 weeks and tolerated the study drug well with minimal side effects.[65,66] Primary and secondary endpoints were measured at 2 h post-dose on day 1 and 6 h post-dose on day 14, both demonstrating improvement in MRD-1 and LPFT scores compared to baseline. A third study of similar design also demonstrated successful tolerability of the drug when applied once daily in the morning to both eyes over 12 weeks with a minimal number of adverse events, the majority of which were either mild or self-limited.[66]

With the development of Oxymetazoline HCl 0.1%, there now exists a convenient, effective, safe, rapid, and non-invasive treatment for acquired blepharoptosis due to BoNT-A.

7.2 | Apraclonidine ophthalmic drops

Prior to the advent of Oxymetazoline HCl 0.1%, one of the most commonly used treatments of BoNT-A-induced ptosis is 0.5% apraclonidine eye drops, with 1–2 drops administered three times daily.[8] This α2-adrenergic agonist sympathetically stimulates the superior tarsal muscle, causing the upper eyelid to raise by 1–2 mm.[8] It is indicated for glaucoma patients with maximized medical therapy, and it is effective in treating ptosis of Horner's syndrome.[67,68] Risks of apraclonidine use include mydriasis and closed angle glaucoma, but these are uncommon and limited in scope. It is more likely for apraclonidine to cause contact dermatitis and ocular irritation.[69,70]

In one case report, a 47-year-old woman developed eyelid ptosis 3 days after being injected with BoNT-A into the frontalis, orbicularis oculi, corrugator supercilii, temporalis muscles, and procerus to treat chronic migraine headaches. This was accompanied by conjunctival hemorrhage and pain in the same eye and development of ptosis and similar symptoms in the contralateral eye as well. Treatment with apraclonidine 0.5% ophthalmic solution and dexamethasone 0.1%/tobramycin 0.3% ophthalmic suspension into both eyes resulted in resolution of her bilateral ptosis after 9 days.[16]

In another case report, a 76-year-old female patient with a history of glaucoma and hemifacial spasms received BoNT-A injections. Approximately 2 weeks later, she experienced left blepharoptosis with disabling visual loss (Figure 10). After an ophthalmologist assessment confirming no contraindications to apraclonidine therapy, the patient was treated with apraclonidine 0.5% drops. Immediate assessment of drug efficacy was performed (Figure 10). The patient returned 30 days and 45 days after BoNT-A injections for visual assessment and follow-up, in which her blepharoptosis had improved but was not completely resolved. (Figures 11 and 12).

Although apraclonidine application to treat ptosis is supported in some online resources, there is a limited amount of published literature on its use, likely due to reluctance by physicians to use the drug due to its side effect profile.[71-73] While some dermatologists recommend keeping the drug on hand in the office to administer to patients presenting with BoNT-A-induced blepharoptosis, apraclonidine is not readily used or available worldwide.[74]

7.3 | Phenylephrine hydrochloride ophthalmic drops

Preoperative response to topical phenylephrine is a helpful indicator for successful Müller's muscle resection (MMR) ptosis repair.[75,76] During phenylephrine testing, topical phenylephrine hydrochloride 2.5% or 10% solution is applied to the superior conjunctival fornix. Exposure to this selective α1-adrenergic agonist causes contraction of the sympathetically innervated Müller's muscle and lid elevation, independent of levator function. Patients in whom the ptotic lid elevates are considered ideal candidates for MMR surgical correction. Given its mechanism of action, phenylephrine drops have also been recommended in reversal of BoNT-A-induced ptosis, alone or

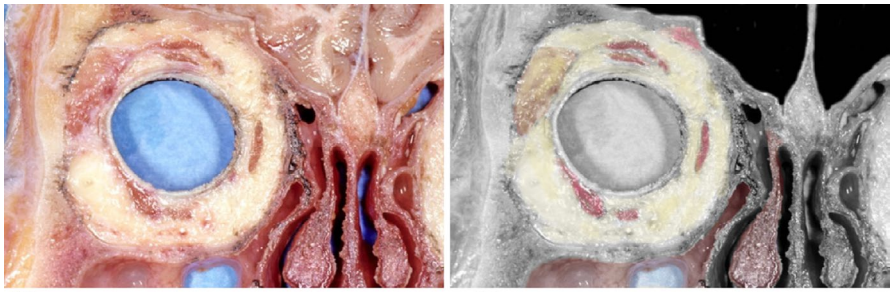

FIGURE 11 (A, B) Coronal anatomic cross section of the orbital meridian and lacrimal gland. Oculomotor muscles surround the orbit and insert at the sclera. The lacrimal gland is located in the orbital superior lateral angle. In the superior orbital compartment, one can recognize the ramus nervus supratrochlearis and supraorbitalis of the nervus frontalis, the musculus levator palpebrae superioris, musculus rectus superior, ligamentum transversum superior (Whitnall's ligament), and glandula lacrimalis

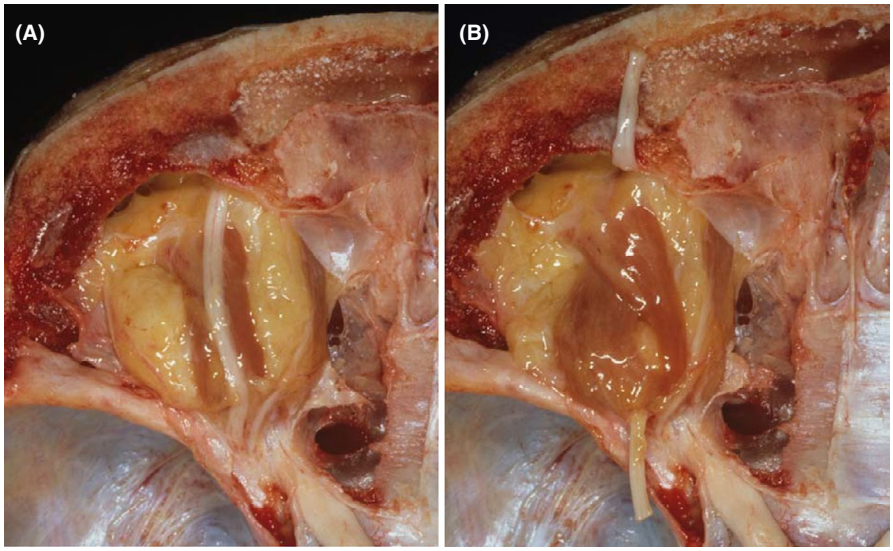

FIGURE 12 (A, B) Anatomic dissection of the orbital roof. Left orbit, superior view. (A): The bony roof and the periosteum have been resected. The first anatomic structure located immediately under the orbital roof is the frontalis nerve that divides into supraorbitalis and supratrochlearis. Located immediately underneath the frontalis nerve, the levator palpebrae superioris lies just above the rectus superior muscle. (B): The frontalis nerve has been divided to show the underlying muscles. The other visible muscle is the superior oblique muscle, oriented medially

in combination with other therapeutic agents. Phenylephrine use has been reported in informal communications; however, there is sparse literature on its dosing and efficacy in BoNT-A-related cases. In a non-randomized clinical trial with 20 healthy subjects, MRD-1 was measured before, 30, 60, and 120 min after administration of one drop of brimonidine 0.2%, phenylephrine 0.12%, or naphazoline 0.05% to the left eye.[77] While the authors observed no statistically significant difference in mean MRD-1 between the brimonidine and phenylephrine groups comparing baseline to study timepoints, naphazoline administration demonstrated an MRD-1 mean increase of 0.56 (+/- 0.11 mm) after 30 min when compared to baseline. Further robust comparison studies between the aforementioned α-adrenergic agonists are necessary to optimize therapeutic regimens for patients with BoNT-A-induced ptosis. Due to its mydriasis effect, phenylephrine is contraindicated in individuals with narrow-angle glaucoma.

7.4 | Anticholinesterases

Anticholinesterases have demonstrated some success in treating BoNT-A-induced ptosis. Karami et al[4] reported a case of unilateral eyelid ptosis following Dysport injection to the glabellar and frontalis rhytids. Because the patient had a history of local allergic reaction to α-adrenergic eye drops, she was treated with 60 mg of oral pyridostigmine. After 30 min, her eyelid began to elevate, and by 2 h she denied lid heaviness. The effects lasted about 4–8 h, and she was advised to continue 60 mg tablets daily (every 6–8 h as needed) for 2 weeks. Importantly, her glabellar and frontalis rhytids were unaffected. Her ptosis completely resolved after 3 weeks.[4] Although a local approach with α-adrenergic eye drops is more commonly used to treat BoNT-A-induced ptosis, the authors suggest a systemic approach with oral acetylcholinesterase inhibitors in particular patients with careful consideration of dosing and potential side effects. Anticholinesterases are contraindicated in patients with some gastrointestinal, urinary tract, bronchial, and cardiovascular disorders.[4]

7.5 | Botulinum toxin A use in the correction of mild ptosis

Transdermal botulinum toxin injections have infrequently been used to correct small eyelid margin asymmetries. In a case series of three patients with mild ptosis, Mustak et al. demonstrated that transdermal administration of BoNT-A to the pre-tarsal orbicularis oculi corrected micro-ptosis and eyelid asymmetry. Specifically, three units of BoNT-A were injected 2 mm above the lash line. At a follow-up visit 6–12 weeks post-injection, the authors observed an increased MRD by approximately 0.9 mm.[78] These findings suggest that botulinum toxin may be used to treat mild ptosis via selectively weakening the pre-tarsal orbicularis, resulting in eyelid retraction. Further studies would be needed to assess the efficacy in patients with severe ptosis; given the dose-dependent nature of BoNT-A, it is expected that administering larger doses to the pre-tarsal orbicularis may yield greater improvements in MRD. However, larger doses may lead to adverse events of lagophthalmos or even worsening ptosis if the toxin spreads to the levator complex.[78]

In addition to medical treatments, muscle exercises and electrical stimulation are also often suggested to help facilitate muscle recovery and lessen the duration of eyelid ptosis. Some practitioners have recommended an electric toothbrush technique in which one places the back of the active brush over the superior portion of the eyelid for several minutes a day.[8]

8 | CONCLUSION

Botulinum toxin is an injectable neuromodulator that achieves its cosmetic effects by temporarily paralyzing facial muscles. Although infrequently reported in the literature, the estimated incidence of BoNT-A-induced blepharoptosis is under 1% among experienced injectors and close to 5.4% among inexperienced injectors.[8] The underlying mechanism involves toxin binding to nerve terminals of the levator palpebrae superioris after traversing the pre-periosteal plane or the tributaries of the superior ophthalmic vein.[8] To help minimize the likelihood of BoNT-A-induced ptosis, practitioners should obtain a full medical history prior to toxin administration and engage in proper administration technique. They should also instruct patients to refrain from certain behaviors for 3–4 h post-treatment such as massaging or rubbing the treatment areas. Oxymetazoline HCl 0.1% eye drops just recently became the only FDA-approved drug for the treatment of ptosis.[64] Other novel treatments exist as well but there is much more research to be done with regard to their efficacy. More research is also warranted to further shed light on the prevention and management of this BoNT-A-induced side effect that practitioners and patients aim to avoid.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

M.N., H.H., A.G., D.F., Y.S., and R.P. contributed to the research and wrote and edited the manuscript. Y.S. and R.P. performed the anatomic dissections. M.N., H.H., A.G., D.F., Y.S., and R.P. have read and approved the final manuscript.

ETHICAL APPROVAL

Review article no subjects were used.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Mark S. Nestor https://orcid.org/0000-0002-8978-7932

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