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Primary and Adjunctive Uses of Botulinum Toxin Type A in the Periorbital Region

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As is true in other surgical fields, there has been a trend in facial plastic surgery toward less invasive techniques [1]. Botulinum toxin is one agent that has afforded many uses as a less invasive option to surgery. The injection of botulinum toxin (Botox; Allergan, Irvine, California) is now established as one of the premier nonsurgical therapies in facial esthetics, and its use is the most common cosmetic procedure performed in the United States [2,3]. One application has been in cosmetic and functional procedures in the periorbital region. The use of botulinum toxin is well established for minimizing glabellar frown lines and lateral crow's feet. Its unique mechanism of action has also led to the elucidation of other useful applications. Although surgical correction has been the mainstay of eyelid procedures, chemodenervation has been shown to be useful as a primary treatment as well as a preoperative, intraoperative, and postoperative adjunctive agent to procedures involving the eyelid and brow. The overall facial appearance can be improved not only by temporarily improving facial rhytids but also by improving primary malpositional changes or postoperative asymmetries. The delicate interplay of the muscles of facial expression allows for artistic use of botulinum toxin type A for facial reshaping beyond the simple elimination of facial rhytids. By understanding of all the applications of Botox in the periorbital region, the knowledgeable surgeon can offer solutions that patients may not have otherwise considered possible. This article reviews the history, mechanics, application, and uses of botulinum toxin in eyelid and brow esthetics through examination of the current medical literature.

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Background

Botulism was first recognized as early as the eighteenth century. In 1897, the toxin of Clostridium botulinum was identified as the paralytic agent. The idea of chemodenervation of skeletal muscles was first established in the 1920s [4]. By the 1970s, Scott and Schantz [5] were using crystalline toxin for paralysis of the extraocular muscles for the treatment of strabismus. Its uses were soon extended to the treatment of other conditions, including dsytonias, spastic disorders, and facial asymmetries 161. In 1987 the US Food and Drug Administration (FDA) approved its use for the treatment of blepharospasm, strabismus, and hemifacial spasm. In 1992, Carruthers and Carruthers [7] noted an improvement in facial rhytids during botulinum toxin injection for the treatment of blepharospasm. By 1997, botulinum toxin type A was reformulated into Botox. Currently, a second subtype of botulinum toxin (type B) is commercially available and has FDA approval for cervical dystonias. Botox was being used as an agent for spastic disorders when its efficacy in temporarily removing facial rhytids was noted. Since that time, Botox has been an integral part of the armamentarium in facial esthetics. The improvement of glabellar furrows first gained attention as patients were treated for medial blepharospasm. Subsequently, its application has been extended to the treatment of lateral canthal rhytids and horizontal forehead furrows, congenital and traumatic facial asymmetry, and postsurgical eyebrow asymmetry.

There are eight immunologically distinguishable polypeptide exotoxins of C botulinum. Botox (type A) is most easily produced in culture and was the first agent to be obtained in a highly purified, stable, and crystalline form. The paralytic effects of Botox are caused by the inhibition of presynaptic acetylcholine release at the neuromuscular junction [4]. The effects are dose related with a peak effect 5 to 7 days after injection. Studies indicate that axonal nerve sprouting in response to chemodenervation accounts in part for its temporary effects [8]. The duration of action has been determined to range from 3 to 8 months, with regeneration of new motor end plates resulting in reversible paralysis [6]. The dose used for eyelid malposition and fissure asymmetries is lower than the standard dose in other areas of facial esthetics; therefore, there is a relatively shorter duration of action (8-16 weeks) [9]. Repeated applications in the same muscle overtime have been implicated to produce a disuse atrophy that can eliminate or reduce facial rhytids. In addition, evidence implicates that, with continued doses of Botox, the time interval between treatments increases secondary to disuse atrophy [1,9].

Anatomy

Central to the proper use of Botox for eyelid and brow procedures is a thorough understanding of the related anatomy. Botox can be used for improving facial wrinkles as well as for lifts and repositioning. The muscles that affect brow positioning can be grouped into elevators and depressors. Paralysis of one group will lead to unopposed action of the other group, resulting in repositioning [10]. Soft-tissue malposition can be a result of chronic dynamic forces that reduce the strength of ligamentous attachments. Alternatively, malposition may be the result of exposures or gravity. Although any two patients' anatomy may be similar, it is rarely identical; therefore, attention to individual anatomy and resultant appropriate dosing are central to the successful esthetic improvements gained by chemodenervation.

The sole brow elevator is the frontalis muscle. Frontalis muscle contraction results in horizontal forehead rhytids. The frontalis muscle interdigitates inferiorly with the brow depressors, which include the procerus, corrugator, depressor supercilii, and lateral orbicularis oculi. The procerus is an inferomedial depressor of the brow and causes horizontal rhytids over the nasal bridge (bunny lines). The corrugator and depressor supercilii are also inferomedial depressors of the brow and causes vertical glabellar furrows (frown lines). The depressor supercilii is a distinct muscle from the corrugator and lies deep to it, attaching to the frontal process of the nasal bone. Because this depressor lies deep to the corrugator, it often escapes chemodenervation when the glabellar region is injected too superficially [6]. The orbicularis oculi is composed of three parts. The innermost pretarsal portion sits directly above the tarsal plates and functions mostly for involuntary eyelid closure. The pretarsal portion has a lesser effect on the development of lines or soft-tissue malposition than the other orbicularis segments. The preseptal portion surrounds the pre-tarsal segment and is responsible for blinking and gentle lid closure. It is opposed by the levator palpebrae muscle and Miiller's muscle. The outermost orbital component is responsible for forceful lid closure. The superior orbital component is a brow depressor that is responsible for periocular rhytids (crow's feet) while also acting as a lower eyelid elevator. Contraction of the orbital component is responsible for lateral canthal and lower eyelid rhytids, lower lid orbicularis hypertrophy, and lateral brow and canthal attenuation [11]. Elevators of the upper eyelid include the levator palpebrae muscle and Milller's muscle. The zygomaticus major muscle pulls the angle of the mouth superiorly, laterally, and posteriorly with laughing and smil-

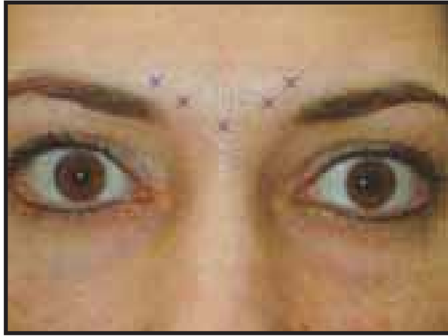

Fig. 1. Injection sites for treatment of glabellar furrows (frown lines), targeting the procerus, corrugator, and depressor supercilii muscles.

-ing. Forceful contraction of this muscle will result in enhanced radial rhytids and soft-tissue redundancy at the lateral canthus. Familiarity with the facial anatomy is essential for proper, successful, and safe use of Botox in the eyelid/brow complex.

Application

In 2004, a Botox consensus group put forth recommendations for the application of this agent. The members of the group agreed that a range of dilutions and volumes was acceptable and was dependant on the total number of units injected and the preference of the practitioner. Although prescribing information recommends use of Botox within 4 hours of reconstitution, the panel agreed with recent literature suggesting that potency can be maintained for up to 6 weeks when stored at 4°C [2]. Less pain has been noted among patients who have an injection of Botox reconstituted with preserved isotonic saline versus nonpreserved isotonic saline. The panel also reported that agitated toxin was as effective as gently reconstituted toxin; therefore, the use of agitated Botox was not as problematic as previously reported. Topical anesthesia including ice packs has been found to be beneficial for some patients. When considering dosing, the total number of units to be injected depends on the region and characteristics of the specific muscle group. One should consider muscle mass, which is influenced by gender. Generally, men have larger muscle mass and may require higher total doses. One should also consider how muscle reacts to animation and maximal contraction to help determine the total dosing [2]. Superficial subcutaneous injection reduces ecchymosis, may increase drug potency with a resultant decrease in bleeding, and allows for more even diffusion over the targeted muscles. Larger deeper muscles such as the corrugator respond better to direct injection into the muscle belly, but with an increased risk of ecchymosis, decreased potency from bleeding, and less even response secondary to the direct injection [12].

Primary Treatment

One can manipulate the soft tissues of the eyelid and brow through the appropriate and precise application of Botox. Use of Botox is well established for the treatment of facial rhytids of the eyelid and brow [2]. Botox can be used successfully with or without surgery for the esthetic treatment of periorbital rhytids and for functional problems of visual impairment and eyelid/brow asymmetries. Initially, Botox was used only for eyelid problems relating to spasm. Currently, it may be used in the treatment of lid ptosis, upper and lower eyelid disparities and asymmetries, brow elevation and depression, and other procedures. Potentially visually impairing malpositions can be treated effectively with Botox with an added benefit of enhanced overall esthetics. Botox can be used as a primary treatment to enhance facial esthetic appeal or as a cosmetic adjunct to surgical procedures, including blepharoplasty and forehead-lift. Similarly, Botox can be used for the treatment of eyelid/brow asymmetries, primary asymmetries, or those related to previous blepharoplasty or forehead-lift.

Primary treatment of periorbital defects with Botox alone provides patients with a safe, inexpensive alternative with temporary effects. Patients who may benefit from Botox use in the periorbital region include those who are not yet ready for surgery secondary to young age, emotional or financial worries, or previous multiple surgeries. Patients who desire an improvement in dynamic facial lines, asymmetries, and facial shape are also excellent candidates [14 The cosmetic uses of Botox as an alternative to surgery in the treatment of vertical glabellar frown lines [Fig. 1], horizontal forehead furrows [Fig. 2], and lateral canthal rhytids [Fig. 3] are well established. In addition to traditional

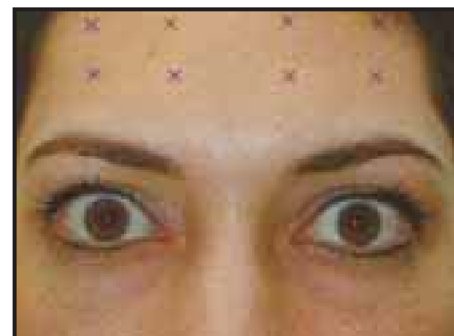

Fig. 2. Gridlike injection sites for horizontal forehead furrows and selective unilateral brown depression, targeting the frontalis muscle.

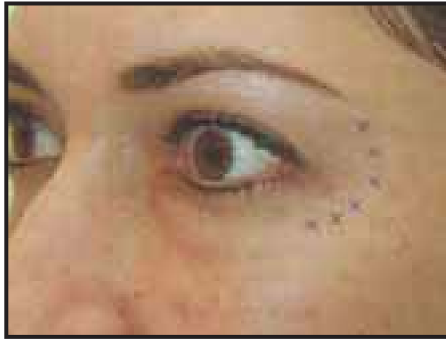

Fig. 3. Injection sites for lateral canthal rhytids (crow's feet), targeting the orbital segment of the orbicularis oculi muscle.

treatments for periorbital rhytids, one can affect esthetic changes of lower lid rhytids with subdermal injections directed to the lateral preseptal segment of the lower lid with decreased doses (1 unit per 0.1 mL) [Fig. 4] [9]. Fagien and Brandt also describe the use of Botox to diminish lateral canthal soft-tissue redundancy owing to zygomaticus major action. In patients with exaggerated crow's feet and soft-tissue redundancy, a low-dose injection (2.5 units) over the mid- to lateral malar eminence can produce the desired effect without resultant upper lip paralysis.

Eyebrow

The cosmetic use of Botox as an alternative to surgery in the treatment of brow positioning and asymmetry has gained popularity. The esthetic ideal for brow position and contour has the highest point of the brow directly above the lateral canthus, with the medial and lateral ends of the brow on the same horizontal plane [1]. The use of Botox has allowed one to strive for this esthetic ideal without surgical intervention. Traditionally, invasive techniques such as a brow-lift and blepharoplasty have been employed to affect change in lid and brow asymmetries. Less invasive techniques were discovered through the work of Isse [13] who considered the muscle to be the problem and who noted improvements in asymmetries with directed myotomies. This idea of a problem-directed treatment evolved to the use of Botox, which affects specific muscular activity while preserving functionality with an even less invasive technique [1]. Today, the use of Botox for lid and brow asymmetries without surgical intervention has become well established in the field of facial esthetics.

Brow ptosis progresses with age secondary to gravitational forces and the action of the muscular depressors of the brow. While treating patients with Botox for glabellar frown lines, it was noted that there was significant brow elevation with an undesirable surprised appearance. From that observation came the idea of chemical brow-lifts. Significant brow elevation can be achieved with Botox, and its use can be considered as an alternative to a surgical procedure [1] . Weakening of the muscular depressors of the brow (lateral orbicularis oculi, procerus, corrugator, and depressor supercilii) allows for unopposed action of the primary brow elevator (frontalis muscle) and resultant elevation of the brow. Injection of Botox to the orbital component of the orbicularis can be used for improving canthal rhytids, eyelid lines, lateral canthal position, and lateral eyebrow ptosis [11]. Ahn and coworkers demonstrated a statistically significant elevation of the brow after injection of 7 to 10 units of Botox into the lateral orbicularis oculi muscle lateral to the midpupillary line [Fig. 5]. Their investigation showed elevation of the height at the midpupillary and lateral canthal lines of 1.02 and 4.83 mm, respectively. Of the 22 patients, one had excess elevation of the brow secondary to injection. This excess was corrected with a 7-unit injection above the overly elevated brow. Often, patients with ptotic brows will compensate by chronically contracting their frontalis muscle. Attempting to chemodenervate the brow depressors in this scenario will not significantly add to the

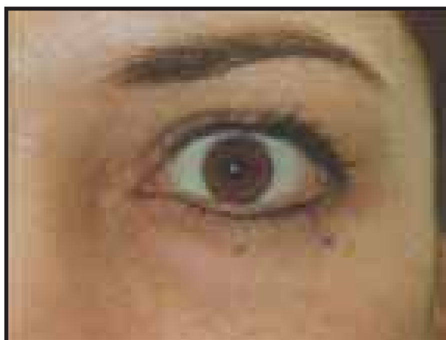

Fig. 4. Midpupillary and lateral preseptal orbicularis oculi muscle injections used for the treatment of lower lid rhytids.

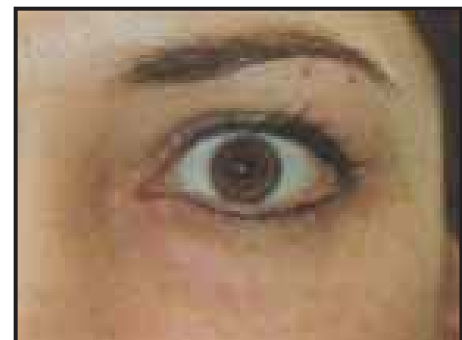

Fig. 5. Injection sites for lateral brow elevation, targeting the superior lateral orbital component of the orbicularis oculi muscle.

unopposed action of the frontalis and will be met with limited success [6]. Additionally, treatment of horizontal forehead rhytids with Botox in these patients will result in further brow ptosis.

Frankel and Kamer [14] described the chemical medial brow-lift (as opposed to a lateral brow-lift) with the injection of 20 units of Botox into the glabellar region [see Fig. 1]. They demonstrated a significant elevation of the brow at the midpupillary line (48% of patients) as well as at the medial canthus (32% of patients). They also noted an increase in the interbrow distance in 59% of patients. Cosmetically as well as functionally, the lateral and medial chemical brow-lift can be used to provide a safe alternative to surgical forehead-lifts.

Just as chemodenervation can be used for a brow-lift can be used to facilitate brow depression to gain symmetry. Patients with brow asymmetry who prefer the positioning of their lower brow may be good candidates for frontalis injection of the overly elevated brow. In this instance, the frontalis muscle can be injected selectively on one side, taking care not to inject below the lowest horizontal forehead rhytid to prevent overdepression [Fig. 2] [6]. The injection should be slowly titrated to the desired effect in this area.

Once the agonist-antagonist roles of the different muscle groups have been fully understood, one can subtly contour the eyebrow shape effectively. Injection of the lateral orbital orbicularis will allow lateral brow elevation. This elevation can be enhanced by injection of the midbrow frontalis, depressing the midbrow and accentuating the new elevation laterally [11]. This technique is just one example of the artistic freedom afforded by proper dosing and placement of Botox injections in the periorbital region.

Eyelid

Botox has been instrumental in producing chemical brow-lifts (lateral and medial) to enhance facial shaping, as well as for the temporary management for upper lid ptosis, lid malposition, and eyelid fissure asymmetry. Eyebrow asymmetries can be seen in numerous situations, including facial spasm, facial nerve trauma, blepharoptosis, asymmetric nonpathologic facial expression, and postblepharoplasty and post–forehead-lift scenarios. Botox has been described in the treatment of many blepharospastic conditions, including benign essential blepharospasm, hemifacial spasm, and aberrant regeneration after facial paralysis [4,15]. Blepharospasm may lead to conditions of asymmetric eyelid fissures, asymmetric vertical palpebral apertures and blepharoptosis These conditions can be treated with low-dose treatment (1 unit of Botox) into the medial and lateral aspects of the pretarsal orbicularis of the upper lid. This injection allows unopposed activity of the levator palpebrae and Muller's muscles, which results in reduction of the etiologic blepharospasm with resultant augmentation of the vertical palpebral aperture and return of symmetry. Even patients with chronic facial spasm and resultant upper eyelid malposition have been shown to have complete resolution with this Botox treatment [4]. Fagien [16] described the use of Botox for the temporary treatment of upper lid ptosis, lid malposition, and eyelid fissure as an alternative to surgery or as a postsurgical corrective treatment in the nonspastic patient in a similar fashion. He also discussed the use of Botox in the lower lid pretarsal orbicularis for the treatment of orbicularis hypertrophy, blepharospasm, or a contralateral retracted lower lid to gain symmetry. He described two injections of the lower lid—one at the extreme lateral aspect and one at the midpupillary aspect of the lower lid pretarsal orbicularis muscle. Dosages were reduced in these areas secondary to an increased risk of diffusion and complications [Fig. 6].

Although initially used for asymmetries related to spasm alone, Botox has been shown to be effective for mild-to-moderate lid ptosis and other upper and lower lid disparities. These techniques can be used for the patient with a functional loss of vision from visual fields deficits as well as for the patient seeking improved esthetic results. Traditionally, the treatment of eyelid malposition, regardless of the etiology, has been corrective surgery of the underlying cause. Lower eyelid malposition, such as retraction, ectropion, and entropion, has been treated with corrective surgery to tighten or shorten the horizontal length of the lower eyelid. Surgery has also been used for the correction of levator dehiscence in the treatment of upper lid ptosis. Temporary nonsurgical methods for the correction of upper lid ptosis were limited to adrenergic topical ophthalmic drops.

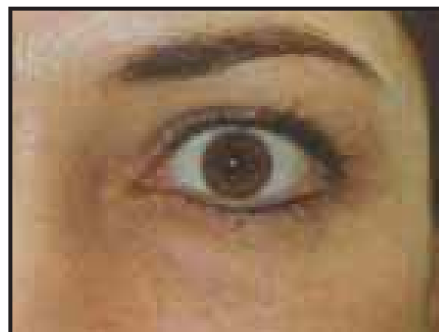

Fig. 6. Midpupillary and extreme lateral pretarsal orbicularis oculi muscle injections used for the treatment of orbicularis oculi hypertrophy and blepharospasm, and to gain symmetry to a contralateral retracted lower lid.

The advent of Botox provided the ability to treat such problems through chemodenervation.

Lower eyelid malposition and asymmetry have historically been treated with surgical intervention. Just as upper lid defects are treated with Botox to reset the muscular antagonist-protagonist tug of war, Botox can be used for lower lid asymmetries. Asymmetries of the lower lid and vertical palpebral aperture height can be treated effectively by weakening the lower lid elevators (orbicularis oculi) on the side opposite to the lower lid retraction. Paralysis of the orbicularis oculi decreases the pumping action of the nasolacrimal outflow and may result in epiphora or ectropion if overdosed. Treatment of lower eyelid rhytids should be directed to the lateral preseptal area of the lower lid to prevent complications while enhancing effect [9].

Another interesting use of Botox in the eyelid/ brow complex is its utility in correcting lid retraction owing to systemic disease. Upper eyelid application of Botox has been shown in the ophthalmologic literature to be useful in lid repositioning. Patients with Grave's disease often have upper lid retraction with significant scleral exposure. Uddin and Davies [17] demonstrated the use of transconjunctival application of Botox (5 units) to Miller's muscles with resultant upper lid ptosis for protection of the eye. After the eye is anesthetized, the upper lid is inverted, and the muscles can be injected. This technique demonstrates another nonsurgical alternative provided by Botox.

Treatment as an adjunct to surgery

Botox injection can be used as an adjunct to several periorbital surgeries. Facial rhytids of the lateral canthus and nasal bridge and glabellar frown lines can be temporarily corrected with the cosmetic use of Botox as a preoperative or postoperative adjunct to surgery. Functional benefits may also be gained through the preoperative, intra¬operative, and postoperative use of Botox.

Frankel and Kamer have discussed the presurgical uses of Botox. They demonstrated the use of Botox injection to the corrugator supercilii for effective elevation of the medial brow. From that observation, they presented the idea of Botox injection as a temporary means of allowing patients to predict their appearance after a brow-lift.

Botox is currently used as an adjunct to endoscopic forehead-lifts [3]. Despite the multiple intraoperative techniques of forehead fixation, 6 to 12 weeks are generally necessary to obtain periosteal fixation. With the adjunctive use of Botox, the brow depressors can be weakened to help promote periosteal fixation to the desired postsurgical brow position. Zimbler and Nassif [3] have demonstrated that targeted Botox treatment with temporal fixation, complete periosteal release, and no central fixation results in long-term brow correction. Patients are treated with Botox directed to the brow depressors 2 weeks before operative lifting. Each supraorbital orbicularis oculi is treated with 4 units of Botox [see Fig. 5]. The glabellar musculature is treated with a total of 20 units [see Fig. 1]. Care must be taken to create a temporal incision parallel to the tail of the brow, with its medial extent at the temporal conjoint tendon. This placement will promote healing in a superolateral vector. The periosteal release will result in a medial brow elevation of 4 to 10 mm alone [3].

Pretreatment with Botox in patients with hyperdynamic rhytids before laser resurfacing has been shown to be effective. The combination of Botox and laser treatment has a synergistic effect by influencing the healing of newly remodeled and resurfaced skin long enough to affect a more permanent eradication of wrinkles [18].

Botox has been used as an intraoperative adjunct to eyelid surgery. Fagien and Brandt recommend the injection of Botox when performing lateral canthal suspension procedures such as the lateral tarsal strip or lateral retinacular suspension. Injection around the lateral canthus reduces orbicularis function. By decreasing orbicularis function, the security of the lateral canthus reconstruction is further protected. Controversy has surrounded the intraoperative use of Botox in periorbital rhytidectomy, with contradicting reports as to its efficacy [9].

In 1997 Choi and coworkers [12] demonstrated the utility of Botox in wound healing. They found that, in 11 high-risk patients undergoing complex eyelid reconstruction, postoperative treatment with Botox and its resultant wound immobilization was superior to simple tarsorrhaphy alone.

Patients may present with eyelid malposition as a presurgical problem, but often malposition is the result of a prior surgical procedure. The failure of many surgical procedures aimed at lifting or tightening soft-tissue malpositions may result from the lack of attention given to the effects of dynamic animation[11]. As described previously, techniques exist that allow for brow elevation, brow depression, eyelid fissure reduction, and eyelid aperture adjustment with the application of Botox. Although these techniques have been described as alternatives to surgery, the facial plastic surgeon may use them in the postoperative setting to correct any remaining or resultant asymmetries.

Complications

Just as most of the beneficial effects of Botox are temporary, so are most of the complications. Adverse outcomes

can be categorized into temporary inconvenient side effects and site-specific anatomic and functional complications. Inconvenient side effects include nausea, headache, fatigue, malaise, and rashes at distant sites. Reported mild complications include ecchymosis and bleeding [19]. Knowledge of the pertinent anatomy and sites of injection is paramount to prevent site-related complications. Most ptosis is the result of diffusion of toxin away from the primary site or improper injection landmarks. Often, injection of the periorbital region will lead to diffusion of toxin into the levator palpebrae superioris with resultant upper lid ptosis. The incidence of upper lid ptosis has been estimated to range from 0.5% to 1% [6]. Alpha-adrenergic ophthalmic drops may cause contraction of Muller's muscle with resultant lid elevation. Patients may have resultant asymmetric ptosis, ectropion, or entropion based on the muscular agonists and antagonists that are adversely affected. Ptosis resulting from toxin injection can often be corrected by injecting the newly unopposed muscle [1].

The selection of appropriate patients and the administration of low doses are essential to prevent functional disabilities. These problems indude lagophthalmos and lid ptosis in procedures involving the upper lid, resulting in visual disability. Visual disability may also be the result of diffusion to the extraocular muscles [6]. Other functional complications include epiphora in procedures adversely affecting the lower orbicularis oculi, exposure keratitis in overtreatment of either lid. diplopia if toxin seeps past the arcus marginalis, and globe penetration by improper injection technique. Exclusion criteria include pregnancy or active nursing and patients with neuromuscular diseases. Botulinum toxin should be used with caution in patients with certain proven risk factors 141. Patients with severe brow ptosis and forehead furrows may develop worsened ptosis with injection of the frontalis muscle. In patients with severe dry eyes or ectropion, injection of the lateral canthal region should be avoided to prevent compromise of function and propagation of symptoms.

Summary

The advent of Botox has revolutionized facial esthetic surgery. Chemodenervation with botulinum toxin type A can be performed successfully as a primary treatment of periorbital rhytids, malpositions, and asymmetries, or as an adjunctive agent to surgery of the periorbital area. A thorough understanding of the agent's characteristics, facial anatomy, and proper technique is imperative to a successful outcome without complications.

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