

Botulinum Toxin Type A: History and Current Cosmetic Use in the Upper Face

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This article reviews the cosmetic use of botulinum toxin in upper face from both the historic and clinical viewpoints. The published literature and our current experience are outlined. Botulinum toxin type A in the upper face has become an extremely popular cosmetic procedure and is outstandingly safe.

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INJECTION of botulinum toxin type A (BTX-A) for aesthetic purposes is one of the most common cosmetic procedures performed today. Since the first few preliminary studies in the early 1990s, the cosmetic use of botulinum toxin injections has gone from being a novel, almost shocking, concept, to a commonly discussed topic in the popular media. First developed as a therapeutic agent for the treatment of disorders characterized by localized muscle hyperactivity, especially around the eyes, botulinum toxin type A is now widely used to treat a number of conditions including most types of focal dystonia.¹ Its safety and efficacy for these uses has been established in numerous clinical studies and in years of successful use in hundreds of thousands of patients. Moreover, physicians are constantly discovering new applications for this drug and new ways to refine its use. Ophthalmologists and neurologists were quick to appreciate the fact that botulinum toxin type A treatment improved the disfigurement as well as the discomfort and disability associated with facial dystonias² and many have expanded their practices to include the cosmetic use of botulinum toxin. Similarly, cosmetic surgeons using botulinum toxin for aesthetic purposes were the first to notice that facial injections provided relief from tension and migraine headaches in certain patients,^{3,4} and this is currently one of the most exciting areas of botulinum toxin research.^{5,6}

This article starts with a brief overview of the

history of the development of botulinum toxin type A for clinical use and of the basic properties of botulinum toxins. A history of botulinum toxin use for cosmetic purposes is then provided as a preface to a series of practical guidelines for specific treatments. These guidelines are meant to aid experienced users in refining or expanding their use of botulinum toxin and to help nonusers to determine how best to incorporate botulinum toxin injections into their current practice. However, these guidelines cannot replace hands-on training with an experienced colleague and no one should begin using botulinum toxin therapy without such training.

DISCOVERY AND DEVELOPMENT OF BOTULINUM TOXIN TYPE A FOR CLINICAL USE

The bacterium *Clostridium botulinum* was first identified as a causative agent in food poisoning more than 100 years ago (in 1895) in Ellezelles, Belgium, by Professor Emile Pierre van Ermenegem.⁷ In the two decades that followed, it was discovered that there were different strains of *C botulinum* and that they produced serologically distinct types of botulinum toxins.⁸ In 1919, Professor Burke of Stanford University proposed an alphabetic classification system for the different botulinum toxins and named the two serotypes identified in his own experiments types A and B.⁸ Subsequent studies led to the identification of

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1085-5629/01/2002-0002\$35.00/0
doi:10.1053/sder.2001.25138

more strains of *C botulinum* and 5 more neurotoxin serotypes, each with its own unique properties.¹

In the 1920s, a crude form of botulinum toxin type A (BTX-A) was isolated,⁹ and Dr Herman Sommer at the University of California, San Francisco, made the first attempts at purification.¹⁰ Dr Edward Schantz and his colleagues began working on purifying the toxin in 1944 and pure BTX-A was isolated in crystalline form in 1946.^{11,12} The first insights into the mechanism of action of BTX-A came in the 1950s when Dr Vernon Brook showed that it blocked the release of acetylcholine from motor nerve endings.^{11,12}

In the 1960s and 1970s, Dr Alan Scott of the Smith-Kettlewell Eye Research Foundation began testing BTX-A in monkeys as a possible therapy for strabismus.¹³ The landmark paper that first showed the safety and efficacy of BTX-A in the treatment of human disease came in 1980.¹⁴ Scott¹⁴ showed that selective weakening of specific extraocular muscles with intramuscular injections of BTX-A could correct gaze misalignment in strabismus. The benefits he documented in the treatment of strabismus led Scott to predict that BTX-A would eventually be found useful in a wide range of other conditions characterized by muscle spasms or hyperactivity.¹⁴

Currently, BTX-A is in use as a treatment for more than a dozen indications and is considered the treatment of choice for most forms of focal dystonia. Consensus statements recognizing the clinical benefits of BTX-A injections for a variety of conditions have been issued by the American Academy of Neurology,^{15,16} American Academy of Ophthalmology,^{17,18} American Academy of Otolaryngology,¹⁹ and the US National Institutes of Health.²⁰ Worldwide, similar consensus statements have also been issued by the Australian Association of Neurologists²¹ and the Australasia Faculty of Rehabilitative Medicine.²²

However, some of the most exciting BTX-A research going on at this time reaches beyond the traditional image of BTX-A as a focal treatment for hyperactive skeletal muscles. The ability of BTX-A to block the release of acetylcholine from autonomic nerve endings innervating smooth muscle or glandular tissue has led to investigation of its use in the treatment of hyperhidrosis^{23,24} and several gastrointestinal conditions,^{25,26} including obesity.^{26,27} Some

promising results have also been obtained from the use of BTX-A in pain syndromes such as headache⁴⁻⁶ and myofascial pain.^{28,29}

BASIC PROPERTIES OF BOTULINUM TOXINS

Pharmacology and Mechanism of Action

The family of botulinum neurotoxins includes 7 distinct subtypes identified as A, B, C₁, D, E, F, and G.¹ Although they are all capable of interfering with acetylcholine release, they vary in their biosynthesis, size, and cellular mechanism of action. Consequently, they also vary in their clinical usefulness. Type A is the most powerful of the 7 types and was the first to be developed for clinical use. Types B and F have also shown beneficial effects in humans and a commercial preparation of type B has recently become available in the United States. The other subtypes are inadequately studied at this time but it is anticipated that some of them will find clinical applications in the future. For example, short-acting toxins such as BTX-E and BTX-F may be of value postsurgically or after trauma.

The 2 clinically relevant subtypes, A and B, are made by different strains of the *C botulinum* bacteria and have some distinct, but overlapping, properties. They are both 150 kD dichain polypeptides composed of a heavy chain and a light chain linked by a disulfide bond.³⁰ The dichain molecules of both A and B are surrounded by nontoxin proteins during their biosynthesis to form a neurotoxin complex. Both A and B complexes can be found in a 500 kD form. Type A neurotoxin complex can also be found in a 900 kD form and this is the size that has been reported for the crystallized type A toxin used clinically.^{31,32} For both A and B, the heavy chain is responsible for selective binding of the neurotoxin to cholinergic nerve terminals, and the light chain acts inside the cell to prevent acetylcholine release.³⁰ At this point, the actions of the A and B subtypes begin to differ. Although both light chains act on proteins involved in different aspects of acetylcholine release, the light chain of type A cleaves SNAP-25, a 25 kD synaptosomal associated protein,³³ while the light chain of type B cleaves vesicle-associated membrane protein (VAMP) (also called synaptobrevin).³⁴ This difference may be

responsible for some of the differences in clinical effect seen for these 2 subtypes.

There is no further information on the intracellular events after type B use. However, after type A use, there is evidence that collateral sprouting of new nerve terminals occurs after a time. Eventually, the original functional endplate is re-established, the sprouts regress, and the clinical effects of the drug subside.³⁵

The fundamental differences between the A and B subtypes result in differences in clinical performance. The few published studies currently available on the clinical use of type B describe doses that are many times greater than those used to treat the same indication with type A.³⁶⁻⁴¹ There are also differences in adverse event profile, and there may be differences in immunogenicity as well. Moreover, formulation details may result in even more differences between commercially available type A and type B products. These differences need to be further investigated now that a product based on type B has become commercially available.

Commercially Available Botulinum Toxin Products

There are currently 3 commercial botulinum toxin products on the market in various parts of the world. BTX-A is available commercially in 2 distinct formulations: BOTOX (Allergan Inc, Irvine, CA) and Dysport (Ipsen Limited, Berkshire, England). Botulinum toxin type B is available as MYOBLOC (Elan Pharmaceuticals, Inc, South San Francisco, CA). BOTOX is available in the United States, Canada, and many other countries throughout the world. Dysport is not available in the United States or Canada, but is available in Britain, France, Germany, and some other countries. MYOBLOC is currently only available in the United States but may become available in Europe in the next year or so. Both BOTOX and Dysport are sold in a lyophilized form that must be reconstituted with physiological saline. MYOBLOC is sold as an aqueous solution of pH 5.6.

Doses of all botulinum toxin products are described in terms of units of biological activity (U). For all products, 1 U is defined as the amount of neurotoxin complex protein that is lethal in 50% of female, Swiss-Webster mice after an intraperitoneal injection (mouse LD₅₀). Even though the

same biological definition of units applies to all botulinum toxin preparations, differences in serotype, formulation, and the way the lethality tests are performed by the different manufacturers results in units that vary greatly in potency between the products. This leads to marked differences in dosing.

For example, the clinical literature describes doses of Dysport that can be anywhere from 3 to 6 times higher than the doses of BOTOX typically used to treat the same condition.^{40,41} The unit doses of MYOBLOC are up to 50 to 100 times higher than those typically seen for BOTOX.^{36,37} Consequently, when communicating about specific uses of botulinum toxin, it is always critical to identify the commercial product that was used. Accidentally using Dysport or MYOBLOC at BOTOX doses is unlikely to have adequate therapeutic benefits, while using BOTOX at Dysport or MYOBLOC doses is very likely to result in significant adverse effects.

Furthermore, the differences in formulation can result in different adverse event profiles as well as potency. The differences in clinical effects may not only require different dosing but different injection sites or dilution parameters to get the desired beneficial effect while avoiding adverse effects. Therefore, before using any brand for a particular indication, it would be wise to consult the available literature on the use of that specific brand.

Immunogenicity

Botulinum toxins are proteins capable of eliciting an immune response. This immune response could result in the development of antibodies that block the therapeutic effects of the drug (neutralizing antibodies). In the therapeutic use of botulinum toxin, it is important to avoid the production of neutralizing antibodies because patients that can no longer respond to botulinum toxin must turn to less effective treatments with more adverse effects. In the cosmetic use of botulinum toxin, it is also important to avoid triggering the production of neutralizing antibodies so that the patient's ability to benefit from future therapeutic use is not jeopardized.

In the many years that BTX-A has been used clinically, the number of patients that have developed neutralizing antibodies has been quite low.

In the treatment of cervical dystonia, approximately 5% of patients lost their ability to respond to BTX-A because of neutralizing antibodies.^{42,43} It is believed that most of those patients developed their antibodies in the early days of BTX-A therapy when clinicians tended to use higher doses and more frequent injections. Current dosing practices, which advocate using the lowest effective dose and the longest possible inter-treatment intervals (generally above 3 months) have greatly reduced the risk of antibody formation to the type A serotype.

It should be noted that there are no reports of patients losing their ability to respond to BTX-A because of neutralizing antibodies following the low doses used to treat blepharospasm and other facial dystonias (less than 100 U). Moreover, there have been no reports of any patients developing neutralizing antibodies after the cosmetic use of BTX-A. In our 15 years of experience with more than 30,000 injection sessions involving BTX-A (BOTOX) we have not documented a single case of antibody-mediated treatment resistance. We conclude that the risk of antibody formation during the cosmetic use of BOTOX, at the doses described below, is negligible.

Conventional wisdom holds the antigenicity is influenced by the total amount of protein that the immune system is exposed to with each dose. In 1997, Allergan produced a new batch of BOTOX that has a lower protein load per dose, which suggests that it should be inherently less antigenic than the original product. Preliminary results in experimental animals⁴⁴ and in clinical use⁴⁵ appear to confirm this. The antigenic potential of botulinum toxin type B is unknown, but the 50-fold to 100-fold higher doses required will result in a 10 to 20 times larger protein load per dose (the difference in protein load does not parallel the difference in dosing because of differences in the number of units per nanogram). The clinical significance of the high protein load with type B has not yet been studied.

COSMETIC USE IN THE FACE

The idea of using BTX-A to treat hyperfunctional lines in the face is appealing because it allows the clinician to relax the muscles responsible for producing the lines rather than just treating the appearance of the lines—and to do so without

surgical intervention. It is also appealing for its long history of safe use for other indications; especially for the 20-year history of safe use of BOTOX in the face.

At this time, all of the published information on the cosmetic use of botulinum toxin refers to the type A serotype, and the majority refers specifically to the BOTOX formulation of type A. There is no information on the cosmetic use of type B. Consequently, this section will exclusively address the cosmetic use of BTX-A, and the overwhelming majority of all practical guidelines will be for the use of the BOTOX formulation (this is the only formulation with which we have significant personal experience). When available, dosing and dilution guidelines will also be provided for Dysport.

History

The first systematic study of the use of BTX-A in facial rejuvenation looked at the effect of BTX-A on glabellar lines and was presented by us in 1990 and 1991 and later published in 1992.⁴⁶ However, we know that Dr Scott had successfully used BTX-A for cosmetic purposes in the mid-1980s. It is likely that many other clinicians were also dabbling with the cosmetic use of BTX-A around this time because of the inherent ease and safety of the technique and the fact that patients treated with BTX-A for facial dystonias were reporting aesthetic as well as clinical benefits.^{47,48} Subsequent reports in the literature documented the effectiveness and safety of BTX-A injections for different types of hyperfunctional facial lines.⁴⁸⁻⁵³

The medical literature pertaining to the cosmetic use of botulinum toxin is dominated by reports of open label, uncontrolled studies and reviews of personal experience. Currently, only 2, small, double-blind placebo-controlled studies involving a total of 42 patients treated with BTX-A (BOTOX) have been published.^{50,54} It is unlikely that this is because of a lack of interest in the subject, but rather to a conviction by those of us using this technique that the efficacy is spectacular and the safety impressive. These convictions have recently been confirmed for the use of BTX-A (BOTOX) in glabellar lines in 2, large-scale, multicenter, placebo-controlled, studies involving a total of 535 patients. Both studies showed that BTX-A was highly effective and had an excellent

safety profile. The first of these studies was presented at the American Academy of Dermatology Annual Meeting in March 2000, and both studies were presented side by side at the European Academy of Dermatology and Venereology Meeting in October 2000. These studies are expected to be published in 2001. The treatment parameters used in these studies are discussed in more detail below.

General Considerations

Successful cosmetic use of BTX-A depends on a thorough understanding of the basic principles of BTX-A therapy as well as access to specific guidelines for its use in facial musculature. These principles include dilution and handling of BTX-A, contraindications and precautions, general injection guidelines, typical time course of effect, and patient education.

Reconstitution, Dilution, and Handling Considerations. Both formulations of BTX-A are sold in lyophilized form and must be reconstituted with physiological saline prior to use. The manufacturers of both BOTOX (Allergan Inc) and Dysport (Ipsen Pharmaceuticals) recommend that their products be reconstituted with preservative-free saline and that is the most common practice. Garcia and Fulton⁵⁵ report equal success when using preserved saline but there has been no thorough, systematic study of the effect of preservative on efficacy. Botulinum toxin type B (MYOBLOC, Elan Pharmaceuticals) will be sold as a stable, nonpreserved aqueous solution that may be further diluted with normal saline.

The appropriate diluent volume must be selected based on the desired concentration of the injected solution—this may vary depending on how the drug is to be used. Two studies that have examined the relationship between BTX-A dose, injection volume, and the area of subsequent muscle weakening have shown that higher doses delivered in smaller volumes tend to keep the toxin and its effect more localized.^{56,57} Conversely, smaller doses in larger volumes tend to cause the biological effect to be more widespread. Therefore, both the dose and dilution of type A can be manipulated to help achieve the desired effect. Botulinum type B will be sold as a solution with a concentration of 5,000 U/mL, which can be further diluted if desired.

For BOTOX, a review of the cosmetic use literature reveals dilutions ranging from 2.5 U/mL to 100 U/mL with most investigators using 25 U/mL or 100 U/mL.^{49,54,58-62} These higher concentrations allow for very low-volume injections that permit precise placement of the toxin with little spread to non-targeted areas. A few investigators are using very low concentrations (2.5 to 10 U/mL) in higher volumes to deliberately spread the toxin over a wider area.^{50,63,64} However, a dilution study by Fulton⁶³ suggested that going below 6.7 U/mL produced inferior results. Low concentrations may be useful for some indications, but if adverse effects due to spread of the toxin to unintended targets is a problem, increasing the concentration and decreasing the volume injected may be beneficial.

For Dysport, all 3 articles on its cosmetic use that we consulted recommended diluting a 500 U vial with 2.5 mL physiological saline to obtain a concentration of 200 U/mL.⁶⁵⁻⁶⁷

We recommend adhering to the manufacturer's guidelines for the storage and handling of all botulinum toxin products. Specifically, we recommend that BTX-A reconstituted with non-preserved saline be stored refrigerated (at 2° to 8°C) for no more than 4 hours. Although the product is probably still at full potency after 4 hours,^{55,68} sterility can no longer be guaranteed beyond that point. However, from a practical viewpoint, use of reconstituted BOTOX over a few days is common practice and we have heard neither of adverse events nor of significant loss of potency resulting from this.

Contraindications and Precautions. The primary contraindication for BTX-A therapy is the presence of any neuromuscular disorder that could amplify the effect of the drug such as myasthenia gravis or amyotrophic lateral sclerosis. It is also important to avoid its use in pregnant women as no studies on its use during pregnancy have been conducted. As is true for most injections, BTX-A injections should not be given in any area of active infection.

General Injection Guidelines. All of the usual precautions of sterility and skin preparation common to all injections should be followed during BTX-A use for cosmetic purposes. In addition, most clinicians use a 30-gauge needle to minimize discomfort to the patient. In many of the early

studies, injection under electromyographic (EMG) guidance was common. This was accomplished by the use of a combined EMG/injection needle available through Allergan, Inc. This technique can be useful in locating the muscle activity most responsible for a particular facial line, and the most active part of that muscle. This allows for accurate placement of BTX-A. However, once a thorough understanding of the relevant facial anatomy is attained, EMG guidance provides little benefit and requires the use of a larger needle. This being said, EMG guidance can still be useful to even the most experienced clinician in the occasional difficult-to-treat patient.

Typical Time Course of Effect. Usually, the clinical effects of BTX-A first begin to appear in 1 to 2 days, peak in 1 to 4 weeks, and gradually decline after 3 to 4 months. Although the onset of effect seems to be relatively constant, several physicians report that the duration of clinical effect can be as long as 6 to 12 months. These long durations are more typically seen in patients that have been treated with a series of treatments over the span of a year or more. It seems that, as the total number of treatment sessions increases, the duration of clinical effect lengthens.^{46,61} This is also our experience and suggests that the effects of treatment can outlast the direct effect of the drug on muscle activity.

Patient Education. In preparing the patient for treatment, it is important to respect and address any safety concerns the patient may have as well as to let him or her know exactly what to expect during and after treatment. They should be reassured with a description of the long safety history of BTX-A, but also made aware of any potential adverse effects. They should be informed of the typical time course of the clinical effects and the need for retreatment after 3 to 6 months. However, it may be a good idea to mention to some patients that the retreatment interval may become longer after several treatments, particularly if the patient is concerned about the need to receive regular injections indefinitely.

SPECIFIC COSMETIC TREATMENTS

Glabellar Frown Lines

Relevant Anatomy. Muscles controlling the frown include corrugator and orbicularis

which move the brow medially and procerus and depressor supercilii, which pull the brow inferiorly. Location, size, and use of muscles vary greatly between individuals. Therefore, the best outcomes will come from individualizing the treatment sites and doses to match each patient's needs. Because the frown muscles are used only to control facial expression, the goal of treatment should be to provide a significant weakening or even complete paralysis of these muscles.

Injection Sites and Dosing. A variety of different injection techniques and BOTOX doses have been reported over the years. They range from a single injection of 10 U into the belly of each corrugator⁶⁰ to total doses of 20 to 50 U spread over 7 sites⁵⁸ (Fig 1).

In 1997, Pribitkin et al⁶⁰ conducted a pair of studies (reported in the same paper) designed to shed light on optimum BOTOX dosing, the benefits of EMG guidance, and patient selection. They determined that, when delivering a single injection to each corrugator, 10 U/side was a good starting dose. Starting at lower doses and follow-

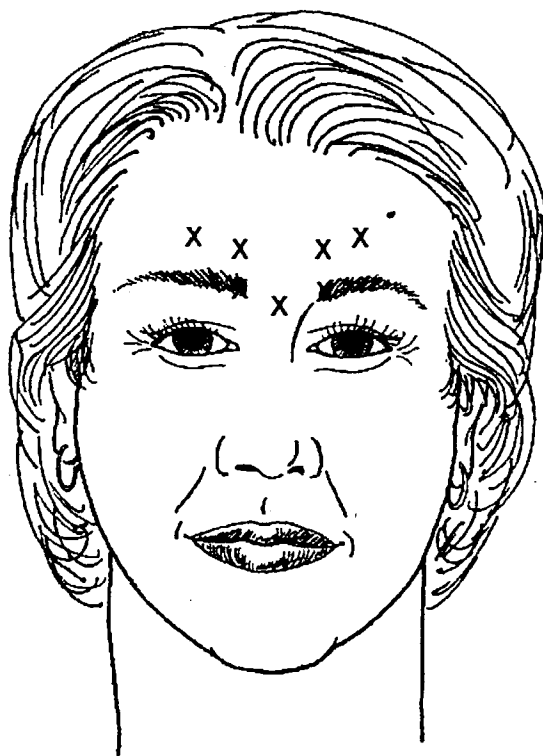


Figure 1. Approximate injection sites for the treatment of glabellar frown lines.

ing with booster injections after 2 weeks did not work well for most patients. In these studies, it was not clear if EMG-guidance improved outcome, but post-treatment EMG recordings in patients with poor results revealed that there was still some EMG activity in the corrugator muscles. The patients with the worst outcomes tended to have thick, sebaceous skin with deep dermal scarring and exceptionally deep glabellar crevices that could not be pulled apart with the fingers. The best results were seen in patients with thin skin and fine wrinkles or shallow folds that were amplified by scowling but that could still be spread out with the fingers.

Another dose-ranging study was conducted by Hankins et al⁶⁹ in 1998. They injected 46 patients with BTX-A (BOTOX) using 5 injection sites (1 in the midline glabellar area 4 mm below brow line; and 2 more on each side, one just above and one just below the medial brow in line with the medial canthus of the eye). They varied the total dose from 1 to 10 U per site while holding the volume constant at either 0.05 or 0.1 mL per site. They determined that the minimum effective dose was 2.5 to 4 U per site and that there was no significant increase in efficacy at higher doses. Both injection volumes used were equally effective.

In the most recent studies, and in our clinical practices, multiple injections of relatively high doses in low volumes are common. In the 2 large, multicenter, controlled studies described above, 4 U BTX-A (BOTOX) were injected in each of 5 sites (1 in the procerus and 2 in each corrugator). These injections gave good results in the overwhelming majority of patients while producing only a few, transient, adverse effects.

The most undesirable adverse event reported with BTX-A treatment of glabellar frown lines is blepharoptosis. This happens when the injected toxin diffuses to the upper eyelid levator muscle. Injection technique should be designed to keep the risk of this complication as low as possible.

In our clinic, we currently use 7 injection sites when treating glabellar frown lines, and vary the dosage depending on the individual brow. In an average female brow without a great deal of muscle mass we use a total of 25 U BTX-A (BOTOX). When there is a greater muscle mass, a total dose of 35 U or even higher is necessary.

During a typical injection, the patient is seated with chin down and head slightly lower than the physician's. For the first injection, 5 to 10 U are injected into the procerus in the midline (at a point below a line joining the brows and above the crossing point of the X formed by joining the medial eyebrow to the contralateral inner canthus). The area is massaged firmly, horizontally with the thumb. Then the needle is inserted directly above the caruncle of the inner canthus and just above the bony supraorbital ridge. After injecting 4 to 7 U in that location, the needle is partially withdrawn but kept beneath the skin. The needle is repositioned until it angles superiorly. The tip is advanced until it is at least 1 cm above the previous injection site in the orbicularis oculi, and then 3 to 7 U more are injected. This is repeated on the contralateral side. In most individuals, especially those with horizontal brows, 3 to 5 U is injected 1 cm above the supraorbital rim in the midpupillary line on each side.

After the injections are complete, patients are instructed to remain vertical for the next 2 to 3 hours. They should frown as much as possible while the toxin is binding, but should not press or manipulate the treated area. Patients are advised that they should be reinjected every 3 to 4 months during the first year, but that after that time they should return for reinjection when they feel in need of retreatment. To minimize the risk of ptosis (which is <1% in our clinic), we recommend keeping the injected volume at the minimum needed for efficacy, accurately placing the injection (no closer than 1 cm above the central eyebrow), and advising the patient to stay vertical and not to manipulate the injected area for several hours after injection.

The doses of Dysport that have been reported in the literature for glabellar lines range from a total of 16⁷⁰ to 80 U.^{65,66}

Crow's Feet

Relevant Anatomy. Crow's feet in the lateral canthal area are produced by the action of the orbicularis oculi, whose fibers are arranged in a circular pattern around the eyes, and also by the elevators of the corner of the mouth, risorius and zygomaticus. Contraction of orbicularis is needed for forceful closure of the eyelids; therefore, the goal of treatment is to produce a weakening just

in the area of the crow's feet lines, rather than a complete paralysis of the muscle. Innervation studies of the orbicularis oculi have shown a diffuse distribution of neuromuscular junctions.⁷¹ This suggests that specific portions of this muscle can be weakened selectively and that multiple injections will be required to weaken broad sections of the muscle.

Injection Sites and Dosing. In the literature, the total doses of BTX-A (BOTOX) used to treat crow's feet range from 4 to 5 U/side^{53,64} to 5 to 15 U/side,^{49,50} distributed over 2 or 3 injection sites. Some physicians use EMG guidance^{49,50,72} to locate the most active part of the muscle while the patient grimaces, while others⁶⁴ inject the "hills" formed between the crow's feet lines when the patient grimaces. The reported duration of effect for these injections range from 3 to 6 months⁴⁹ to 5 to 6 months.⁷²

Most of these studies reported a high level of success and few, if any, adverse effects. In an early study by Keen et al,⁵⁰ they report a few cases of temporary lower eyelid droop in some of the first patients enrolled in their study. This complication



Figure 2. Approximate injection sites for the treatment of glabellar crow's feet.

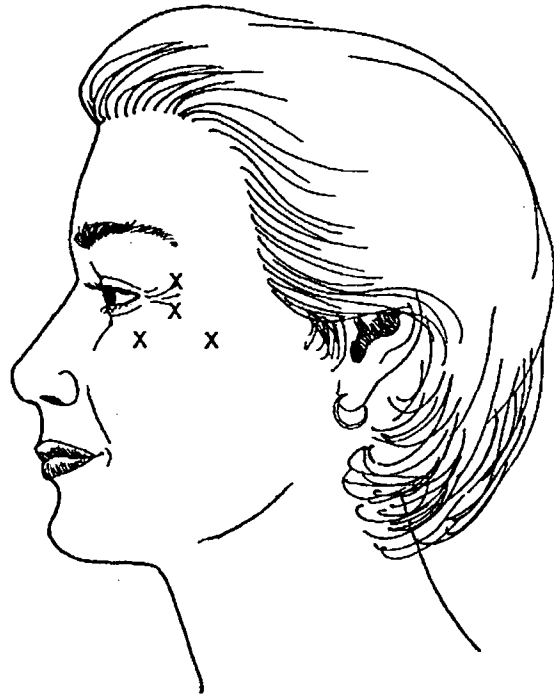


Figure 3. Approximate injection sites for the treatment of glabellar crow's feet and infraorbital lines.

was eliminated by moving the injection site farther away from the lateral canthus.

A particularly interesting method for treating crow's feet with BTX-A (BOTOX) was described by Guerrissi.⁶² He injected 15 to 50 U directly into the exposed orbicularis oculi during blepharoplasty or face lift. The toxin was injected into the inner surface of the muscle during blepharoplasty and into the outer surface of the muscle during face-lifts. He describes effects lasting for 9 to 10 months.

In our clinic, we start with 12 to 15 U per side, distributed in equal parts between 2 to 4 injection sites (Figs 2 and 3). Since this area is notable for showing bruising we try to use as few and as superficial injections as possible. In our hands, bruising is minimized if the injections are made intradermally and confined to 2 sites. However, some individuals require a greater distribution and up to 4 injection sites (particularly in the most lateral regions). We do not see any notable adverse effects following this procedure.

The doses of Dysport that have been reported in the literature for the orbicularis oculi range from a total of 8⁷⁰ to 60 U.⁶⁵

Horizontal Forehead Lines

Relevant Anatomy. Horizontal forehead lines are produced by the action of the frontalis. This is a large, vertically oriented muscle that inserts superiorly into the galea aponeurotica and inferiorly into procerus, orbicularis oculi, corrugator supercilii, depressor supercilii, and the skin of the brow. The challenge in treating this area is to lessen the undesirable forehead lines without causing brow ptosis or a complete lack of expressiveness. Therefore, the goal is to soften the forehead lines without eliminating them completely. Patients should be warned that this may be difficult to achieve if there is a pre-existing significant degree of brow ptosis.

Injection Sites and Dosing. A wide range of doses and dilutions are described in the literature, but most emphasize keeping the injection sites well above the brow to avoid ptosis. Guerrissi and Sarkissian⁵¹ used 14 to 20 U BTX-A (BOTOX; in a 25 U/mL dilution), depending on the number of lines and their lateral extension. The pattern of injection sites is not specified, but no sites were injected below 2.5 cm above the brow. All patients had satisfactory improvements, but 2 of 17 had long-lasting (55 to 70 days) brow ptosis. In another study, Goodman⁶⁴ asked patients to raise their eyebrows and then injected the ridges appearing between the lines. He used a concentration of 10 U/mL and injected 1 to 2 U per site into 2 sites per wrinkle on each side. To prevent ptosis, no injection was made within 2 finger-breadths above the brow. Two of the 4 patients treated had their lines eliminated. Complications included minor discomfort on injection and some bruising. The results of these 3 studies are not described in sufficient detail to determine if one technique is superior to the other.

In our clinic, patients are treated with a total of 10 to 20 U BTX-A (BOTOX) distributed in 4 to 5 injection sites horizontally across the midbrow and 2 to 3 cm above the eyebrows. In individuals with a narrow brow (less than 12 cm between the temporal fusion lines at the mid-brow level) we use 4 injection sites. For broader-browed individuals (greater than 12 cm) we use 5 injection sites

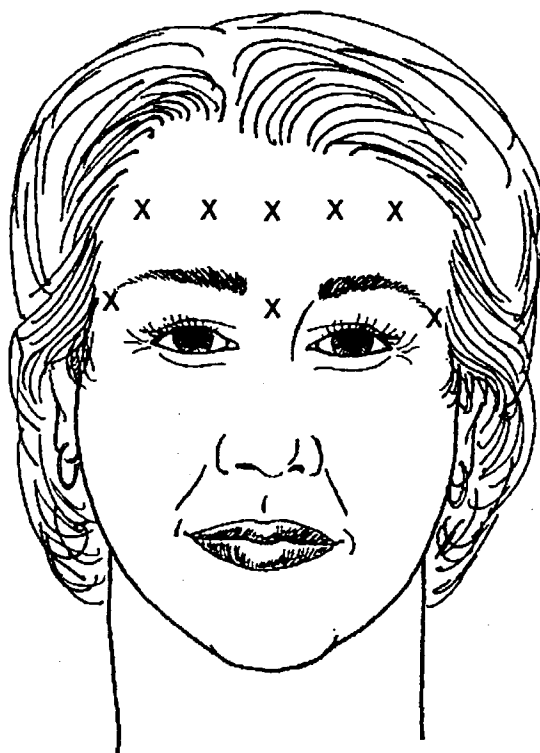


Figure 4. Approximate injection sites for the treatment of glabellar horizontal forehead lines.

and a slightly higher total dose (Fig 4). It is our belief that the brow depressors should always be treated at the same time as frontalis. The technique is described under "Brow lift" below. Even with this cautious approach we still see a minor degree of brow ptosis or swelling of the upper eyelids in a few patients. The beneficial effects typically last from 4 to 6 months.

The doses of Dysport that have been reported in the literature for the frontalis muscle range from a total of 40 U⁶⁵ to 70 U.⁷⁰

Brow Lift

Relevant Anatomy. Overactivity of the brow depressors can lead to a lowered brow and an angry, scowling expression. The medial brow depressors are corrugator supercilii, procerus, and the medial portion of orbicularis oculi. The lateral depressor is the lateral portion of orbicularis oculi. Unfortunately, the lower portion of frontalis (which elevates the brow) interdigitates with the 3 brow depressors and may be affected by

toxin injections in those locations. However, the bulk of frontalis is superior to the brow depressors, so keeping the injection sites low should prevent significant brow ptosis.

Injection Sites and Dosing. Several clinicians have noticed that an elevation of the medial brow often accompanies BTX-A treatment for glabellar lines.⁷³ In 1998, Frankel and Kamer⁵² set out to study this effect systematically. Each patient was treated with 20 U BTX-A (BOTOX) injected into the glabellar area to treat glabellar frown lines. The specific injection sites were identified by having the patient frown repeatedly so that the muscles responsible could be identified. Unfortunately, the results were equivocal. Slightly more than half of the patients were judged to have a more open, elevated brow when evaluated subjectively, but slightly less than half showed measurable increases in either medial or midpupillary brow height or inter brow distance.

We reported the effect of treating the brow depressors alone to elevate the brow while preserving the natural shape of the brow.⁷⁴ One injection of 7 to 10 U BTX-A (BOTOX) was made in the glabellar area at the midline, immediately below the line joining the eyebrows, followed by 1 injection on each side into the supralateral eyebrow where orbicularis is curving inferolaterally, outside the bony orbital rim. This resulted in a modest (mean of 1 mm) brow elevation in 5/7 patients. Neither Frankel & Kamer⁵² nor our study reported any significant adverse effects.

Slightly greater brow elevations were obtained in 2 more recent studies. Ahn et al⁷⁵ produced average midpupillary elevations of 1 mm and average lateral brow elevations of 4.8 mm by injecting 7 to 10 U into the superolateral orbicularis oculi at 3 sites below the lateral third of the brow (but superior and lateral to the orbital rim). These effects were accompanied by mild bruising in 5 patients and minimal ptosis in 2 patients. Both of these adverse effects resolved within 7 days. There was also 1 case of excess brow elevation which was corrected by frontalis injection. Huang et al⁷⁶ injected a total dose of 10 U (in a 50 U/mL dilution), distributed in 2.5 U increments between 4 sites along the underside of the lateral half of the brow. An additional 5 U was injected into each corrugator muscle just above and medial to the brow. The injection needle was aimed in an up-

ward and horizontal position. Mild pressure was applied after each injection to prevent bruising. There was a statistically significant elevation of the lateral, central, and nasal portions of the brow during both rest and voluntary brow elevation. The greatest elevation was seen in the central brow. The mean increase in brow height at rest was 1.9 mm on the right side and 3.1 mm on the left. The mean increase in brow height while elevated was 2.1 mm on the right side and 2.9 mm on the left. No ptosis, bruising, or other adverse effects occurred in this study.

In our clinic, we currently use the same approach as described in the paper by Huilgol et al discussed above.⁷⁴

Facial Asymmetry

It stands to reason that any application of BTX-A that has been shown to be effective in producing a symmetrical aesthetic improvement in the face, could be used to correct facial asymmetry or synkinesis arising from imbalanced or undesirable muscle activity. There have been several reports of the successful use of BTX-A in the treatment of facial asymmetries due to a variety of facial nerve palsies,^{53,77-79} facial dystonia,^{2,48} surgery,^{47,53} or trauma.⁵³ In cases of hemiparesis, BTX-A is used to decrease expressivity on the unaffected side. In cases of hyperkinesia, the affected muscles are treated.

Adjunctive Use

Botulinum toxin injections can be combined with other cosmetic procedures to produce a more polished and refined result, or to prolong the effects of the other procedure.⁸⁰ In many situations, the constant action of facial muscles can interfere with or reverse the results of cosmetic surgery. The weakening of certain muscles with BTX-A before surgery can make it easier to manipulate the tissues during surgical procedures, allowing for a greater surgical correction or for a better concealment of the surgical incision. In addition, BTX-A during or after a procedure can prevent or slow the return of wrinkles by reducing the action of the muscles that created the wrinkles in the first place. Finally, BTX-A can be used to reduce tension exerted on a wound or surgical incision by the underlying muscles, thereby allowing for better healing with less scar formation.

With Surgical Brow Lift. As mentioned above, BTX-A can be used on its own to create a mild brow elevation. However, surgery is often required when brow ptosis is moderate to severe and a greater elevation is desired. Preoperative relaxation of the brow depressors with BTX-A may allow for a greater brow elevation. Postoperatively, BTX-A treatment may help prolong the benefits of surgery by relaxing the muscles that are working to reestablish the depressed brow.

With Upper and Lower Lid Blepharoplasty. As mentioned above, Guerrissi⁶² achieved excellent improvements in crow's feet lines by infiltrating a triangular area of the lateral orbicularis oculi while the muscle was exposed during blepharoplasty procedures. We have found that pretreatment of the crows feet area with BTX-A allows the muscles to relax, leading to a more accurate estimation of the amount of skin to be resected during surgery and better placement of the incision so that it is concealed within the orbital margin.

With Lower Eyelid Ectropion and "Roundeye" Repair. After these procedures, the quality of the surgical result can be damaged by dehiscence of the temporal incision. The use of BTX-A to transiently weaken the lateral fibers of the orbicularis (the muscles that are pulling on the medial side of the incision) can prevent this. First briefly reported in an article in *Ophthalmology Times*,⁸¹ we use this technique routinely and dehiscence has been eliminated.

With Laser Resurfacing. The habitual use of the muscles of facial expression will eventually recreate the glabellar furrows and crows feet removed by the laser. The adjunctive use of BTX-A gives a superior and longer lasting outcome by preventing the underlying muscles from shaping the newly forming collagen into furrows and wrinkles again. Regular postoperative injections (every 6 to 12 months) can prolong the effects of this procedure.

We first described the use of BTX-A injections in combination with laser resurfacing in 1998.⁸² West and Alster⁸³ then conducted a controlled study in which the effects of combined CO₂

laser resurfacing and BTX-A (BOTOX) were compared with laser resurfacing alone. They demonstrated an enhanced and more long-lasting improvement of forehead, glabellar, and canthal rhytides when BTX-A injections were given postoperatively than when patients were not given BTX-A. At 9 months, the average clinical score among patients without BTX-A was 1.2/3 (mild to moderate rhytides) while the average score in the BTX-A-treated group was 0.5/3 (none to mild rhytides). Many clinicians now use BTX-A injections as part of their standard laser resurfacing protocol.⁸⁴

With Repair of Facial Wounds. Any incision or wound that is unfavorably oriented with respect to the relaxed tension lines of the skin will be subjected to repeated tension that will slow healing and promote scar formation. Gassner et al⁸⁵ showed that immobilization of underlying musculature with BTX-A (BOTOX) promoted the healing of experimentally induced facial wounds in monkeys. As mentioned above, we have seen similar improvements in wound healing when BTX-A is used with eyelid surgery. However, the utilization of this type of pharmacological wound immobilization may be particularly important in the repair of traumatic injury. The successful cosmetic repair of such injuries is often difficult, and of great psychological as well as aesthetic value to the patient.

SUMMARY AND CONCLUSIONS

The growing medical literature on the use of BTX-A for cosmetic purposes reinforces what many physicians have learned from their own personal experience: that BTX-A therapy is highly effective in treating a wide variety of hyperfunctional facial lines. Moreover, it is easy to use, well-tolerated by patients, and extremely safe. Its versatility allows physicians to effectively treat conditions for which surgery would not be appropriate and to enhance and prolong the effects of other procedures. It may not be long before BTX-A therapy becomes an integral part of all cosmetic practices.

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