



Update on botulinum toxin for facial aesthetics

Q1 Jennifer Clay Cather, MD^{a,b,*}, J. Christian Cather, MD^{a,b},
Alan Menter, MD^{a,b}

^aTexas Dermatology Research Institute, 5310 Harvest Hill Road, Suite 260, Dallas, TX 75230, USA

^bBaylor Medical University, TX, USA

Q2

Q3

Clostridium botulinum was implicated over 100 years ago as the cause of muscle paralysis secondary to food poisoning [1]. This gram-positive anaerobic bacterium produces the most potent neurotoxins known to mankind. Seven distinct antigenic botulinum toxins (A, B, C1, D, E, F, and G), produced by different strains of *C. botulinum*, have been described. Human disease is caused by five of these serotypes (A, B, E, F, and G) [2]. Type A is the strongest, followed by types B and F, which are potentially of value in patients who develop antibodies to type A [3,4]. Botulinum toxin types E and F are short acting [5].

Botulinum toxin is synthesized as a single-chain protein, which is inactive until it is cleaved by bacterially produced proteases into its active form. All active botulinum toxins are comprised of two chains: one heavy chain joined to one light chain by a disulfide bond.

Clostridium botulinum has been in therapeutic use since the 1970s. Scott [6] is largely responsible for the initial clinical use of botulinum toxin in the treatment of strabismus where botulinum toxin injected into extraocular muscles results in selective muscle paralysis and improved ocular alignment. Since that time, numerous other conditions including dystonias (ie, blepharospasm and torticollis), involuntary muscle hyperactivity (ie, hemifacial spasm, tremors, and tics), and spasticity (as in multiple sclerosis and

cerebral palsy), have been treated successfully with botulinum toxin [7].

Facial rejuvenation has been revolutionized by the use of botulinum toxin over the past 15 years with safe use by clinicians using botulinum toxin type A producing excellent cosmetic results [5,8,9].

The toxins: Botox, Dysport, and Myobloc

There are three sources of botulinum toxin commercially available. Type A botulinum toxins include Botox (Allergan, Inc., Irvine, CA) and Dysport (Ipsen Limited, Maidenhead, Berkshire, UK). One type B botulinum toxin is currently available: Myo(neuro)bloc (Neurobloc in the United States) (Elan Pharmaceuticals, South San Francisco, CA). Currently, in the United States, only Myo(neuro)bloc and Botox are available. Botox was approved by the Food and Drug Administration (FDA) for ophthalmic indications in 1989 and for cervical dystonia in December 2000. Formal approval for its use in the glabellar wrinkles is imminent. Myo(neuro)bloc was approved by the FDA for the treatment of cervical dystonia in December 2000.

Mechanism of action

Botulinum toxins act by a three-step process: (1) binding, (2) internalization by receptor-mediated endocytosis, and (3) enzymatic activation (Fig. 1). Different serotypes bind to different sites on the motor nerve terminal and within the motor neuron. The heavy chain mediates the selective saturable binding to the presynaptic cholinergic neuromuscular end plate. The light chain acts inside the cell to block

Q4

* Texas Dermatology Research Institute, 5310 Harvest Hill Road, Suite 260, Dallas, TX 75230.

E-mail address: amresearch@texasderm.com (J.C. Cather).

Q5

0733-8635/02/\$ – see front matter © 2002, Elsevier Science (USA). All rights reserved.

PII: S0733-8635(02)00043-8

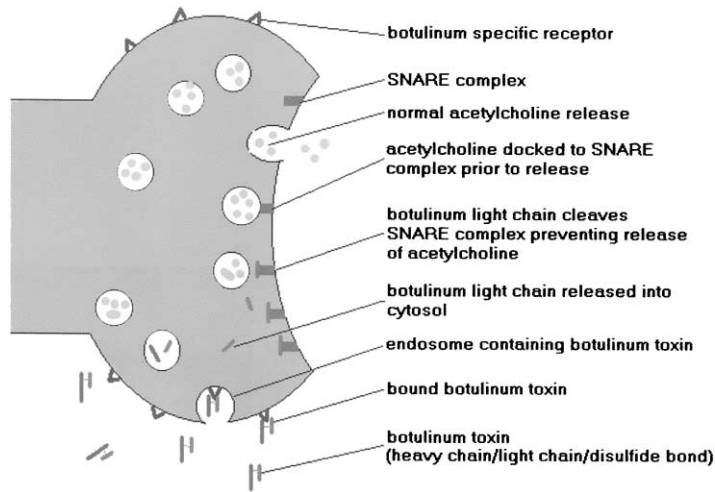


Fig. 1. Botulinum toxin mechanism of action at motor end plate.

the release of the vesicle-bound neurotransmitter acetylcholine from autonomic nerve endings [10]. Botulinum toxins have specific light-chain intracellular binding sites and different sites of action on different SNARE (synaptosomal associated protein receptor [SNAP]) proteins, which is a neuronal exocytotic apparatus that regulates the membrane docking and fusion of synaptic vesicles and the release of acetylcholine. The SNARE proteins, which include vesicle-associated membrane protein (VAMP), syntaxin, and SNAP-25, are intimately involved in releasing acetylcholine at presynaptic terminals [11]. Botulinum toxins type A, C1, and E cleave SNAP-25 [12]. Botulinum toxins type B, D, F, and G all cleave synaptobrevin (VAMP) each at different sites [13]. Synaptobrevin is an intracellular protein necessary for the fusion of the synaptic vesicle to the cell membrane leading to the eventual release of acetylcholine into the neuromuscular junction [14]. Myo(neuro)bloc acts on synaptobrevin at Gin76-Phe77. Restoration of muscle activity usually commences between 3 and 4 months after injection probably because of the regeneration of new end plate units [15].

The toxicity of all botulinum toxins is expressed in units. One unit is the amount of toxin required to kill 50% of a group of female Swiss-Webster mice weighing 18 to 20 g after intraperitoneal injection [16]. It is essential to recognize that units vary greatly between the different botulinum toxin preparations. In the literature the approximate equivalencies are as follows: 1 U Botox = 3 to 5 U Dysport = 50 to 100 U Myo(neuro)bloc [11,15,17,18]. The commercial product name is mandatory for medical communica-

tions addressing specific applications to avoid complications related to dosing. The lethal dose of Botox for humans is estimated to be between 2500 and 3000 U for a 70-kg person [7,19,20]. The administration of the entire contents of one vial of Botox (ie, 100 U) is way below the lethal dose for a human and because most cosmetic applications usually require less than 30 U per session, the safety margin is great [7,19,20].

Botox is a protein that is capable of inducing the formation of IgG-neutralizing antibodies [21]. These antibodies are more likely to form with larger protein loads per session. Neutralizing antibodies have only been documented in the neurologic literature in cases involving more than 100 units or more of Botox per injection session [22]. The incidence of antibody production is estimated to be between 3% and 5% in neurology cases; however, no antibody resistance has been reported to date in dermatologic cases using Botox [23]. It is wise for clinicians using Botox for cosmetic purposes to limit the total amount of Botox injected to less than 100 units per session [22]. The antigenic potential of Botox was further decreased when a new batch was released in 1997 with a lower protein load per dose [24]. In patients with neutralizing antibodies to Botox and no clinical improvement after injection, the serologically distinct Myo(neuro)bloc has been found effective in neurologic cases [13,18,25]. Neutralizing antibodies to type A toxins do not cross-neutralize the activity of type B [26]. The antigenic potential of Myo(neuro)bloc is unknown, although 50- to 100-fold higher doses are required resulting in a 10 to 20 times larger protein load per dose [5].

Preparation of toxins

Preparation of Botox

Botox is available in vials containing 100 U vacuum-dried type A toxin, albumin, and sodium chloride, which must be kept frozen at -5°C or colder until reconstituted. Most clinicians use between 1 and 3 mL of saline to reconstitute Botox [27]. To produce a preparation of 5 U per 0.1 mL, 2 mL of preservative-free saline is mixed carefully and slowly into a 100-U vial of Botox. Acceptable results have also been reported by diluting one vial in up to 10 mL preservative-free saline (1 U/0.1 mL) [28]. If vigorously mixed, inactivation of toxin may result in decreased potency [2]. Once diluted, the mixture should be stored in a refrigerator at 2° to 8°C and used within 4 hours [15,29], although some authors have found the potency to decrease slowly over a 1-week period, with minimal to no activity remaining at 2 weeks [15]. Although the solution is rarely used after 1 week given the lack of preservative in the dilutant, effectiveness has been noted 1 month after reconstitution with preserved saline and refrigeration [30].

The dilutant volume used can be adjusted to give two different outcomes. A smaller dilutant volume translates into a higher dose delivered in a smaller volume and a more localized effect [27,31,32]. A larger dilutant volume translates into a smaller dose per volume injected and a more diffuse effect [27]. Larger injection volumes, however, are possibly associated with more discomfort [33].

Preparation of Myo(neuro)bloc

Myo(neuro)bloc is available in vials containing 2500, 5000, and 10,000 U. The aqueous solution (5000 U per milliliter) does not require constitution and is ready to use at pH 5.6. It can be diluted to desired concentration. Because of the acidic pH it may possibly produce more stinging than type A. The solution is composed of albumin, sodium succinate, and sodium chloride, and is stable in sealed unopened vials for up to 21 months if refrigerated; however, once diluted with preservative-free normal saline it should be injected within 4 hours because of lack of preservative.

Preparation of Dysport

Similar to Botox, this product must be reconstituted. Usually a 500-U vial, which may be stored at room temperature, is diluted with 2.5 mL of

preservative-free saline per vial to obtain a concentration of 200 U per milliliter [15,34–36].

Clinical uses

Skin changes associated with the aging face are categorized as either wrinkles or lines [37]. Wrinkling consists of many multidirectional, superficial indentations of the skin, which result from thinning of the dermis with age [33,37]. Lines are single distinct depressions of the skin and are further classified into superficial creases (extending to dermis) or deeper furrows (extending to subcutaneous tissue); regardless, these generally result from underlying hyperfunctional muscles [37,38]. The term *rhytide* is derived from the Greek word *rhytis*, which means wrinkle.

Facial rhytides have been categorized based on whether they are static or dynamic and whether they are caused by tissue redundancy or tissue loss (Fig. 2). Dynamic rhytides are common over the upper one third of the face, especially the glabella and forehead. Static rhytides are caused by exogenous sources, such as gravity, and environmental toxins, such as smoke and ultraviolet radiation. Static and dynamic rhytides are seen together around the eyes (crow's feet); forehead; and cheeks.

Treatments for facial rhytides include peels; laser resurfacing; fillers (collagen, fascia, or hyaluronic acid); fat injections; and surgical procedures, such as rhytidectomy, eyebrow lift, and blepharoplasty [37]. Surgical procedures correct gravity-induced changes and can remove excess tissue; however, these procedures may lead to significant downtime, nerve damage, and infection [37]. Fillers replace volume lost through aging or disease; they correct the static changes within the skin. Additionally, fillers improve facial contours and augment facial features, such as lips, cheekbones, and chin, but in most instances only have temporary effect.

Most facial rejuvenation techniques do not target the cause of hyperfunctional lines: the muscle. The chemical paresis induced by botulism toxin is a relatively noninvasive and safe means of eliminating muscle contraction, which leads to dynamic wrinkles and furrows. With aging, ridges and wrinkles appear perpendicular to the causative muscle fibers [39]. There are multiple reports attesting to the excellent cosmetic results obtained with Botox injections [7,8,15,40–44]. In one study involving 162 patients, statistically significant reduction in hyperfunctional facial lines were found at 2 to 3 weeks after Botox injection; 95% of the patients treated had cosmetic

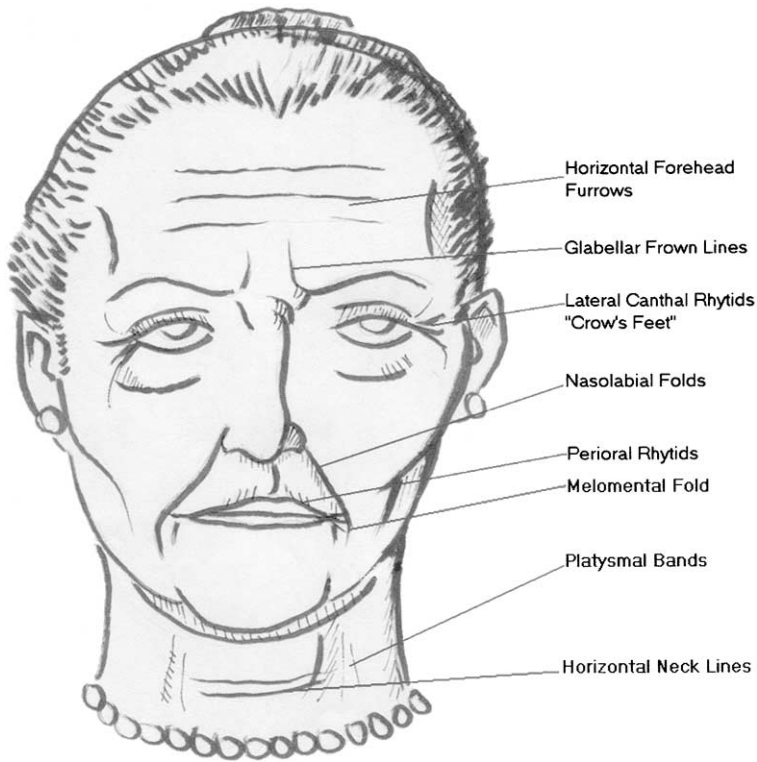


Fig. 2. Hyperfunctional lines of the face.

improvement with the best results noted with forehead lines, followed by glabellar furrows and crow's feet [40]. More than 80% of these patients were extremely pleased with their results and returned for further treatment at 4 to 5 months when the effects wore off [40]. Horizontal forehead lines, glabellar forehead furrows (frown lines), and lateral canthal lines (crow's feet) are the most common dynamic, hyperkinetic facial lines treated with Botox [45,46]. Complications are rare and mostly temporary (see later) [3,47,48]. A site-specific review follows.

Upper one third of the face

Glabellar furrows

Glabellar furrows are formed by the actions of the procerus, corrugator supercilii, and medial fibers of the orbicularis oculi (Fig. 3) [49]. Numerous injection techniques have been described with early injections incorporating electromyographic guidance to locate the muscle accurately [45,50,51]. In a placebo-controlled study of 263 patients with glabellar lines of at least moderate severity [42], Botox decreased glabellar lines in 80% to 90% as assessed by both

physician and patient measures and photographic methods (Fig. 4). Injection of Botox into the corrugator supercilii muscles gives temporary chemical denervation muscle paralysis for up to 6 months followed by full recovery [7,8,38,40,41,51,52]. A double-blind placebo-controlled study with an

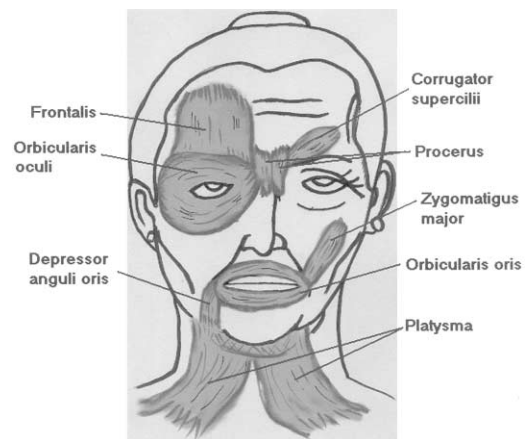


Fig. 3. Important facial musculature (not drawn to scale).



● = Allergan FDA study injection technique

Fig. 4. Glabellar injection sites. Solid circles = Allergan FDA study injection technique.

electromyographic injection technique involving 30 patients found Botox to be effective and safe for the reduction of glabellar frown lines [51]. Another pilot study involving 57 patients using Botox injected under electromyographic guidance found that 81% (46 of 57) of patients injected with 10 U into each corrugator achieved full corrugator muscle paralysis and 67% (38 of 57) were satisfied with their improvement and desired continued injections [52]. Four patients who were pleased with their improvement but wanted complete disappearance of glabellar wrinkles were found to have minimal activity of their corrugators on electromyographic analysis; however, their lateral brow musculature seemed to contribute to their glabellar wrinkling. After 5 U Botox was injected into these accessory muscles two of the four patients had disappearance of their glabellar wrinkles. In experienced hands, electromyographic guidance is seldom used except in rare instances where clinical response was not obtained with prior injections. Superior results are more difficult to obtain in patients with thick sebaceous skin and deep dermal scarring [52], especially those with a single midline deep glabellar furrow. The glabellar spread test (spreading the glabellar wrinkles apart with the thumb and index finger) is helpful in estimating the maximal results likely from Botox [52,53].

A Botox dose-ranging study on glabellar creases by Hankins et al [33] involving 46 patients using the five standard injection site technique (one midline glabellar injection 4 mm below the brow line, and two on each side, one just above and one just below the medial brow in line with the medial canthus of the eye) determined that the minimum effective dose was 2.5 to 4 U per injection site. The founders of Botox for facial cosmetic purposes, Allstair (dermatologist) and Jean (ophthalmologist) Carruthers, currently use seven injection sites with a total of 20 to 25 U for a

female brow and 35 U for a male brow [5,47]. If Dysport is used, the doses reported in the literature range from 16 to 80 U for the glabellar region [15,34,36,54].

Transient ptosis is the most significant complication of injection in the glabellar area and can occur in up to 5% of patients [42,55]. The risk of ptosis is minimized by the correct injection volume and site (ie, staying above the orbital ridge), possibly by the patient staying vertical for 4 hours, and the injection site not being manipulated [53]. Lid ptosis results when Botox affects the levator muscle, which normally elevates the eyelid and may persist for 2 to 4 weeks. A placebo-controlled trial involving electromyographic-guided injections of 10 U Botox into each corrugator revealed increased incidence of ptosis when injections were given in a downward and medial direction [56]. In an excellent review by Werschler and Baumann [57], the following clinical pearls were given to minimize complications. First, placing a fingertip against the medial to superior orbital rim during injection decreases the risk of toxin migration [3,57]. Second, all Botox injections should be intramuscular with the needle bevel down to direct the toxin directly to the targeted muscle and limit diffusion elsewhere unless specified otherwise. Finally, if ptosis is severe, one to three drops of aproclonidine 0.5% eye drops (Iopidine) can be given three times a day to the affected side to give 1 to 2 mm of elevation [3,47,53].

Horizontal forehead lines

The frontalis (see Fig. 3), a vertically oriented muscle, is responsible for horizontal forehead lines [49]. To soften or eliminate forehead lines and to “open” the eyes, injections are given at 4 to 8 sites, 2 to 3 cm above the orbital rim with several injection techniques and doses reported in the literature (Fig. 5). Guerrissi and Sarkissian [58] injected 17 patients with 14 to 20 U Botox (25 U per milliliter) and achieved satisfactory results. Despite avoiding injecting below 2.5 cm above the brow, 2 out of the 17 developed brow ptosis (lasted 55 to 70 days). Another technique used involves asking patients to raise their eyebrows and then injecting Botox 10U per milliliter into the ridges between the lines, again avoiding injecting below two finger-breaths above the eyebrow [59]. Some authors believe the elevations between the lines contain the most frontalis muscle and are the optimal injection sites [53,57,59]. Carruthers and Carruthers [5,47] use 10 to 20 U Botox for women distributed over four to five injection sites (the lateral two at the midpupillary line and then two further injections spaced equally

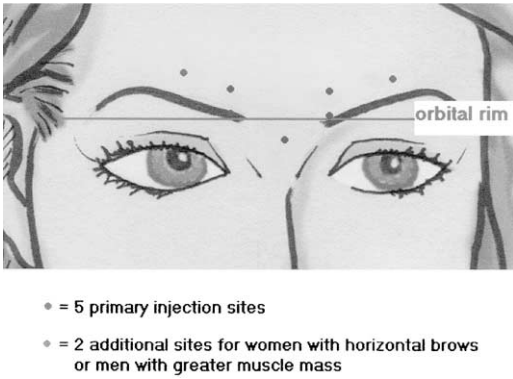


Fig. 5. Carruthers injection sites.

between) across the midbrow (an imaginary horizontal line halfway between the eyebrows and the hairline). Care must be taken to ensure that injections are given at least 2 cm above the eyebrow. Additionally, for individuals with lower brows or any degree of brow ptosis, injecting up to 2.5 U in the lateral aspect of the eyebrow (see later) along with glabellar injections lifts the lateral brow, thereby avoiding brow ptosis, improving the treatment of forehead lines [47,60]. The result is a greater opening of the orbit and a more relaxed appearance. For men with male pattern balding, injections are typically given higher up on the lateral forehead (Fig. 6) [57]. The amount of Dysport reported in the literature for this site ranges between 40 and 120 U [15,36,54].

Complications in this area, primarily brow ptosis, may result from overtreating the frontalis muscle

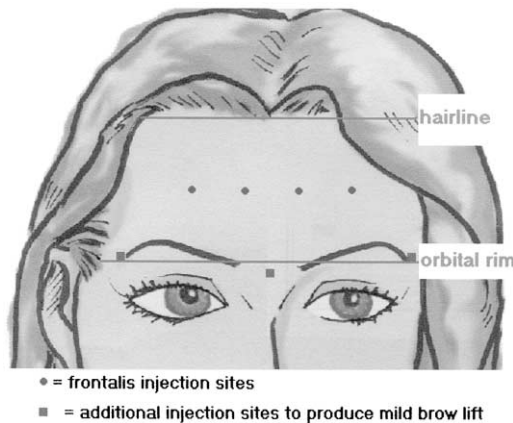


Fig. 6. Forehead injection sites. Solid circles = frontalis injection sites; solid squares = additional injection sites to produce mild brow lift.

(ie, injecting too much of the frontalis with no skip areas allowing movement or treating within one fingerbreadth or 1 to 2 cm of the eyebrow) [3,49]. Also, treating the lateral frontalis past its temporal insertion (ie, lateral to the midpupillary line) can lead to drooping of the lateral eyebrow and eyelid complex, resulting in a tired appearance [47,49,57]. Additionally, patients who recruit the frontalis to elevate the eyebrows above the superior orbital rim may benefit from surgical correction of the lid and brow [49,57].

Brow lift

A temporary chemical brow lift can be obtained by chemoparalysis of the brow depressors, which include the procerus; medial fibers of orbicularis oculi (depressor supercillii); and corrugator supercillii (see Fig. 3) [49]. The elevation results from an unopposed action of the frontalis muscle, which raises the brow [60–63]. Huang et al [63] reported the largest brow lifts (2 to 3 mm at central brow) after 5 U Botox (5 U/0.1 mL) was injected into the glabellar region of each brow along with an additional 10 U given in four injections along the orbital rim starting at the midpupillary line and extending to the lateral brow on each side (Fig. 7). To avoid eyelid ptosis, the author advised slowly injecting Botox with the needle aimed at an upward and horizontal direction above the orbital rim to decrease the incidence of toxin dispersion to the upper eyelid levator muscle [63]. It is worthwhile noting that injections performed below the orbital rim in the medial and midorbital region are associated with a greater risk of ptosis.

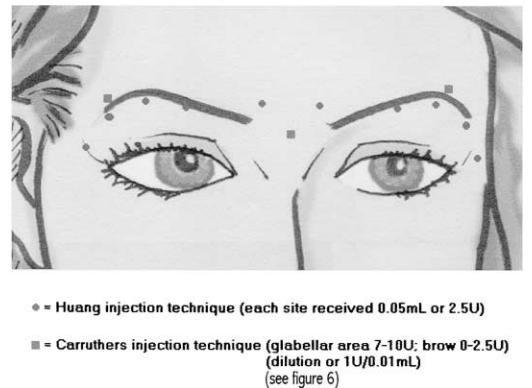


Fig. 7. Brow lift. Solid circles = Huang injection technique (each site received 0.05 mL or 2.5 U); solid squares = Carruthers injection technique (glabellar area, 7 to 10 U; brow, 0 to 2.5 U; dilution or 1 U/0.01 mL).

Another technique involves one injection of 7 to 10 U Botox in the midline glabellar area immediately below the line joining the eyebrows, followed by one injection on each side into the supralateral eyebrow outside the bony orbital rim (see Fig. 7) [60].

Obtaining a brow lift in men is more difficult, because the muscle mass is larger and 35 U or more are frequently required [47]. Male brows are typically horizontal, and often they have lateral depressors. Botox brow lift injections should be given in the medial and lateral brow (2 to 3 U injected directly above the lateral canthus just above the orbital rim) [47,57]. Medial elevation of the brow occurs with injection into the midpoint of the root of the nose at the level usually equal to the medial canthi. Injections at this site weaken the medial orbicularis oculi muscle fibers (depressor supercilli), which interdigitate with the most medial aspect of the insertion of the corrugator complex [49]. These fibers have a tendency to pull the brow in a downward direction; weakening leads to slight median brow elevation and at times a widening of the glabella because of the unopposed action of the frontalis [7,43,49]. Massaging the procerus muscle after injection may help enhance this effect [7,47].

Women have two options: accentuation of the midbrow arch or a flare brow [57]. To obtain a midbrow arch, a single injection of 2 to 4 U at the midpupillary line into the muscles of the depressor of the brow, staying 1 cm above the orbital rim, results in unopposed elevation of the midbrow by the frontalis [47,57]. A flare brow (ie, greater elevation laterally) is obtained by doing the midpupillary injection above along with another injection at the lateral aspect of the brow at the lateral canthal line and at the midpoint between the medial and lateral injections [57]. For greatest effect, the lateral orbicularis muscle fibers also should be injected, as described later.

Periocular crow's feet

Contraction of the orbicularis oculi along with the risorius and zygomaticus (mouth corner elevators) gives rise to crow's feet [49]. The lateral orbicularis is injected in one to four sites with total doses ranging from 5 to 15 U Botox followed by gentle massage for a more even result (Fig. 8) [47,64]. In one study involving 15 women, 2 U of Botox injected subdermally 3 mm inferior to the lid margin at the midpupillary line improved lower eyelid wrinkles [65]. It is important to avoid injecting too deeply at this site because the toxin may migrate into the orbit and paralyze the extraocular muscles. When this 2-U injection is given in combination with 12 U Botox



Fig. 8. Injection sites for crow's feet.

at the lateral orbital area, further improvement was seen [65]. Three lateral injection sites were chosen, all at 1.5-cm radius from the lateral canthus, which is 1 cm outside orbital rim. The superior injection point was 3 mm above the horizontal, the middle injection site located 1 cm below the first, and the inferior injection site just lateral to the vertical 1.5 cm below the lateral canthus. A significant increase in palpebral aperture was seen when both the lower lid and the lateral orbital area were treated; lateral rounding of the lower eye was found to be inviting or attractive according to the study patients. This lateral rounding is especially evident in Asian eyes. Areas injected are the lateral canthal or orbital orbicularis and the malar area near the inferior aspect of the orbicularis oculi muscle.

One case of herniation of the orbital fat has been reported 1 week after routine periocular injection. This presented as a deformity of the inferior orbital rim that persisted as chronic edema for 5 months after the procedure. To avoid this complication the authors recommend avoiding the inferior aspect of the orbicularis of the lower eyelids [66]. In addition, to reduce purpura, the injection sites must be chosen carefully (possibly under magnification), making every effort to avoid the numerous vessels around the lateral eye region, and pressure should be applied immediately after injection. Injections over the proximal aspect of the zygomaticus major muscle may soften lateral canthal rhytides associated with smiling; however, an asymmetric smile may result if injecting below the inferior margin of the zygoma [46]. Younger patients with minimal skin laxity do better than older patients with redundant skin [64]. The amount of Dysport reported in the literature for this region is 20 to 30 U per side [15].

It is important to individualize treatment and see where the crow's feet are located when patients squint and smile. For many patients they are both above and below the lateral canthal line and all dynamic sites should be treated for the best results [57]. Injections can be done every 1 cm where there is muscle movement up to the midpupillary point [57]. Additionally, the lower eyelid can be treated by asking the patient to hold their head back and look up, retracting the lid inferiorly, injecting 2 to 3 U subcutaneously at the midpupillary line and then distributing the Botox by rolling a cotton swab in the area (beware of bruising). For a more rounded appearance one can inject 2 U at the midpupillary line and another 2 U halfway between the midpupillary line and the lateral canthus; again, especially useful in Asians. It is important to remember that injections below the orbital rim are associated with an increased risk of diplopia because of diffusion of Botox into the extraocular muscles [49,57]. Injections within 1 cm of the lateral canthus may also allow toxin migration to the lateral rectus, which may result in diplopia. Also, Werschler and Baumann [57] note that lateral eyebrow elevation usually occurs to some extent when the lateral orbicularis oculi muscles are weakened because of the unopposed elevation of the lateral brow by the lateral frontalis. If too much elevation occurs, a few injections into the frontalis reposition the brow in a downward position.

Middle and lower face

Lips

Perioral rhytides, accentuated by pursing the lips, may be softened when small amounts of Botox are injected symmetrically. Vertical upper lip wrinkles (smoker's lines) are caused by contraction of the orbicularis musculature. One to 2 U under each wrinkle at the vermilion border may soften the lines, but no more than 1 to 2 U should be injected per lip quadrant (ie, on either side of Cupid's bow) and only two to three wrinkles should be treated at a time [47,67]. Alternatively, this may be performed using injections 5 mm above the vermilion, 1 to 2 cm apart, or by injecting from the buccal surface of the upper lip, outward, using lidocaine gel anesthesia (Nick Lowe, personal communication). Microparesis may be a concern in this area interfering with whistling, suction, and elocution. Lip orbicularis muscle injections must be done using small volumes with a high dilution, and produce only partial and short-term results.

Mouth frowns

The downward turn of the lateral corners of the mouth (marionette lines, drool groove, or melomental folds) may be improved by chemodeneration of depressor anguli oris, thereby allowing elevation of the mouth corners by the unopposed zygomaticus major and minor; additionally, platysmal injections may also be helpful because the lateral bands of platysma help pull the mouth down [47,68,69]. Depressor anguli oris muscle injections may produce a good lift of the corners of the mouth but may produce transient smiling and elocution problems; it is not recommended for singers, musicians, or patients who use their perioral muscles with intensity [67]. The depressor anguli oris can be located inferior to a point 1 cm lateral to the commissure while pulling down on the corners of the mouth [47]. Three to 5 U of Botox are injected 10 mm lateral to the angle of the lips. This technique may be useful in conjunction with soft tissue filling agents in this area because it prevents molding and contortion of the filler [67,69].

Mentalis

A prominent mental fold and a pebbly or cobblestone "peau d'orange" chin may be improved by injection of 5 to 10 U Botox into the point of the chin; this may also flatten the mental fold [45,47,69]. Injection here can also augment the use of fillers. If the injection is done into the mental fold area, however, an incompetent mouth may result [47]. Gentle massage after injection may be helpful [3].

Nasolabial folds

Injection to weaken the zygomaticus major has not given dramatic results and may not be uniformly useful [47]. The upper lip may lengthen or droop, which simulates aging [47]. If a short lip is present, Botox may be useful because it may flatten the nasolabial fold, lengthen the lip, have a prolonged effect of up to 6 months, and augment the use of fillers. Injection of 2 to 3 U into the levator labii superioris alaeque nasi, on either side of the nose, may smooth out the superomedial nasolabial fold [3,47,69].

Neck

The first report of platysmal rejuvenation using Botox was by Blitzer et al [70]. Both hypertrophic platysmal bands and horizontal neck lines have improved after Botox [45,47,69,71]. The central platysmal bands thicken and contract with time and contribute to the formation of jowls and loss of definition of the neck [68,72]. The platysma originates in the superior fascia of the upper chest (the pectoralis and deltoid fascia) and extends over the full length of

the neck up past the mandible. Most fibers (two of three) interlace in the midline [72]. Some of the fibers insert into the mandible and a few insert at the lateral oral commissure, and result in a downward pulling on the corners of the mouth (see Fig. 3) [72]. A variety of different injection techniques have been reported in the literature [3,47,68]. Patients are requested to contract the platysma, the hypertrophic band is grasped, and injections given at regular intervals from 1 to 3 cm from the jaw line to the lower neck for a total dose of 15 to 21 U per band [3,45,47,68]. Usually two to four bands are treated in one session using 50 to 100 U per session [3]; however, up to 200 U has been required in one session [68]. Immediate relaxation of the platysma is seen with onset of weakness occurring in 3 to 5 days. Repeat injections every 4 to 6 months are required with prolonged effects seen with each subsequent injection [68]. Horizontal neck lines are injected in the deep intradermal plane with a total of 10 to 30 U given at intervals of 2 to 3 cm [47,69]. Complications seen in this region include transient edema, ecchymoses, muscle soreness, neck flexor weakness, and headaches [68]. Rarely, laryngeal muscle weakness, hoarseness, and dysphagia may occur 3 to 4 days after injection, especially with doses around 75 to 100 U [3,47]. Meloclopramide hydrochloride (Reglan) may improve swallowing because it stimulates the upper gastrointestinal tract [3].

Hyperhidrosis

Hyperhidrosis most commonly involves the axilla, palms, or soles. For all these sites Botox has effectively decreased sweating [73–78]. Hyperhidrosis may also involve the face and neck. Gustatory sweating (Frey's syndrome and auriculotemporal syndrome) may occur after parotid gland surgery or after the preauricular region has been traumatized. Denervated sweat glands may become inappropriately reinnervated by parasympathetic nerve fibers that previously had the salivary gland as their target. As a result, sweating of the facial skin occurs during meals. Intracutaneous injections of Botox, 2.5 U per square centimeter in doses up to 21 to 38 U, depending on affected area, using 7 to 25 sites, lead to satisfactory responses lasting an average of 17.3 months [79–83]. Complications reported include weakness of the mimic muscles; no masticatory muscle weakness has been reported.

Botox as adjunct to surgical procedures

When used in conjunction with surgical procedures, Botox is frequently helpful [67]. Plastic sur-

geons have come to appreciate the effect of Botox when used before the surgical resection of the corrugator musculature for the permanent correction of glabellar creases [84,85].

Botox and brow lift

Botox-assisted brow lift has stable, long-lasting, aesthetic results with minimal morbidity [61,71]. Brow lifts may have an unpredictable cosmetic outcome based on postsurgical healing. Stabilization of brow musculature is important for a predictable final brow position. Studies have suggested that after surgical elevation, periosteal reattachment requires 12 weeks to become adherent. The hypokinesis provided by Botox injections provides more predictable healing during this interval [61]. Some surgeons believe Botox-assisted brow lifts may help improve the cosmetic outcome.

Botox and laser resurfacing

In general, lasers address static wrinkles and stimulate new collagen, whereas Botox prevents the recurrence of dynamic wrinkles [53,67,86]. Botox injection 2 to 3 weeks before laser resurfacing may produce superior results [67]. In one study involving 53 patients, the group that received Botox before and after laser resurfacing (N = 37) had an aesthetic outcome that was rated 21% greater after 6 months than those who underwent laser resurfacing alone [87]. By using Botox along with skin resurfacing, the recurrent muscle activity that can disturb the lamellar organization of the newly rejuvenated skin is prevented, and the cosmetic improvement achieved by the laser resurfacing is better maintained giving an improved and longer-lasting outcome [67]. Botox prevents muscle contractions from shaping new collagen into wrinkles.

Botox and peels

Botox should be done 2 to 3 days before chemical peels and not immediately before or after peels because soft tissue swelling may result in increased migration of the toxin [57].

Botox and fillers

Botox may decrease the amount of fillers required for lines. Giving Botox 2 to 4 weeks before fillers softens the muscle contractions and gives a more accurate idea of how much filler is required [57].

Doing Botox and tissue fillers on the same day may possibly lead to overcorrection.

Clinical response

There is no clinical standardization on the use of botulinum toxin type A. Known factors affecting clinical response are commercial preparations, reconstitution, anatomy, dose and response relationship, storage, immunogenicity, and operator skill [2]. When feasible, injections should be performed intramuscularly. Intradermal injections are associated with less efficacy because Botox can only reach the muscle fiber by dispersion. Injection technique varies greatly in the literature and is site specific as previously described (see individual sites). Some authors advocate tangential injections instead of perpendicular injections [28,53,86]. The toxin diffuses an average of 1 cm in all directions from injection sites [47]. The greater the dilutant, the greater is the diffusion. Site manipulation (rubbing or massaging) also increases diffusion. For botulinum toxin type B, the extent of diffusion may be increased because its molecular weight is less than the type A toxins [11]. Many authors advocate overuse of muscles for 2 to 4 hours after injection to encourage toxin uptake and obtain optimal responses [86]. Effects usually appear in 1 to 3 days [40] and at-rest appearance effects last longer with over 85% of patients responding in 7 days of treatment and peak response occurring 30 days after injection. Forty percent of patients are likely to report moderate or better improvement 4 months after treatment [42].

Adverse effects

Botox has been associated with side effects that are minor and transient [3,7]. No reports of allergic or urticarial reactions have been reported with facial aesthetic procedures. A psoriasiform eruption, which resolved spontaneously after 5 months, has been reported in one patient who received 15 U Botox for a lateral rectus palsy [88]. Transient bruising at injection site (especially common in patients taking aspirin, nonsteroidal anti-inflammatory drugs, warfarin, vitamin E, and in crow's feet injections), transient headaches (13.3%), and pain (2.2%), have been reported [42]. Bruising can be minimized by using a 30-gauge needle and changing it every three to seven injections, preinjection application of ice or topical anesthetics, and avoidance of blood thinners [28,47,57]. Application of pressure after injection

minimizes bruising and deep muscle hematomas, which may be painful for days after the procedure [57,86]. Headaches may be the result of hitting the periosteum or deep muscle hematomas [57]. Interestingly, relief of tension headaches and migraine headaches is more commonly reported [47,89]. Pain may be more often severe for women when they are menstruating [57]. Unbuffered lidocaine has been added to reconstituted Botox; however, the injections are more painful with this acidic mixture and it is not recommended [57].

Contraindications

There are no reported cases of teratogenicity from Botox injection. One study involving nine patients who were pregnant during injection (dose unspecified) had one premature delivery, which was not thought to be related to the toxin [16]. Despite the lack of teratogenicity, most of the scientific community refrains from injecting pregnant or lactating women. A history of a neuromuscular disease or a known history of sensitivity to Botox or human albumin should exclude patients from Botox injection. Aminoglycosides can interfere with neuromuscular transmission and potentiate the effects of Botox injections [90]. Areas with active infection should not be injected.

Summary

The use of botulinum toxin has revolutionized the treatment of facial lines with an incomparable safety record over the past 14 years. The most common used injection sites are shown in Fig. 9. FDA approval for Botox in the treatment of glabellar lines is imminent and as a result its use will likely increase dramatically. It is essential that practitioners have a detailed and specific knowledge of the facial and neck musculature to be injected to minimize untoward side effects, especially in the early days of new users' learning curve. The specifics of the dilutions and units per amount used for the various different commercial forms of botulinum toxin types A and B need to be understood fully and standardized together with the potential for antigenicity with the higher protein load of type B. In addition, specific indications for the use of botulinum toxin as adjunctive therapy for specific facial surgical procedures (ie, blepharoplasty, surgical brow lift, and laser resurfacing) will become better understood.

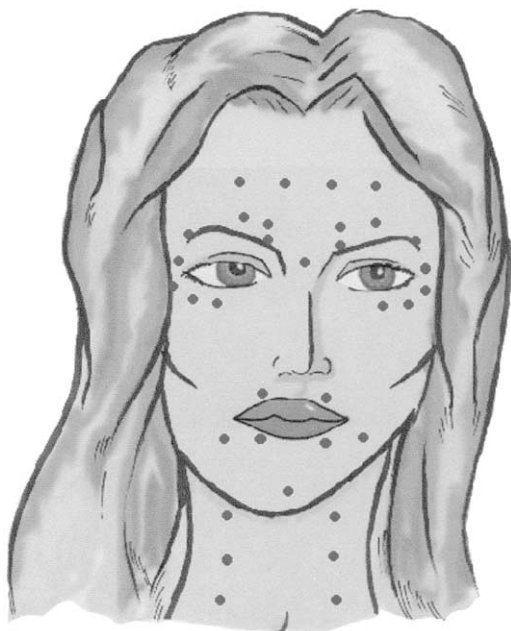


Fig. 9. Injection summary.

Finally, even though the anatomy of the facial musculature is well described, individual differences in men and women, in different population groups, and in tissue qualities, such as turgor and elasticity [89], are important factors to be considered before undertaking botulinum toxin injections. It is likely that the use of specific measuring devices, such as digital imaging, will further help define the use of botulinum toxin for different muscle groups and facial aesthetic indications.

References

- Q7**
- [1] Scott AB, Rosenbaum A, Collins CC. Pharmacologic weakening of extraocular muscles. *Invest Ophthalmol* 1973;12:924.
 - [2] Huang W, Foster JA, Rogachefsky AS. Pharmacology of botulinum toxin. *J Am Acad Dermatol* 2000;43:249.
 - [3] Klein AW. Complications and adverse reactions with the use of botulinum toxin. *Semin Cutan Med Surg* 2001;20:109.
 - [4] Shimizu T, Sakaguchi G. Production and properties of type F toxin. In: Jankovic J, Hallet M, editors. *Therapy with botulinum toxin*. New York: Marcel Dekker; 1994. p. 87.
 - [5] Carruthers A, Carruthers J. Botulinum toxin type A: history and current cosmetic use in the upper face. *Semin Cutan Med Surg* 2001;20:71.
 - [6] Scott AB. Clostridial toxins as therapeutic agents. In:

- Simpson LL, editor. *Botulinum neurotoxin and tetanus toxin*. New York: Academic Press; 1989. p. 399.
- [7] Carruthers A, Kiene K, Carruthers J. Botulinum A exotoxin use in clinical dermatology. *J Am Acad Dermatol* 1996;34:788.
- [8] Carruthers A, Carruthers J. Botulinum toxin in the treatment of glabellar frown lines and other facial wrinkles. In: Jankovic J, Hallet M, editors. *Neurological disease and therapy: therapy with botulinum toxin*. New York: Marcel Dekker; 1994. p. 577.
- [9] Carruthers JDA, Carruthers A. Botulinum A exotoxin in clinical ophthalmology. *Can J Ophthalmol* 1996; 31:389.
- [10] Simpson LL. The origin, structure and pharmacological activity of botulinum toxin. *Pharmacol Rev* 1981;33:155.
- [11] Carruthers A, Carruthers J. Toxins 99. new information about the botulinum neurotoxins. *Dermatol Surg* 2000; 26:174.
- [12] Binz T, Blasi J, Yamasaki S, et al. Proteolysis of SNAP-25 by types E and A botulinum neurotoxins. *J Biol Chem* 1994;269:1617.
- [13] Callaway JE, Arezzo JC, Grethlein AJ. Botulinum toxin type B: an overview of its biochemistry and pre-clinical pharmacology. *Semin Cutan Med Surg* 2001; 20:127.
- [14] Schiavo G, Benfenati F, Poulain B, et al. Tetanus and botulinum-B neurotoxins block transmitter release by proteolytic cleavage of synaptobrevin. *Nature* 1992; 359:832.
- [15] Lowe N. Botulinum toxin type A for facial rejuvenation. *Dermatol Surg* 1998;21:1215.
- [16] Schantz EJ, Johnson EA. Dose standardization of botulinum toxin. *Lancet* 1990;335:421.
- [17] Brashear A, Lew MF, Dystra DD, et al. Safety and efficacy of NeuroBloc (botulinum type B) in type A-responsive cervical dystonia. *Neurology* 1999; 53:1439.
- [18] Brin MF, Lew MF, Adler CH, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. *Neurology* 1999; 53:1431.
- [19] Lamanna C, Hillowalla RA, Alling CC. Buccal exposure to botulinum toxin. *J Infect Dis* 1967;117:327.
- [20] Scott AB, Suzuki D. Systemic toxicity of botulinum toxin by intramuscular injection in the monkey. *Mov Disord* 1988;3:333.
- [21] Goschel H, Wohlfarth K, Frevert J, Dengler R, Bigalke H. Botulinum A toxin therapy: neutralizing and non-neutralizing antibodies—therapeutic consequences. *Exp Neurol* 1997;147:96.
- [22] Matarasso SL. Update on the aesthetic uses of botulinum-A neurotoxin in facial rejuvenation. *Curr Probl Dermatol* 2001;13:46.
- [23] Zuber M, Sebald M, Bathien N, et al. Botulinum antibodies in dystonic patients treated with type A botulinum toxin: frequency and significance. *Neurology* 1993;43:1715.
- [24] Aoki R, Merlino G, Spanoyannis A, et al. Botox

Q8

Q9

- (botulinum toxin type A) purified neurotoxin complex prepared from the new bulk toxin retains the same preclinical efficacy as the original but with reduced immunogenicity. *Neurology* 1999;52:A521.
- [25] Bowmer EJ. Preparation and assay of the international standards for *Clostridium botulinum* types A,B,C,D, and E antitoxins. *Bull World Health Organ* 1963; 29:219.
- [26] Arron SS, Schechter R, Inglesby TV, et al. Botulinum toxin as a biologic weapon: mental and public health management. *JAMA* 2001;285:1059.
- [27] Klein AW. Dilution and storage of botulinum toxin. *Dermatol Surg* 1998;24:1179.
- [28] Fulton JE. Utilizing botulinum toxin in your cosmetic surgery practice. *Cosmetic Dermatology* 1997;10:41.
- [29] Alcon Pharmaceuticals. Botox package insert. Irvine, CA: Alcon Pharmaceuticals;.
- [30] Garcia A, Fulton JE. Cosmetic denervation of the muscles of facial expression with botulinum toxin. *Dermatol Surg* 1996;22:39.
- [31] Borodic GE, Ferrante R, Pearce B, et al. Histologic assessment of dose-related diffusion and muscle fiber response after therapeutic botulinum toxin A injection. *Mov Disord* 1994;9:31.
- [32] Shaari CM, Sanders I. Quantifying how location and dose of botulinum toxin injection affect muscle paralysis. *Muscle Nerve* 1993;16:964.
- [33] Hankins CL, Strimling R, Rogers GS. Botulinum A toxin for glabellar wrinkles. *Dermatol Surg* 1998; 24:1181.
- [34] Ascher B, Klap P, Marion M-H, et al. Le toxine botulique dans le traitement de rides fronto-glabellaires et de la region orbitaire. *Ann Chir Plast Esthet* 1995; 40:67.
- [35] Le Louarn C. A new injection procedure. Toxine botulique et rides faciales: Une nouvelle procedure d'injection (FRE). *Ann Chir Plast Esthet* 1998;43:526.
- [36] Lowe NJ. Botulinum toxin type A for facial rejuvenation. *Dermatol Surg* 1998;24:1216.
- [37] Carter SR, Seiff SR. Cosmetic botulinum toxin injections. *Int Ophthalmol Clin* 1997;37:69.
- [38] Keen M, Blitzer A, Aviv J, Binder W, Prystowsky J, Smith H, et al. Botulinum toxin A for hyperkinetic facial lines: results of a double-blind, placebo controlled study. *Plast Reconstr Surg* 1994;94:94.
- [39] Moore KL. Clinically oriented anatomy. Baltimore: Williams and Wilkins; 1992.
- [40] Blitzer A, Binder WJ, Aviv JE, Keen MS, Brin MF. The management of hyperfunctional facial lines with botulinum toxin. *Arch Otolaryngol Head Neck Surg* 1997;123:389.
- [41] Carruthers J, Carruthers A. Treatment of glabellar frown lines with C. botulinum-A exotoxin. *J Dermatol Surg Oncol* 1992;18:17.
- [42] Carruthers JA, Lowe NJ, Menter MA, Gibson J, Nordquist M, Mordaunt J, et al. A multicenter, double blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. *J Am Acad Dermatol*, in press.
- [43] Foster JA, Barnhorst D, Papay F, Oh PM, Wulc AE. The use of botulinum A toxin to ameliorate facial kinetic frown lines. *Ophthalmology* 1996;103:618.
- [44] Guyuron B, Huddleston SW. Aesthetic indications for botulinum toxin injection. *Plast Reconstr Surg* 1994; 93:913.
- [45] Binder WJ, Blitzer A, Brin MF. Treatment of hyperfunctional lines of the face with botulinum toxin A. *Dermatol Surg* 1998;24:1198.
- [46] Fagien S. Botox for the treatment of dynamic and hyperkinetic facial lines and furrows: adjunctive use in facial aesthetic surgery. *Plast Reconstr Surg* 1999; 103:701.
- [47] Carruthers A, Carruthers J. Clinical indications and injection technique for the cosmetic use of botulinum A exotoxin. *Dermatol Surg* 1998;24:1189.
- [48] Matarasso SL. Complications of botulinum A exotoxin for hyperfunctional lines. *Dermatol Surg* 1998; 24:1249.
- [49] Wieder JM, Moy RL. Understanding botulinum toxin. *Dermatol Surg* 1998;24:1172.
- [50] Klein AW, Mantell A. Electromyographic guidance in injecting botulinum toxin. *Dermatol Surg* 1998; 24:1184.
- [51] Lowe NJ, Maxwell A, Harper H. Botulinum A exotoxin for glabellar folds: a double-blind, placebo-controlled study with an electromyographic injection technique. *J Am Acad Dermatol* 1996;35:569.
- [52] Pribitkin EA, Greco TM, Goode RL, Keane WM. Patient selection in the treatment of glabellar wrinkles with botulinum toxin type A injection. *Arch Otolaryngol Head Neck Surg* 1997;123:321.
- [53] Edelstein C, Shorr N, Jacobs J, Balch K, Goldberg R. Oculoplastic experience with the cosmetic use of botulinum A exotoxin. *Dermatol Surg* 1998;24:1208.
- [54] Tambasco N, Lalli F, Manicini ML, Rossi A. Botulinum toxin in the treatment of facial expression wrinkles (ITA). *Riv Ital Chir Plast* 1997;29:197.
- [55] Carruthers A, Carruthers JDA. Botulinum toxin in the treatment of glabellar frown lines and other facial wrinkles. In: Jankovic J, Hallett M, editors. *Therapy with botulinum toxin*. New York: Marcel Dekker; 1994. p. 577.
- [56] Lowe NJ, Wieder JM. Botulinum toxin for hyperkinetic facial lines: a placebo-controlled study. *Cosmetic Dermatology* 1995;8:46.
- [57] Werschler P, Baumann L. Everything you need to know about Botox injections. *Skin & Aging* 2001;36.
- [58] Guerrissi J, Sarkissian P. Local injection into mimetic muscles of botulinum toxin A for the treatment of facial lines. *Ann Plast Surg* 1997;39:447.
- [59] Goodman G. Botulinum toxin for the correction of hyperkinetic facial lines. *Australas J Dermatol* 1998; 39:158.
- [60] Huilgol SC, Carruthers A, Carruthers JDA. Raising eyebrows with botulinum toxin. *Dermatol Surg* 2000; 25:373.
- [61] Dyer WK, Yung RT. Botulinum toxin-assisted brow lift. *Facial Plast Surg* 2000;8:343.

Q10

Q11

Q12

- [62] Fagien S. Temporal brow lift using botulinum toxin A: discussion. *Plast Reconstr Surg* 2000;105:1136.
- [63] Huang W, Rogachefsky AS, Foster JA. Browlift with botulinum toxin. *Dermatol Surg* 2000;26:55.
- [64] Keen M, Kopelman JE, Aviv JE, Binder W, Brin M, Blitzer A. Botulinum toxin A: a novel method to remove periorbital wrinkles. *Facial Plast Surg* 1994;10:141.
- [65] Flynn TC, Carruthers JA, Carruthers JA. Botulinum-A toxin treatment of the lower eyelid improves infraorbital rhytides and widens the eye. *Dermatol Surg* 2001;27:703.
- [66] Paloma V, Samper A. A complication with the aesthetic use of Botox: herniation of the orbital fat. *Plast Reconstr Surg* 2001;107:1315.
- [67] Carruthers J, Carruthers A. The adjunctive usage of botulinum toxin. *Dermatol Surg* 1998;24:1244.
- [68] Brandt FS, Bellman B. Cosmetic use of botulinum A exotoxin for the aging neck. *Dermatol Surg* 1998;24:1232.
- [69] Carruthers J, Carruthers A. Botox use in the mid and lower face and neck. *Semin Cutan Med Surg* 2001;20:85.
- [70] Blitzer A, Brin M, Keen MS, Aviv JE. Botulinum toxin for the treatment of hyperfunctional lines of the face. *Arch Otolaryngol Head Neck Surg* 1993;119:1018.
- [71] Ascher B. Botulinum toxin: anatomic basis, classical and new aesthetic indications. *Mov Disord* 2000;15 (suppl 2):27.
- [72] Hoefflin SM. Anatomy of the platysma and lip depressor muscles. *Dermatol Surg* 1998;24:1225.
- [73] Glogau RG. Botulinum A neurotoxin for axillary hyperhidrosis. *Dermatol Surg* 1998;24:817.
- [74] Naumann M, Hofmann U, Bergmann I, Hamm H, Toyka KV, Reiners K. Focal hyperhidrosis. *Arch Dermatol* 1998;134:301.
- [75] Odderson IR. Axillary hyperhidrosis: treatment with botulinum toxin A. *Arch Phys Med Rehabil* 1998;79:350.
- [76] Odderson IR. Hyperhidrosis treated by botulinum A exotoxin. *Dermatol Surg* 1998;1237, 1998
- [77] Schnider P, Moraru E, Kittler H, Voller B, Auff E. High-dose botulinum toxin type A for axillary hyperhidrosis. *Arch Dermatol* 2000;136:1567.
- [78] Shelley WB, Talanin NY, Shelley ED. Botulinum toxin therapy for palmar hyperhidrosis. *J Am Acad Dermatol* 1998;38:227.
- [79] Bjerkhoel A, Trobbe O. Frey's syndrome treatment with botulinum toxin. *J Laryngol Otol* 1997;3:839.
- [80] Drobik C, Laskawi R. Frey's syndrome: treatment with botulinum toxin. *Acta Otolaryngol (Stockh)* 1995;115:459.
- [81] Laskawi R, Drobik C, Schonebeck C. Up to date report of botulinum toxin type A treatment in patients with gustatory sweating (Frey's sweating). *Laryngoscope* 1998;108:381.
- [82] Nauman M, Zellner M, Toyka KV, Reiners K. Treatment of gustatory sweating with botulinum toxin. *Ann Neurol* 1997;42:973.
- [83] Schulze-Bonhage A, Schroder M, Ferbert A. Botulinum toxin in the therapy of gustatory sweating. *J Neurol* 1996;213:143.
- [84] Hamas RS. Reducing the subconscious frown by endoscopic resection of the corrugator muscles. *Aesthetic Plast Surg* 1995;19:21.
- [85] Hamas RS. An endoscopic brow lift that does not raise the hairline. *Aesthetic Surgery Journal* 1997;17:127.
- [86] Fulton JE. Botulinum toxin. *Dermatol Surg* 1998;24:1219.
- [87] Worcester S. Use Botox before and after laser facial resurfacing. *Skin Allergy News* 2000;31:6.
- [88] Bowden JB, Rapini RP. Psoriasiform eruption from intramuscular botulinum A toxin. *Cutis* 1992;50:415.
- [89] Heckmann M, Schon-Hupka G. Quantification of the efficacy of botulinum toxin type A by digital image analysis. *J Am Acad Dermatol* 2001;45:508.
- [90] Santos JJ, Swenson P, Glasgow LA. Potentiation of clostridium botulinum toxin aminoglycoside antibiotics: clinical and laboratory observations. *Pediatrics* 1981;68:50.