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RESEARCH ARTICLE

TAMING THE BOTULINUM TOXIN TO ENHANCE FACIAL ESTHETICS

[1]Abhishek Gupta and [2,*]Niharika Jain

[1]Department of Orthodontics and Dentofacial Orthopaedics, Hitkarini Dental College & Hospital, Jabalpur, India
[2]Department of Conservative Dentistry & Endodontics, Triveni Dental College & Hospital, Bilaspur, India

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ABSTRACT

Botox Cosmetic (Botox) is a formulation of the neuromuscular blocking agent botulinum toxin type A (BTX-A). The use of botox for enhancement of facial esthetics is most common procedure currently undertaken in clinical practice all around the globe. Dentists are highly knowledgeable and precise regarding facial anatomy and therefore it seems reasonable for them to be at the forefront in providing these services. This review encompasses the pathogenesis of facial lines and wrinkles, toxin overview, preparation, uses, complications and contraindications of botox therapy and provides the practitioners in-depth and current knowledge of use and handling botox for facial rejuvenation. Factors unique to each area are presented, highlighting the key elements that can increase the likelihood of a successful outcome.

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INTRODUCTION

Botox (botulinum toxin type A) is a novel therapeutic agent derived from the bacterium Clostridium botulinum. Botulinum toxin, when taken in large quantities is the primary source of botulism food poisoning and has been perceived as a lethal threat for many centuries. This toxin is a natural poison found in decomposing food, from the soil and is 40 million times more powerful than cyanide. However, if injected in small doses, it can cause controlled weakening of the muscles to produce desirable cosmetic and medical effects. This review will provide the specialists in depth understanding of botox therapy, of the variety of applications for the drug, the potential risks and complications, the latest medical research literature, and the most current standard of care.

Pathogenesis of facial lines and wrinkles

When the contraction of a facial muscle is accompanied by a lack of shortening of the skin, a wrinkle is produced. The amount of facial change is related to the depth of the depression within the mucosa or submucosa of the tissue. A fold develops when the depression extends through the dermis and approximates the subcutaneous tissues. A wrinkle proceeds through the epidermis and extends to the dermis of the skin. A line remains completely within the epidermis and does not approach the dermis of the skin (Smith, 1989).

Corresponding author: Niharika Jain,
Department of Conservative Dentistry & Endodontics, Triveni Dental College & Hospital, Bilaspur, India.

Factors that can affect the depth of a wrinkle include skin texture, amount of subcutaneous fat, water content of the skin, distribution and ratio of collagen and elastic fibers, biochemical changes in the connective tissue, and interstitial spaces (Fenske and Lober, 1986; Uitto, 1986). The Facial rhytides or wrinkles have been categorized based on whether they are static or dynamic.

Dynamic rhytides: Dynamic wrinkles occur during the repeated and habitual contraction of underlying muscles of facial expression and are most prominent in the upper one third of the face, especially forehead and periorbital regions of the face.

Static rhytides: Static wrinkless are caused by aging and exogenous sources, like, gravity, smoke and ultraviolet radiation, trauma and scarring. Certain diseases, such as, progeria, Ehlers-Danlos syndrome, and pseudoxanthoma elasticum, can also enhance facial wrinkles due to alteration in the quality of collagen in the dermis, increasing skin laxity or premature aging. Aging enhance tissue laxity, especially in nasolabial fold. The effect of gravity can deepen facial wrinkles. Also, atrophy of the skin occurs, in which there is loss of dermal papillae, reduction in the number of Langerhans cells, melanocytes, and the total amount of dermal connective tissue (which is composed of glycosaminoglycans and proteoglycans) decreases. There is a clinically significant loss of collagen fibers to the point that the elastin to collagen ratio may change in favor of elastin. Ultraviolet radiation (as recorded in normal sunlight, most fluorescent light, and in sun-tanning booths), (Sams, 1989) via generation of superoxide

radicals, causes actinic skin damage, which causes a decrease in mature type I collagen and an increase in immature type III collagen (Sarosh *et al.,* 2007). Static and dynamic rhytides are seen together around the eyes, forehead and cheeks.

Case Selection

Static wrinkles are not caused by hyper functional muscles and these a represent even when the skin is relaxed. Thus, these wrinkles are not amenable to treatment with botulinum toxin, rather they are appropriately treated with dermal fillers such as collagen, hyaluronic acid, subcutaneous fat, or various nonresorbable materials (Sclafani *et al.,* 2003; Lindqvist *et al.,* 2005). Dynamic wrinkles, as caused by hyperfunctional muscles, are best treated with a paralyzing drug such as botulinum toxin (Hallett, 1999). Botulinum toxin is a deadly toxin produced by the Clostridium botulinum bacterium. Clinical applications include blepharospasm, strabismus, and hemispacial spasm. New clinical uses in the fields of cosmetic dermatology include the management of hyperfunctional facial lines, most commonly in the regions of the glabella, periorbial crow's feet, and forehead lines. Various studies have outlined certain characteristics of patients successfully treated with the toxin. The ideal patient should have thin skin, fine wrinkles, lines that are exacerbated by muscle contraction, and hyperfunctional lines that can be spread out with the fingers (Blitzer *et al.,* 1997; Pribitkin *et al.,* 1997).

Botulinium toxin overview

Botulinum toxin is a deadly poison produced by a gram-positive anaerobic bacterium, Clostridium botulinum. The bacteria produces 7 antigenically distinct toxins, lettered A to G. Toxin A, however, has been the most extensively studied. The clinical syndrome of botulism can occur after ingestion of contaminated food, from colonization of the infant gastrointestinal tract, or from wound infection (Cherington, 2004). When foods infected with the toxin are ingested, the toxin spreads to peripheral cholinergic nerve endings, blocking acetylcholine release. This results in a bilateral symmetric descending neuroparalytic illness. The incubation period after ingestion is 18 to 36 hours. In human beings, botulism is mainly caused by types A, B, E, and rarely F, whereas in animals it is caused by types C and D. This toxin is heat labile and denatured by cooking. German physician Justinus Kerner (1786–1862) first observed that the toxin acted by interrupting signal transmission within the peripheral sympathetic nervous system, leaving sensory transmission intact. Later, in 1870, John Muller, coined the name ''botulism'' (from the Latin root botulus, which means ''sausage''). Subsequently the bacterium was isolated and cultured by other investigators. In 1949, Burgen, first discovered, that the toxin acted by blocking neuromuscular transmission. This was proved experimentally by Scott and colleagues who administered the type A strain in monkeys. In 1989, this strain was approved by the US Food and Drug Administration (FDA) ,under the trade name Botox (Allergan, Inc, Irvine, Calif) for treating strabismus (commonly known as ''lazy eye''), blepharospasm (inability to move the eye in certain ways), and hemifacial spasm in patients younger than 12 years old. In 2000, Botox was approved for use in treating cervical dystonia (wry neck) and 2 years later for the temporary improvement of moderate to severe frown lines between the eyebrows (glabellar lines). Serotype B has been FDA approved for treating cervical dystonia, and serotype F is under investigation in patients who are resistant to serotypes A and B (Sarosh *et al.,* 2007; Greene and Fahn, 1996).

Mechanism of action

The botulinum toxin inhibit acetylcholine release at the neuromuscular junction causing muscle paralysis.this action occurs in 3 steps.

- The toxin binds to the nerve
- The toxin is internalized into the nerve by receptor mediated endocytosis
- Enzymatic activation, resulting in the inhibition of the exocytosis of acetylcholine, causing a neuromuscular blocking effect.

Large doses of botox can result in complete paralysis, but,therapeutic doses allow partial activity, thereby decreasing the visual effects of hyperfunctional wrinkles.

Preparation

Laboratory fermentation of C botulinum leads to lysis and liberates the toxin into the culture, which is then harvested, purified, crystallized with ammonium sulfate, diluted with human serum albumin, lyophilized, bottled in vials, and sealed. Each vial contains 100 U vacuum-dried type A toxin, albumin, and sodium chloride, which must be kept frozen at -5°C or colder until reconstituted. One unit is equal to the amount that will kill 50% of a group of 18 to 22 g Swiss Webster mice when injected intraperitoneally. The human lethal dose is estimated to be approximately 3,000 U. Botox dosages used for cosmetic purposes typically are less than 100 U.

Most clinicians use 1 - 3 mL of saline to reconstitute Botox.

Acceptable results have also been reported by diluting one vial in up to 10 mL saline (1 U/0.1 mL). If mixed vigorously, inactivation of toxin may cause decreased potency. After dilution, the mixture should be stored in a refrigerator at 2° to 8°C and used within 4 hours, although some authors have found the potency to decrease slowly over a 1-week period, with minimal to no activity remaining at 2 weeks. Although the solution is rarely used after 1 week due to the lack of preservative in the dilutant, effectiveness has been noted 1 month after reconstitution with preserved saline and refrigeration (Jennifer Clay Cather, 2002). Botulinum toxin B is marketed under the trade name Myobloc (Elan Pharmaceutics, San Francisco, Calif). Its relative potency to Botox is 50 to 125 U of Myobloc to 1 U of Botox. This product does not require reconstitution and is stable for up to 21 months in a refrigerator.

Therapeutic uses

Botulinum toxin may be used for a variety of disorders ranging from pain management to treatment of tremors and tics, to improvement of the appearance of dynamic facial wrinkles (Table 1). The FDA states that Botox Cosmetic is a prescription medicine which is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in people 18 to 65 years of age for a short period of time (temporary).

Table 1. Summarizes the therapeutic uses of Botox

Focal dystonia	Blepharospasm
	Oromandibular-facial-lingual dystonia
	Cervical dystonia
	Laryngeal dystonia (spasmodic dysphonia)
	Task-specific dystonia (occupational cramps)
	Other focal dystonias(idiopathic,secondary)
Non-dystonic disorders of involuntary muscle activity	Voice,head and imb tremor
	Palatal myoclonus
	Hemifacial spasm
	Tics
	Heriditary muscle cramps
spasticity	Cerebral palsy
	Multiple sclerosis
	Spinal cord injury
	Traumatic brain injury
	Stroke
Strabismus and nystagmus	
Disorders of localized muscle spasms and pain	Myofacial pain
	Neck/low back pain
	Tension and migraine headache
	Bruxism and other temporomandibular joint disorders due to increased muscle activity
Disorders of smooth muscle hyperactivity	Achalasia (oesohageal and cardiac)
	Chronic anal fissures
Cosmetic use	Hyperkinetic facial lines (glabellar, forehead,crow's feet,platysmal bands,perioral)
	Gummy smile
Sweating disorders	Frey syndrome
	Axillary and palmar hyperhydrosis

Table 2. Summarizes the complications of botox therapy

	Cause	Management/prevention
Injection site pain, bruising	Diffusion of toxin to adjacent muscles	bruising can be reduced by using fresh 30-gauge needles (changing the needle after every three to four injections), icing the injection site before injection, and injecting intradermally. Pain can be reduced by topical anesthetics and icing the treatment site immediately before injection.
headaches	the needle hitting the periosteum or from deep muscle hematomas. Toxin related muscle spasms immediately postinjection. the stress of the injections	NSAID's
skin infections	the skin barrier is violated	proper injection site skin cleansing and site selection (avoiding injections adjacent to acne)
localized skin reaction such as dry skin and flakiness	decreased sweat gland activity	Using skin moisturizers
Lid ptosis	Diffusion of toxin into orbicularis oculii, corrugators supercilii, procerus or levator palpebrae muscle	alpha-adrenergic agonist ophthalmic eye drops.
diplopia	After Lateral periorbital injections, leading to Botox diffusion and lateral rectus weakness. After misplaced nasalis muscle injections (for ''bunny scrunch'' lines).	Prevent violation of ''orbital zone'' while injecting Botox
Lagophthalmos (rarely seen following esthetic Botox treatments)	large quantities of Botox injected into the lateral canthal area, compromising orbicularis functions, leading to weak eye closure and secondary dry eyes.	
Dysphagia and hoarseness	Larger doses (50 units and higher) of Botox placed into the neck leading to localized diffusion into the deeper cervical structures, such as the sternocleidomastoid (SCM) and strap muscles	In most cases, the dysphagia is mild and transient. If severe dysphagia is noted, a temporary change to a soft diet or pureed foods may be instituted until full recovery occurs
Asymmetry of face	Difference in injection technique or doses between the two sides of the face	Avoid different injection techniques and vastly different doses
Antibody development	Excessively large doses	EMG-guided injections can help to minimize total dosage. Use other serotypes (F or B) if antibody resistance has been developed

Contraindications

Botox is contraindicated in individuals with hypersensitivity or allergy to botulinum toxin A or human albumin. Also, Botox is not recommended in individuals with disorders, where neuromuscular transmission is compromised, such as myasthenia gravis, multiple sclerosis, and Eaton Lambert syndrome (Huang *et al.,* 2000). Additionally, Botox treatments are not administered during pregnancy and while nursing. However, there are no reports of teratogenic effects in humans from in utero botulinum toxin exposure. Nevertheless, the FDA classifies Botox as a category C drug, indicating that its safety profile during pregnancy has not been adequately evaluated. Until additional evidence supporting the safe use of Botox during pregnancy and nursing is reported, pregnant women and nursing mothers should not be treated (Jankovic and Brin, 1991). Botox application in patients older than 75 years of age has not been adequately studied. These patients

are initially treated more conservatively to offset the greater frequency of undiagnosed neurologic and medical disorders, higher likelihood of other drug therapy interactions, and higher susceptibility of older patients to functional problems (Mosby's Drug Consult, 2003).

Drug interactions

The quantities of Botox used in esthetic cases are usually small enough to initiate any drug-drug interactions (Mosby's Drug Consult, 2003; Aoki, 2001). Nevertheless, drugs that interfere with neuromuscular transmission could potentially interact with Botox: aminoglycosides (gentamycin), cyclosporine, D-penicillamine, muscle relaxants (curare-type nondepolarizing blockers, succinylcholine), aminoquinolones, quinidine, magnesium sulfate, and lincosamide (Wang *et al.,* 1984). Large doses of aminoglycosides (like gentamycin) can prevent the release of acetylcholine into the neuromuscular junction (NMJ), inducing a botulism-like clinical state. Cyclosporine can induce muscle weakness secondary to neuromuscular blockade, and, in one case report, led to respiratory failure (Kadieva *et al.,* 1992). D-penicillamine was found to induce antiacetylcholine antibodies in a small percentage of patients who had rheumatoid arthritis and who received this drug. These patients can develop muscle weakness similar to patients who have myasthenia gravis (Bucknall, 1977; Albers *et al.,* 1980). In contrast, aminoquinolones, such as chloroquine and hydroxychloroquine, can inter with botulinum toxin interaction within the cell and inhibit Botox activity by (Simpson, 1982).

Complications

Following a complete history and a physical examination, possible risks and complication are shared with the patient and written informed consents are obtained. Most of the complications are however temporary.The common complications of Botox therapy are summarized in Table 2

Combination treatment with botox

Botox can be administered in appropriate cases to rejuvenate aging, in combination with fillers, chemical peels, microdermabrasion, IPL, laser resurfacing, infrared technology and radiofrequency. Botox with fillers: Botox with dermal fillers can restore facial esthetics by complimentary modes of operation, relaxation and volume enhancement (Coleman and Carruthers, 2006). BTX-A is used with fillers to correct brow height, smoothening of forehead lines and nasolabial fold and re-setting of facial esthetics. Botox may also decrease the amount of fillers required for lines. Doing Botox 2 to 4 weeks before fillers, softens the muscle contractions and gives a more accurate idea of how much filler is required. (Coleman and Carruthers, 2006).Giving Botox and tissue fillers on the same day may lead to overcorrection. Botox and chemical peels: Botox should be avoided immediately before or after peels because soft tissue swelling may result in increased migration of the toxin. BTX-A should be administered 2 to 3 days before chemical peels, however, the specific timing of peels in combination with botox depends upon individual patient's responses and practitioner's level of experience (Werschler and Baumann, 2001).

Botox with laser resurfacing: Lasers stimulate neocollagenesis, prevents static wrinkles and botox prevents the recurrence of dynamic wrinkles (Carruthers and Carruthers, 1998; Fulton, 1998). Botox is ideally delivered 1-3 weeks prior to laser treatment, which enables the hyperactive muscle action to be reduced; thereby, reducing the cause of facial lines. In a study done on 53 patients, the group that received Botox before and after laser resurfacing (N = 37) reported an aesthetic outcome of 21% greater after 6 months than those who underwent laser resurfacing alone (Worcester, 2000). Botox with IPL(Intense pulsed light) :Intense pulsed light therapy uses both visible and infrared light spectrum to treat pigmentation and vascular problems related to chronic photodamage (Atiyeh, 2009). Vascular lesions such as rosacea, telangiectasis, flushing, erthyema repond well to this therapy (Bosniak, 2006). Botox with Radiofrequency: RF systems uses impedance to convert electric energy into thermal energy. Therapeutic energy levels are unknown,but the critical temperature for collagen shrinkage and repair ranges from 55-75°C depending upon the duration of application.before RF administration, the epidermis is cooled to prevent thermal injury to superficial skin layers (Atiyeh, 2009). RF systems are being used for thermalifting of face, brows and neck, as well as treatment of periorbital rhytids (Bosniak, 2006). The application of IPL and RF systems immediately following botox-A injection has been found effective for the treatment of glabellar area or crow's feet without loss of efficacy or any other negative side effect (Semchyshyn *et al.,* 2005).

Conclusion

The demand for facial rejuvenation is increasing, everyday, in all age groups. The use of botulinum toxin has revolutionized the treatment of facial lines with an incomparable safety record over the past 14 years and continue to expand, with new techniques and formulations. A detailed and specific knowledge of use of these techniques is becoming imperative for the practitioners, especially in early days of new user's curve.

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