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Biomodelation of Gummy Smile with Botulinum Toxin: An overview

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Abstract: *Gingival smile is a constant complaint and its treatment modalitiesvary from simple methods like use of botulinum toxin, to even complex ones as orthognathic surgery.In this era of passion to look beautiful, various new technologies are emerging to enhance and improve the physical appearance. Use of this toxin is emerging as a popular, cost effective and least invasive treatment option to improve facial anomalies. Botulinum toxin is a protein produced by the bacterium Clostridium botulinum, and is considered one of the most powerful neurotoxins ever discovered and is now marketed under the trade name of Botox. The use of Botox is now common and is provided by many dental practitioners as an adjunct to the range of cosmetic treatments they offer to the patients. In spite of few pit falls, weighing the amount of psychological benefit to the patient, it is quite a breakthrough in the field of cosmetic surgery in the treatment of gingival smiles. This article elaborates on the treatment of gummy smile through orofacial biomodelation with Botulinum toxin, which creates a shield in the canine fossa area, avoiding the exaggerated gingival display on smiling due to a wide action of the levator muscle of angle of mouth.(201 words)*

Keywords: *Botox, Botulinum toxin, gummy smile*

Background: Botulinum toxin (BTX), also called a "miracle poison," is a neurotoxin produced by the bacterium Clostridium botulinum. JustinusKerner, a German physician and poet, first identified botulinum toxin between the years of 1817 and 1822. He described it as a "sausage poison"(sausage in Latin is botulus) and "fatty poison," as this bacterium often caused poisoning by growing in improperly handled or prepared meat products.[1]The toxin was first isolated in 1946 and a medical application for the substance was discovered in the 1950s. There are seven main serotypes of the neurotoxin that have been identified: A, B, C (1 and 2), D, E, F, and G. All seven serotypes are structurally similar but immunologically distinct in their potency, duration of action, and cellular target sites. They possess similar molecular weights and subunit structure, but have different amino acid sequences.[2]

Humans canbe affected by the toxins of five strains(A, B, E, F, and G) and are not affectedby the toxins of strains C and D.[3]When injected, the various preparations of BTX produce local, temporary, and reversible cholinergicchemodenervation of muscles and glands. The property of the toxin that interferes with neural transmission and blocks the release of acetylcholine, causing muscle paralysis, plays an important role in the management of many cosmetic, medical, and dental conditions. Dependingon the target tissue, BTX can blockcholinergic neuromuscular innervations of intra- and extrafusal muscle fibersor cholinergic autonomic innervations of sweat, lacrimal and salivary glands,and smooth muscles. Thus, it acts as aversatile clinical tool for a growing listof conditions resulting from muscularhyper function.[4]It gains its appeal as a cosmetic drug because it does not require general anesthesia or surgery. BTX is widely used in cosmetic applications for the treatment of facial wrinkles after local injection, but conditions such as cerebral palsy, muscular spasms, urinary incontinence, headaches, tinnitus, excessive sweating, cricopharyngeal achalasia, post-stroke spasticity, hemifacial spasms, temporomandibular joint disorders, bruxism, sialorrhea, neuropathic facial pain, muscle movement disorders (dystonias), masticatory myalgias, and facial nerve palsy could be treated with this drug.[5,6]

In pedodontics and orthodontics, it can be used to treat developing gummy smiles, lip augmentation, and also for cases where retraining of the facial muscles is required. Many other indications are under investigation, and further applications for BTX are likely to be developed. Botulinum toxin in the dental officeoffers a reversible alternative to moreaggressive procedures such as fullmouthreconstruction, orthodontics, andorthognathic surgery. Recently, BTX isreported to be clinically used in dentalimplantology for the prophylactic reductionof masseter and temporalis musclestrength after implantation in immediateload protocols.[8]

In December 1989, BTX-A was approved by the U.S. Food and Drug Administration(FDA) under the trade name Botox (Allergan, Irvine, CA, USA) forthe treatment of strabismus, blepharospasm, and hemifacial spasm in patients younger than 12 years old. In 2000, Botox was approved for treating cervical dystonia (wry neck) and two years later, on April 15, 2002, the FDA announced the approval of botulinum toxin type Ato treat

moderate-to-severe frown linesbetween the eyebrows (glabellar lines). Since then, BTX has been evaluated boff-label for the treatment of spasticityand muscle pain disorders. Botulinumtoxin type B (BTX-B) received FDA approvalfor treatment of cervical dystoniaon December 21, 2000. Trade namesfor BTX-B are Myobloc in the UnitedStates and Neurobloc in the European Union. Serotype F is also under investigationin patients who are resistant toserotypes A and B.

At present, there are six different BTXpreparations available commercially,out of which five contain BTX-A (Botox,Dysport, Xeomin, Prosigne, and PurTox)and the sixth contains BTX-B (Myobloc/Neurobloc). Botulinum toxin A is usuallypreferred because of its long durationof action and ease of production.Approval procedures are complex andvary between preparations and countries,but in general Botox has garneredthe most approvals worldwide, followedby Dysport. Active research is underway onthe possible uses of this toxin in severalfields of medicine and dentistry.Though more extensive confirmation ofits use in multiple dental applications isneeded, it is evident that the potentialuse of BTX in the dental professioncan be of great value. Judicioususe of BTX will ensure that itcontinues to be an important therapeuticoption and improves the quality oflife of patients.

What is Botox®?

Botox® is the trade name for the neurotoxinprotein BTX type A produced byfermentation of anaerobic bacteriumclostridium botulinum. Type A is one of theseven distinct botulinum toxins produced bydifferent strains of the bacterium. It is astable, sterile, vacuum-dried powder sold in vials that isdiluted with saline solution withoutpreservatives for it to be injected.

BTX in dentistry [9]

BTX is nowadays commonly used to treat:

1. Gummy smiles
2. Temporomandibular disorder (TMD),
3. Dental implants and surgery,
4. Masseteric hypertrophy,
5. Mandibular spasm,
6. Headache,
7. Migraine, and trigeminal neuralgia,
8. Myofacial pain and neck pain,
9. Bruxism and clenching cases,
10. Angular cheilitis,
11. Orthodontic relapse and depressed orthodontic appearance ,
12. For reducing muscle hyperactivity for retention of removable prosthodontics

What is Gummy Smile?

When an excess of gingiva superior to the maxillary anterior teeth is displayed upon full smile, it istermed a gingival smile. The gingival smile is known by a variety of terms including ―gummy smile, high lipline, short upper lip, and full denture smile.‖ Perhaps this variety in terms is indicative of the many differentcauses of a gummy smile. The smile itself and the aesthetics of the smile are influenced by 3 components: teeth, gums, and lips.An attractive smile depends on the proper proportion and arrangement of these 3 elements. The upper lip shouldsymmetrically expose up to 3 mm of the gum and the gum line must follow the contour of the upper lip.Theexposure of more than 3 mm of the gum during the smile is known as gingival or gummy smile. For somepatients, gummy smile represents an aesthetic disorder. Hulsey noted that the most attractive smiles were thosein which the upper lip rested at the height of the gingival margin of the maxillary incisor.[11]

Tjan et alreported gender differences in the smile line. The low smileline is predominant (2.5:1) in men, whereas high smile lines are predominant in women (2:1). Gummy smiles range from mild, moderate, and advanced, to severe. Rosemarie Mazzuco et al.,classified gummy smile into anterior, posterior, mixed, or asymmetric, based on the excessive contraction ofmuscles involved. Goldstein classified the smile line (consisting of the lower edge of the upper lip during thesmile) according to the degree of exposure of the teeth and gums into 3 types: high, medium, or low.[13]

Etiology of gummy smile [14]

Some people with excessive gingival display are self-conscious or embarrassed about it, and some are psychologically affected. Etiological factors involved in the formation of gummy smile can be:

1. Skeletal (vertical maxillary excess),
2. Gingival (passive eruption) or
3. Muscular (hyper functional upper lip)

Possible Causes of Gummy Smile development during Orthodontic Treatment:
1. Unexpressed Vertical Growth
2. Extrusive Forces
3. Anterior-Posterior Position of the Maxilla

Treatment options range from Le fort I osteotomy, crown lengthening, intrusion, myectomy to muscle resection etc.

BTX and Gummy smile:
BTX is indicated when the gummy smile is due to hyper function of upper lip elevator group of muscles **(Fig 1):**
1. Levatorlabiisuperioris (LLS)
2. Levatorlabiisuperiorisalaequenasii (LLSAN)
3. Zygomaticus major
4. Zygomaticus minor
5. Depressor septii

Storage and Preparation of commercially available BTX:*[15]*

Botox is kept frozen (2–4 degree celcius) in a vial untilit is ready to use. The drug is put intosolution, following manufacturer'sguidelines, by adding normal saline(preservative-free 0.9% saline solution).Duringreconstitution, the rubber seal on the vial should be wiped with an alcohol swab before pricking. Rotating the vial during injectionalso assists a gentle reconstitution. Botox® should be reconstituted after any transport/journey. Agitation during transportmay denature the toxin and greatly reduces its duration of action. Each vial of Botox® contains 100 unit of BTX-A toxin. According to manufacturer's recommendations, a dose of 2.5U/ 0.1ml is prepared by adding4.0 ml normal saline solution to 100 units of vacuum-dried Clostridium botulinum toxin type-A. Once prepared it should be used within 4hours. Reconstituted Botox® shouldbe clear, colorless and free of particulatematter.The preferred syringe is a calibrated1.0-ml tuberculin syringe, and the needleselected for injection usually is between 26and 30 gauge. Skin preparation involvesalcohol wipes and dry sterile gauze sponges.Aspiration before injection is recommended.Usually, dosing is established by thediagnosis and reason for use of the toxin,size of the muscle, and medical conditionsor medications. Until studies narrow downall specifics, the final dilution and dosageused is left to the clinical experience anddiscretion of the practitioner. The number ofinjection sites usually is determined by thesize of the muscle.

Theoretically, it may beappropriate to inject more sites with smallerdoses, and using more injection sites shouldfacilitate a wider distribution of BTX tonerve terminals; however, too manyinjection sites may cause local injection sitepain. The proper targeting of muscles is acrucial factor in achieving efficacy andreducing adverse effects from BTX-Ainjections. Its therapeutic effects first appear in 1 to 3 days, peak in 1 to 4weeks, and decline after 3 to 6 months.

Titration:

Diluents added (0.9% NaCl)	Resulting dose: Units per 0.1ml
1 ml	10 Units
2 ml	5 Units
4ml	2.5 Units
8ml	1.25 Units

Injection technique:

1. Conventional Technique:[16]

Mario Polo has advocated2.5 units of BTX-A is injected under sterile conditions at 4 sites, 2 oneach side of the face. The needles are inserted at theoverlapping points of **(Fig. 2 & Fig. 3):**

I. Levator labii superior isalaeque nasi and levator labii superioris muscles;
II. Levator labii superioris and zygomaticus minor muscles

- On each side of the face. The injection sites were determined by muscleanimation (smiling) and palpation on contraction to ensure precise muscle location before injection. A skin marker was used to mark the injection points to reduce the risk of asymmetry.

Reference points used for measurements:

A. Lowest margin of upper lip perpendicular and superior to the midportion of maxillary central gingival margin.
B. The maxillary central incisors gingival margin at its midpoint.
C. The midpoint of the incisal edge of the maxillary central incisor.

Fig2. Overlapping area of levatorLabiisuperiorisalaequenasi and levatorlabiisuperioris
Fig3. Overlapping area of levatorLabiisuperioris and Zygomaticus minor

2. Yonsei point[17]:

Hwang et al at Yonsei university college ofdentistry, Seoul, Korea have proposed a single injection point for BTX-A andnamed it as Yonsei point. A dose of 3U isrecommended at each injection site. It isbasically a point located at the centre oftriangle **(Fig.4)** formed by levatorlabiisuperioris,levatorlabiisuperiorisalaequenasi andzygomaticus minor. If applied in small,carefully titrated doses, these muscles can beproportionately weakened with BTX, whichwill reduce exposure of the upper gumswhen smiling.

Fig4. Photograph indicating Yonsei point for the single injection technique

Followup:

Effect of BTX is seen within 5-10 days andlasts about 6 months, with a range of 4 to 8months, at which time the patient can returnto repeat the process. It is important not togive injections prematurely (before theeffects of the treatment have worn off), asthis can result in a buildup of antibodies toBTX that would dilute the effect of furthertreatments.

Mechanism of Action [18]

BTX decreases muscle activity byblocking overactive nerve impulses thattrigger excessive muscle contractions orglandular activity:

1. Phase I.

Nerve-Muscle Communication is blocked:

BTX blocks the transmission ofoveractive nerve impulses to the targetedmuscle by selectively preventing the releaseof the neurotransmitter acetylcholine (ACh)at the neuromuscular junction, temporarilypreventing muscle contraction. This isprimarily a local effect. BTX may alsoprevent the release of pain-stimulatingneuropeptides in peripheral nerves.

A) Binding:

The heavy chain portion of the activeingredient in BTX binds to the cellmembrane of the motor nerve via anunidentified high-affinity "acceptor"molecule. This high-affinity binding actionallows for efficient uptake of BTX bythe motor nerve and facilitates selective,targeted treatment at the injection site.

B) Internalizing:

After binding, the BTX protein moleculepasses through the cell membrane of themotor nerve and into its cytoplasm via aprocess called endocytosis. It is here that theenzymatic component (light chain) of theBTX protein molecule is activated.

C) Blocking:

Inside the motor nerve, the light chain of theBTX protein molecule cleaves apart aprotein (called SNAP25) that enablesvesicles which store the neurotransmitteracetylcholine to attach to the cell membrane.Cleaving SNAP25 prevents these vesiclesfrom fusing with the membrane andprevents the release of acetylcholine into theneuromuscular junction (the space betweenthe motor nerve and the muscle). Thus,nerve impulses that control musclecontractions are blocked decreasing muscleactivity. Cleaving SNAP25 also blocksrelease of neuropeptides involved in thetransmission of painful sensations(including substance P, glutamate andcalcitonin gene-related peptide, or CGRP),theoretically reducing pain sensitization ofperipheral nerves. This may be howBTX reduces the neck pain associatedwith cervical dystonia, although the exactmechanism of action is unknown.

2. Phase II.

Nerve-Muscle Communication is restored

The effect of BTX is generallytemporary. Previous nerve impulse activityand associated muscle contractions resumeover the course of a few to several months,depending on the individual patient and theindication for which they are being treated.

A) Nerve Sprouting:

New nerve endings sprout and connect to themuscle after the original nerve ending isblocked, renewing the ability of the nerve tocause muscle contractions.

B) Original Nerve Connection Reestablished:

Eventually, the new nerve sprouts retractand the original nerve ending regains itsfunction, suggesting that treatment withBTX does not permanently alter the neuromuscular junction.

Advantages of BTX

1. Psychological benefit to the patient
2. Minimally invasive

Disadvantages of BTX

1. Short term effect
2. Asymmetrical/unnatural appearance of smile sometimes due to improper injection technique
3. Cost factor

Complications of BTX therapy: [19]

As previously noted, there are a number of complications associated with the use of BTX. These complications may include the following:

1. Mild pain with injection.
2. Local edema.
3. Erythema.
4. Transient numbness.
5. Mild nausea.
6. Transient headache.
7. Production of neutralizing (IgG) antibodies against Btx-A (in injections over 200U given at once or repeated injections within one month of treatment session).
8. Muscle weakness at sight of injection.
9. Post-injection bruising.
10. Local spread, causing unwanted paralysis of nearby muscles.
11. Flu-like symptoms.
12. Development of tolerance.

Contraindications of BTX therapy:[19]

1. During pregnancy or while breast feeding
2. Presence of inflammation or infection at the site of proposed injection
3. Anyone with known hypersensitivity or allergies to human albumin, BTX, or saline solution.
4. Anyone with known motor neuropathy, neuromuscular disorders such as myasthenia gravis, Lambert-Eaton Syndrome, muscular dystrophy, multiple sclerosis etc.
5. Anyone taking Aminoglycoside antibiotics because aminoglycosides may interfere with neuromuscular transmission and potentiate the effect of BTX therapy.
6. Anyone taking Calcium Channel Blockers.
7. It will be important for the patient to avoid taking aspirin or related products, such as ibuprofen (e.g., Advil) or naproxen if possible after the procedure to keep bruising to a minimum

If there is an accidental overdose, an antitoxin is available that will neutralize the toxin, if given within a few hours of the overdose. Also, BTX is contraindicated for people with diseases that affect neuromuscular transmission, such as myasthenia gravis and women who are pregnant or nursing.

Administration of BTX by dentists: The Indian Scenario:

We performed a pubmed/medline search and reviewed 20 Indian case reports and review articles. We found that still there is no published guideline/protocol by any dental authority/association on administering BTX by a dentist in India till date. But certain Indian case reports [20, 21] have reported administration of BTX in a dental setup, but all the administrations were done by dermatologists who were licensed in administration of BTX.

3. Conclusion

BTX is no doubt is emerging as an attractivetreatment option in comparison to surgicalalternatives. However is much more is stillto be discovered to allow its routine use indental clinics for various problems. Thereare still many dental conditions whichrequire FDA approval to be treated byBTX. The use of BTX isminimal invasive and will surely take dentalprofession to one step ahead in the field ofprogress.

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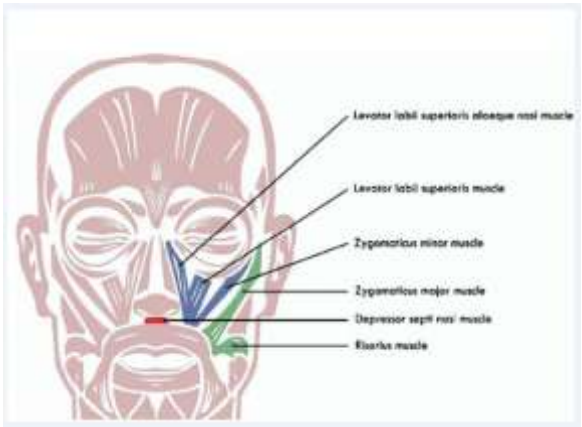

Fig 1: upper lip elevator group of muscles

Fig2. Overlapping area of levatorLabiisuperiorisalaequenasi and levatorlabiisuperioris

Fig3.Overlapping area of levatorLabiisuperioris and Zygomaticus minor

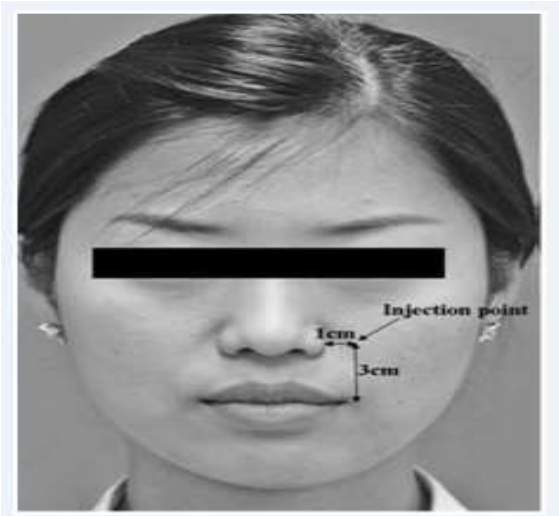

Fig4. Photograph indicating Yonsei point for the single injection technique

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