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REVIEW ARTICLE: BOTOX IN DENTISTRY

***[1]Dr. Sajna K. A. BDS, [2]Dr. Dhanya John MDS, [3]Dr. Jiss Mary G. MDS and [4]Dr. Giju George Baby MDS**

[1]House Surgeon, Annoor Dental College and Hospital, Muvattupuzha Kerala, India.
[2]Assistant Professor Department of Conservative Dentistry and EndodonticsAnnoor Dental College and Hospital, Muvattupuzha Kerala, India.
[3]Assistant Professor Department of Oral Medicine and Radiology, Annoor Dental College and Hospital, Muvattupuzha Kerala, India.
[4]Professor and Head of the Department of Oral Medicine and Radiology, Annoor Dental College and Hospital, MuvattupuzhaKerala, India.

***Corresponding Author: Dr. Sajna K. A. BDS**
House Surgeon, Annoor Dental College and Hospital, Muvattupuzha Kerala, India.
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ABSTRACT

Background: Botulinum toxin [Botox] has been known to mankind for ages but has not been gaining enough popularity lately. It has been used in the medical field primarily for its cosmetic treatment of lines and wrinkles on face and can be used as an alternative treatment modality working through chemo denervation methodology in several medical and dental conditions. The use of Botox is a minimal invasive technique of treatment. The new prototype is the intramuscular injection of Botulinum toxin type A (BOTOX-A) into the affected muscles. It is a macromolecule produced by Clostridium botulinum. The toxin inhibits the release of acetylcholine (ACh), and results in inhibition of muscle contraction. **Aim:** This article explains the fundamentals of Botox and its uses in dental medicine. **Conclusion:** This article gives an understanding into the applications, limitations and different downsides of Botox separated fromits usual utilization. **Clinical significance:** Have shown favorable results in the management of muscle-generated dental diseases like extra capsular myogenic temporomandibular disorders, trismus, bruxism, clenching, masseter hypertrophy, headaches accompanying these conditions and used to treat functional or esthetic dental conditions like deep nasolabial folds, radial lip lines, high lip line and black triangles between teeth.

KEYWORDS: Botox, Botulinum toxin, Muscular disease, clostridium botulinum, bruxism, trismus.

INTRODUCTION

Botox is the most commonly known commercial name for the Botulinum toxin that can be considered as a neurotoxin present in nature. It is produced by the Clostridium botulinum bacteria. Commercially available Botulinum toxin is a purified exotoxin of Clostridium botulinum. Ingesting of a few (30-100) milligrams of such toxin in contaminated food can result in severe illness or even death to mortals, wherein the toxin acts by preventing the release of acetylcholine. This neurotoxin is the cause of botulism-A serious paralytic illness. Botulinum toxins exists in seven types A to H but only type A and type B is available commercially.

Botulinum toxin type A is used in the treatment of blepharospasm, severe primary axillary hyperhidrosis and cervical dystonia and in the temporary improvement in the appearance of wrinkles. Type B botulinum toxin is approved by Drug Administration (US) to be used in treatment of dystonia. Recently botulinum toxin has been included in the treatment of orofacial conditions.[2] Dental diseases caused due to the overactive orofacial musculature leads to muscular damage resulting in bruxism, TMJ disorders, asymmetrical smiles, oromandibular disorders, excessive gingival display and many others which can be treated by non-surgical and surgical methods, but are invasive, irreversible and expensive for most of the patients.[3] With the promising results obtained since the past two decades in the facial esthetics, Botox is recognized by the dentists and introduced into clinical dentistry [1].The aim of this article is to elucidate on restorative aspect of this toxin and how it can be benefitted on different treatments along with its safety and dependence on routine clinical uses.

History

The word botulinum is derived from the Latin word botulus, meaning sausage. A German physician Justin Kerner (1786-1862) was the first to propose the therapeutic use of Botulinum toxin. He named this toxin "Sausage Poison" as it was noticed that the illness

followed after consuming spoiled sausages. According to Justin Kerner the toxin mainly acts by interfering in the signal transmission within the peripheral sympathetic nervous system.[1] The term "Botulism" was coined by another German physician John Muller in the year 1870.[2] In 1949, Burgen discovered that the toxin block the neuromuscular transmission, which was later proved by Scott et al in 1989 on Monkeys.[1,2] Scott et al.[8,9] isolated 7 antigenically distinct toxins of Clostridium Botulinum which were marked A through G.[1] It was observed that when type A strain was introduced to monkeys, there was a blockage in the release of acetylcholine. Type A strain was approved by the US Food and Drug Administration (FDA) in 1989 under the trade name – Botox, primarily used in treatment of hemi facial spasm, strabismus and blepharospasm in young individual. In the year 2000, type B strain was approved to treat cervical dystonia (wry neck) and in 2002 Botox was accredited to treat glabellar lines. In 2005, Mario Polo used Botox for the treatment of gummy smile.[4,5] In 2014, Michigan board of dentistry and New Jersey state board also approved the use of Botox and dermal fillers by general dentists.[1]

Drug Pharmacology

Botulinum toxin is synthesized by an anaerobic bacteria, namely Clostridium botulinum. Spores produced by these bacteria are resistant to high temperature and are capable of germinating in anaerobic condition, liquid medium and in low acidic foods. Botox is ingested and absorbed through the gastrointestinal tract and into the systemic circulation.[1]

Mechanism of Action

Acetylcholine is a neurotransmitter, released by neurons responsible for muscular contraction. Injecting hyperactive muscles with Botox results in decreased muscular activity, wherein there will be an interim denervation of muscles resulting in disruption of nerve transmission leading to decreased release of acetylcholine responsible for muscle paralysis.[1,2] Thus the vesicles stored with acetylcholine are prevented from binding to the membrane where neurotransmitter can be released.[1] This process of vesicle fusion to the plasma membrane is interfered by the degradation byproducts of the toxin which are cleared by internal proteolytic enzymes.[2,3] Thus there will be termination of exocytosis of acetylcholine leading to neuromuscular blocking effect. This effect of Botox is achieved by its endopeptidase activity against SNARE proteins that are required for anchoring acetylcholine vesicle to presynaptic membrane.[1,4] Muscular paralysis usually occurs depending on the dose administered. Larger dose cause complete paralysis whereas smaller dose prevails for its therapeutic activity of decreasing the hyperfunction wrinkles and weakens the muscle for 3-4 months.[2] This effect is temporary and resolves by the growth of new axonal terminals .Botox has also proven responsible for the inhibition of other neurotransmitters causing generation of pain such as glutamate, substance P, and calcitonin gene-related peptide and this action have been beneficial to surgeons for the treatment of TMJ disorders.[3]

Dosage and Commercial Availability

The commercially available form of botulinum toxin type A are Botox, Dysport and Xeomin and that of type B is MyoBloc.[1] Each vial of Botox comprises of:

1. 100 Units (U) of Clostridium botulinum neurotoxin (type A) complex.
2. 0.5mg of Albumin Human.
3. 0.9 mg of sodium chloride in a sterile, vacuum dried form without a preservative.[1,5]

Method of Administration

Patient is introduced with either 1, 2 or 3 sets of injections, intramuscularly, depending on the clinical response to the treatment. Once Botox is injected into the patient a minimum of 10 days are required for the complete results and will last for about 2-3 months.

Therapeutic Uses of Botox in Dentistry

Botulinum toxin is used for treatment of wide range of disorders of both medical and dental condition ranging from management of pain to the treatment of tremors and tics, to the improvement of the appearance of dynamic facial wrinkles and even for retention of removable prosthesis by reducing muscle hyperactivity.[2,3,6]

Botox can be used in following dental conditions:

1. **Gummy smile:** An excessive display of the maxillary gingiva upon smiling or the "Gummy smile" is actually an esthetic concern for most of the patients with no simple remedy. Principle cause of gummy smile is either the hyper functional upper lip or the over-contraction of the muscles of the upper lip, including levator labii superioris, levator labii superioris alaque nasi, Zygomaticus major and minor muscles, of which levator labii superioris, levator labii superioris alaque nasi and Zygomaticus minor muscles determine the amount of lip elevation during smiling. Several surgical techniques have been reported for correction of hyper functional upper lip elevator muscles such as the Rubinstein and Kostianovsky, Miskinyar and Rees and LaTrenta technique,but are not the commonly used, whereas techniques like LeFort I maxillary osteotomies and gingivectomies are routinely used. Botox is injected in small, carefully titrated doses to limit the over-contraction of the upper lip thereby reducing exposure of the upper gums on smiling. Hwang et al.[10] at the Yonsei University College of dentistry, Seoul, Korea proposed the Yonsei point, an injection point for Botox. The point is located at the center of the triangle formed by levator labii superioris, levator labii superioris alaeque nasi and zygomaticus minor. Polo M[11] in the year 2005 introduced 0.25U of Botox injection, per muscle, bilaterally into the levator labii superioris, levator labii Superioris alaeque nasi, and at the overlap

areas of the levator labii superioris and zygomaticus minor muscles in five patients with hyperfunctional upper-lip elevator muscle, under electromyographic guidance. The results procured were effective in all the patients with an increase in the length of the upper-lip on smiling with the duration of the effect lasting up to 3-6 months with no reported adverse effects. However, the treatment being temporary, the injection must be repeated every 6 -12 months. A combination of dermal fillers with Botox injections was used by Freund B[12] in 2014 in patients with gummy to observe the esthetic and functional refinement and also to manage smoker's lines which were exterminated by relaxing the orbicularis oris muscle.[1,4, 6]

2. **Dermal fillers**: These filler products can be classified as permanent which include PMMA (polymethylmethacrylate), calcium hydroxyl appetite and ePTFE (expanded Polytetrafluoroethylene) and non-permanent which includecollagen or hyaluronic acid and are known to increase the volume of subcutaneous tissues of which the hyaluronic acid incorporated products like Juvederm (Allergan) and Restylane (Medicis) are viscous, easy to use andantigenically safe.[1]
3. **Facial aesthetics**: Facial aesthetics can be enhanced by the administration of dermal fillers along with Botox that increases the volume around the mouth such as the nasolabial folds, marionette lines, creating smile lines and lip-line.[1]
4. It has been advised as to use Botox in the upper face and fillers in the lower face.[1,2] Juvéderm and Restylane are dermal fillers known as volumizers or plumpersthat fill out lips and static folds in the face caused by collagen loss. Lip deformities like lip rise on one side than the other can be treated with Botox by injecting at a specific site depending on how much it is raised.[4]
5. **Treatment of black triangles**: one of the most commonly challenging aesthetic problem is the "Black triangles" and are treated by injecting dermal fillers into the interdental papilla to increase the tissue volume by puffing up the tissue and close the space. The treatment outcome last for about eight months after which the treatment has to be repeated.[1,4]
6. **Dental implants and oral surgery:** Once multiple implants or immediate loaded implants are placed, osseointegration and/or fracture callus formation can be hindered or prevented by excessive functional forces. This can result in the loosening of the implant components.[6] According to Nishimura K. and Kayikvioglu A.[13] the muscular relaxation achieved with botulinum toxin type A injections to the masticatory muscles can be therapeutically beneficial by allowing implants better unimpeded osseointegration and fracture healing in a more stable environment.[1,4] Kayikvioglu and colleagues.[14] injected 100 U of botulinum toxin Type A as an adjunct to zygomatic fracture fixation surgery, so as to reduce the number of fixation sites and to prevent the dislocation of zygomatic bone The injection was given on the masseter muscle of the fractured site. Later the patients were operated on 12 to 48 hrs after the injection and EMG (electromyography) confirmed the muscle denervation After the administration of the Botox ,masseter muscle showed temporary paralysis that allowed for the insertion of few miniplates and microplates in patients with no complications associated. Similar benefits were observed for the surgical reduction of mandibular and condylar bone fractures.[1,4]
7. **Bruxism:** Botulinum toxin has also shown promise in relieving the symptoms caused by bruxism. Van Zandijcke and Marchau.[15] injected 100 U of type A Botox injection into the masseter and temporalis muscle after which symptoms shown by the patient were reduced. A dosage of 200 U of type A Botox injection was introduced to the masseter muscle by Ivanhoe et al.[16] and appreciated a therapeutic response after 19 weeks.[1]
8. **TMJ disorders:** Temporomandibular joint disorder (TMD) is a title used to describe number of other diseases affecting masticatory function that may be pathologic or due to dysfunction of masticatory muscle.[1,4] These disorders manifests with headache, facial pain, neck and peri-auricular pain, joint sounds or decreased jaw excursion. The majority of TMD cases include a myogenic component and muscular spasticity secondary to bruxism, external stressors or oromandibular dystonia. TMD caused by excessive biting forces can be corrected with occlusal adjustments, restorations or intraoral appliances or surgeries and these techniques are invasive, irreversible, and expensive for the majority of patients. As an alternative to these techniques, muscular relaxation with Botox A injection is of prime choice as it produces the relaxation of the muscles of mastication thus providing relief to the muscle-centered TMDs. The pain reduction was attributed to the Botox A injection which blocked the neurotransmitters (CGRP, NGF1 and NP-Y) along with acetylcholine, that also relaxed the temporalis muscle and reduced the headache induced by temporalis hyperactivity secondary to clenching.[1,4]
9. **Oromandibular dystonia:** Oromandibular dystonia (OMD) is a movement disorder characterized by involuntary spasms and muscle contractions that results in difficulty in swallowing, eating and speaking. Eventhough being a neurologic disorder it is included under the TMD because of its involvement of the masticatory apparatus. Injecting type A Botox into the masseter and submentalis complex reported improvement of OMD, chewing and swallowing.[1,4]
10. **Mandibular spasm:** Mandibular spasm results from spasm or semi contraction of all muscles of mastication and associated mandibular muscles

resulting in limited mouth opening leading to limitations on completing the basic oral hygiene measures and difficulty in eating. Treating the masticatory musculature with Botox reduces the effect of spastic or hyperfunctional muscles and can significantly improve mouth opening, and effectively decrease pain and tenderness to palpation.[1,5,6]

11. **Orthodontic consideration of Botox:** Some Orthodontic patients delivers excessive force onto the periodontium and leads to gingival recession and bone loss, along with temporomandibular disorders. Type A Botox was introduced to such orthodontic patients who had the clenching habit, by Freund B. and Schwartz M.[17] After the treatment with Botox it was observed that there was a reduction in the orthodontic treatment time and patients were more comfortable while swallowing, eating and chewing. Other orthodontic consideration included the prevention of orthodontic treatment in patients with stronger mentalis muscle activity along with the reduction in the intensity of the muscle post treatment and ease the muscle training to a more physiologic movement.[1]
12. **Prosthodontic consideration of Botox:** Botox injections are given to patients on new denture particularly in case of edentulousness for a long period of timeand a decreased vertical dimension.[1]
13. **Toothache:** According to Rao LB,[18] muscle pain from anterior temporalis is referred to the teeth and the use of type A Botox can rule out if the toothache is from the pulpal or muscular origin thus Botox being both diagnostic as well asprophylactic.[1]
14. **Sialorrhea:** Botox acts by blocking the release of acetylcholine at the cholinergic synapses of autonomic nervous system and thereby blocking the cholinergic parasympathetic secretomotor fibers of the salivary gland. According to the study by Lim and Choi [19]. Botox Type A injection is effective in the treatment of acute postparotidectomy salivary fistula, Gustatory sweating (Frey syndrome) and achalasia, mucoceles and ranula.[1]
15. **Trigeminal neuralgia:** A unilateral neurologic condition affecting the trigeminal nerve and orofacial muscles. Standard medications that are given can result in various adverse effects and such side effects are relatively rare in case of Botox. Botox 25-75 U injected into the pericranial muscles can actively block the nerve impulses causing trigger contractions and relieve the pain by relaxing the overactive muscles. In case of migraines, muscle involvement is absent where in Botox act by blocking protein that carries the message of pain to the brain and relieves the pain within 2-3 weeks after injection.[1,3]
16. **Pathological clenching:** Traumatic effect on gingiva, teeth and adjacent tissues can be seen associated with pathological clenching. Periodontal trauma caused due to parafunctional clenching can be healed by limiting clenching before and after surgery with the use of type A Botox.[3,6] In such situations the use of a splint is often contraindicated (teeth should be functional during healing), so Botulinum toxin acts as a pharmaceutical splint.[4]
17. **Masseteric hypertrophy:** Masseter hypertrophy are frequently seen in chronic jaw clenchers and are usually presented with an increase in size of the masseter muscle evident in the patients face along with a swollen and misshapen jaw. Surgical resection was the only treatment option before the introduction of Botox, but it usually resulted in contractures. Injecting Botox onto the masseter muscle showed reduction in the hyperactivity of the muscle along with a reduction in gross masseter size (maximum reduction 35.4%). The reduction in masseter hypertrophy remains an enduring effect even after the cessation of Botox application, if the underlying pathology for the hyperactivity is resolved.[4,6]

Contraindications[1,3,6]

1. Patients with unrealistic expectations
2. Patients with neuromuscular disorders
3. Hypersensitivity to any botulinum toxin preparation
4. Pregnant or lactating mothers
5. Patients on medications like aminoglycosides, penicillamine, quinine and calcium channel blockers because they can interfere with neuromuscular impulse transmission and can potentiate the side effect ofBotox.
6. Infection at the proposed injection site
7. Renowned individuals like actors, singers, musicians, who are much dependent on their facial expressions and movements for their livelihood
8. Psychologically unstable patients
9. Patients with motor neuron diseases

Side Effects Of Botox[1,2]

Side effects usually reported after the injection of Botox are usually seen on the injection siteand it includes:

1. Mild and temporary effects like palpitations, tingling sensation, and fever are the preliminary symptoms and usually subside within 1-2 days.
2. Transient muscle paralysis
3. Nausea
4. Occasional vomiting
5. Utricaria
6. Dry mouth
7. Dysphagia
8. Dysphoria
9. Muscle soreness.
10. Atrophy of the muscle, if Botox is used for a long period and is reversible if treatment isdiscontinued.
11. Droopy eyes, eye swelling
12. Facial pain
13. Indigestion or heartburn
14. Tooth problems
15. High blood pressure
16. Edema around the injection site
17. Mild, localized and transient headache

18. Ecchymosis lasting 3 – 10 days

Drug Interaction

Some drugs like Muscle relaxants, Aminoquinolenes, Linosamide, Magnesium Sulphate, Quinidine, D-Penicillamine, Cyclosporin, and Aminoglycosides were noticed creating change inthe effect of botulinum toxin.[2]

CONCLUSION

The advancing front in the use of toxins is an emerging science for the beautification of a face and Botox have undoubtedly proven its significance in it. The all out efficiency of Botox is because of its minimally invasive nature, effectiveness and productive results. Even though it is not routinely used because of its temporary results, side effects and complications, it has becomean auxiliary treatment in Dentistry were surgical treatment was of paramount choice. The use of Botox as in the treatment of gummy smile, bruxism, TMDs, aesthetic dentistry and lip deformities has proven it to be indeed an advancement in dentistry.

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