

BOTOX: EXPANDING THE RANGE OF DENTISTRY - A REVIEW

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ABSTRACT

Muscle generated dental disease are quit common in dentistry. A number of diseases affect masticatory function including Temporomandibular joint disorders and masticatory function diseases. Presently these diseases are treated by intraoral appliances, occlusal adjustment and various dental restoration or surgical intervention. There is definite need to expand the current option available for the preventive treatment of such diseases. Botox (Botulium toxin type A) is a new paradigm treatment modality in the form of intramuscular injection. It is an extremely effective way of preventing muscle

damage caused by dental hard tissue and restoration. It is a natural protein produced by anaerobic bacterium, Clostridium botulinum. The toxin inhibits the release of acetylcholine (ACH), a neurotransmitter responsible for the activation of muscle contraction and glandular secretion, and its administration results in reduction of tone in the injected muscle. There are seven distinct serotypes of Botulinum toxin, viz., A, B, C, D, E, F and G, which differ in their potency, duration of action, and cellular target sites. This article describes the different applications of BOTOX in dentistry.

KEYWORDS: Botox, Clostridium botulinum, Temporomandibular joint, muscle, acetylcholine, dentistry.

INTRODUCTION

Botulinum toxin which is commercially available as purified exotoxin of *Clostridium botulinum*, an anaerobic bacteria. This neurotoxin is the cause of botulism—a serious paralytic illness. Botulinum toxins exist in seven types A to G but only type A and type B are available commercially.^[1] Botulinum toxin type A is used in the treatment of blepharospasm, severe primary axillary hyperhidrosis, 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 congenital dystonia. Recently botulinum toxin has been included in the treatment of orofacial conditions.^[2]

Botulinum toxin used in dentistry for the treatment conditions, such as parafunctional clenching, extracapsular myogenic temporomandibular disorder, trismus and the associated headaches, is a new option for symptom relief in patients in whom conventional treatments are not effective.^[3] Three forms of botulinum toxin type A (Botox, Dysport and Xeomin) and one form of botulinum toxin type B (MyoBloc) are available commercially for various cosmetic and medical procedures.^[4]

Botulinum Toxin Overview

Botulinum toxin is a deadly poison produced by a Gram-positive bacterium called *C. botulinum*. The bacteria produce 7 antigenically distinct toxins that are lettered A through G. Toxin A, however, has been the most extensively studied. The clinical syndrome of botulism occurs after ingestion of contaminated food, from colonization of the infant gastrointestinal tract or from wound infection. When foods containing the toxin are ingested, the toxin spreads to peripheral cholinergic nerve endings and blocks acetylcholine release. This results in a bilaterally symmetric descending neuroparalytic illness. The incubation period after ingestion is 18-36 hrs. 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. The toxin is heat labile and denatured by cooking.^[5]

History

The idea for a possible therapeutic use for botulinum toxin was first developed by the German physician Justinus Kerner. He deduced that the toxin acted by interrupting signal transmission within the peripheral sympathetic nervous system, leaving sensory transmission intact. He called the toxin a “sausage poison,” because it was observed that illness followed

ingestion of spoiled sausage. In 1870, John Muller, another German physician, coined the name “botulism” (from the Latin root botulus, which means “sausage”).

In 1949, Burgen was the first to discover that the toxin was able to block neuromuscular transmission. Scott *et al.* proved this fact by experimentally administering the Type A strain in monkeys. This strain was approved by the US Food and Drug Administration (FDA) in 1989 under the trade name Botox (Allergan, Inc, Irvine, Calif) for treating strabismus, blepharospasm, and hemifacial spasm in patients younger than 12-year-old.

In the year 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.^[5,6]

Mechanism of Action

Botulinum toxin inhibits the release of acetylcholine at neuromuscular junction leading to the paralysis of muscles. The three steps in the action of botox are

1. After binding the toxin to the nerve it is internalized in the nerve.
2. The normal process of vesicle fusion to the plasma membrane is interfered by the degradation by products of the toxin which is cleaned by internal proteolytic enzymes.
3. This leads to the inhibition of exocytosis of acetylcholine and finally causing the neuromuscular blocking effect. The effect of the paralysis depends on dose administered. Large doses cause complete paralysis while as partial activity results from therapeutic activity hence decreasing the appearance of hyper functional wrinkles.^[7]

The botulinum toxin causes muscle paralysis by inhibiting acetylcholine release at the neuromuscular junction via 3 steps as shown in the Flow chart.^[6]

Mechanism of Action

Toxin binds to the nerve and then it is internalized into the nerve



Toxin is cleaved by internal proteolytic enzymes and the degradation by products interferes with the normal process of vesicle fusion to the plasma membrane



Inhibition of the exocytosis of acetylcholine leading to neuromuscular blocking effect



Although large dose can result in complete paralysis, therapeutic doses allow partial activity, thereby decreasing the visual of hyperfunctional wrinkles.

Preparation: Botox is prepared by laboratory fermentation of *C botulinum*, which lyses and liberates the toxin into the culture. The toxin is then harvested, purified, crystallized with ammonium sulfate, diluted with human serum albumin, lyophilized, bottled in vials, and sealed. Each vial contains 100 U of Botox. 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. Optimal pH of the solution is between 4.2 and 6.8, and vials should be stored at or below -5°C .

Preparations should be reconstituted with 1-5 ml of saline without preservatives just before use. Because Botox is easily denatured via bubbling or agitation, the diluents should be gently injected into the inside wall of the vial. The reconstituted solution should be refrigerated at $2-8^{\circ}\text{C}$ and used within 4 h. Botulinum toxin B is marketed under the trade name Myobloc (Elan Pharmaceuticals, San Francisco, Calif). Its relative potency to Botox is 50-125 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.^[5]

Each vial of BOTOX contains

1. 100 Units (U) of *Clostridium botulinum* type A neurotoxin complex,
2. 0.5 milligrams of Albumin Human,
3. And 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative.^[4]

Therapeutic Uses

Botulinum toxin may be used for a variety of disorders ranging from pain management to the treatment of tremors and tics, to the improvement of the appearance of dynamic facial wrinkles. Table 1 summarizes the therapeutic uses of Botox. Botulinum toxin type A can be used in following dental conditions

1. Temporomandibular joint disorders.
2. Bruxism.

3. Oromandibular dystonia.
4. Mandibular spasm.
5. Pathologic clenching.
6. Dental implant and surgery.
7. Gummy smile.
8. Masseteric hypertrophy.

Temporomandibular Joint Disorders

Temporomandibular disorder (TMD) is a term used to describe a number of diseases affecting masticatory function, which may include true pathology of the temporomandibular joint as well as masticatory muscle dysfunction.^[8,9] TMD manifests with facial pain, joint sounds, headache, peri-auricular pain, neck pain, and/or decreased jaw excursion. The majority of TMD cases include a myogenic component^[10,11] and muscular spasticity secondary to bruxism, external stressors, oromandibular dystonia, and psychomotor behaviours are common aetiologic factors of TMD.^[12]

TMD caused by excessive biting forces has conventionally been treated with intraoral appliances, occlusal adjustments, dental restoration, and/or surgery. These techniques are invasive, irreversible and expensive for the majority of patients.

Techniques currently employed for aesthetic, conservative restorations may not withstand the parafunctional forces continually applied by some patients. Thus, many of these treatment options are not ideal for all patients and muscular relaxation with botulinum toxin A is a viable alternative. When a muscle relaxant is used with the muscles of mastication, this clenching reflex can be reduced or eliminated.^[13] Because a very small percentage of available force is required to masticate food, a slight relaxation of muscle function reduces bruxing and is usually insufficient to affect chewing and swallowing.^[14]

Chronic Migraine

Chronic migraine is a disorder with resulting reduced quality of life associated with discomfort. Botulinum toxin can be used to treat this disorder.

Dosage

The recommended dosage is dilution of 200 units/4 mL or 100 units/2 mL, with a final concentration of 5 units per 0.1 mL. It is administered intramuscularly using a sterile 30-

gauge, 0.5 inch needle as 0.1 mL (5 units) injections per each site to treat chronic migraine. Injections should be divided across following 7 specific head/neck muscle areas. (1) Corrugator: 5 U each side. (2) Procerus: 5 U one side. (3) Frontalis: 10 U each side. (4) Temporalis: 20 U each side. (5) Occipitalis: 15 U each side. (6) Facial paraspinal: 10 U each side. (7) Trapezius: 15 U each side. It has to repeat for every 12 weeks.^[15]

Pathologic Clenching

Pathologic clenching is a disorder leading to chronic trauma to teeth, gingiva, and underlying tissues. Low doses of botulinum toxin Type A can potentially reduce this disorder. Because parafunctional clenching leads to periodontal trauma, limiting clenching before and after periodontal surgery can benefit healing.^[16]

Mandibular Spasm

This type of muscular spasm results from spasm of all muscles of mastication and associated mandibular muscles. This disorder places limitations on completing the basic oral hygiene necessary to prevent oral disease. Other impairments can include: Restrictions on dental treatment, difficulty with eating and diminished oral utility. Botulinum toxin treatment to the masticatory musculature diminishes the effects of hyperfunctional or spastic muscles.^[17,18]

Bruxism

Botulinum neurotoxin has shown promise in decreasing the symptoms of bruxism. Ivanhoe *et al* reported success with a 200 U dose of botulinum toxin Type A in a separate brain-injury case report. A long-term, open-label trial study with a history of severe bruxism who were refractory to medical and dental procedures, to them botulinum toxin Type A injections were given into the masseters (mean dose: 61.7 U/side; range 25 U to 100 U), which results in a total duration of therapeutic response of 19 weeks.^[19,20,21]

Gummy smile

The excessive display of gingival tissue in maxilla while smiling is termed as Gummy smile. Botox can be used as an alternative treatment in use of gummy smile, other treatment options are cosmetic surgical procedures, dermal fillers, orthodontic and orthognathic procedures and dental bleaching.^[22]

Trigeminal Neuralgia

It is a unilateral neurological disorder affecting orofacial muscles leading to acute severe pain. Botox can be used as an adjunctive treatment modality in these patients which acts on nerve endings, thereby reducing the severity of the pain.^[23]

Enhancing Facial Esthetics

The facial wrinkles can be treated with Botox. But, the pathogenesis of wrinkles should be known first. The use of fillers in the lower face and the use of Botox for the upper face are advised. When the rhytid is primarily caused by muscular action deforming the overlying skin, Botox can be extremely effective treatment in the lower face.^[24]

Botox and Dermal fillers can provide immediate volume to areas around the mouth, such as the nasolabial folds, marionette lines, and lips to create the proper lip lines, smile lines, and phonetics. Dermal fillers, such as Juvéderm and Restylane, are volumizers—or plumpers—that fill out lips and static folds in the face caused by loss of collagen and fat.

Botox can also be used in a lip deformity where the lip rises more on one side than the other. It has to be injected at a specific site controlling where the lip goes and how much of it is raised and where and finally, the dreaded “black triangles” which is one of the most challenging aesthetic problems, for which there are very limited successful treatment options. Food particles accumulate in the space and create aesthetic issues. Dermal fillers can be injected into the interdental papilla to plump it and close the interdental space. Treatment outcome usually last for eight months or longer—at which point the treatment needs to be repeated.^[25]

Oromandibular Dystonia

Oromandibular dystonia (OMD) is a movement disorder characterized by involuntary spasms and muscle contractions. It manifests as distorted oral position and function resulting in difficulty in speaking, swallowing and eating. Although it is a neurologic disorder, it is included as a subset of TMD because of its involvement of the masticatory apparatus.^[26] Most of the reported literature on OMD has been open-label studies, but all have reported improvement with botulinum toxin injections.^[27–31] The largest study to date was a prospective open-label conducted by Tan and Jankovic that treated 162 patients with OMD over a 10-year period.^[31] Botulinum toxin type A was injected into the masseters and/or the

submental is complex. Improvement in function for chewing and speaking was reported in 67.9% of the patients, and mean duration of clinical improvement was 16.4 ± 7.1 wk.^[30]

Dental Implants and Surgery

Overloading of the muscles of mastication can prevent or impede osseointegration of implants and/or fracture callus formation. 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.

Kayikvioglu and colleagues^[17] conducted a small open-label study to prospectively examine the use of botulinum toxin type A as an adjunct to zygomatic fracture fixation surgery, in an attempt to reduce the number of fixation sites and to prevent dislocation of the zygomatic bone. Five male patients with zygomatic bone fractures were injected with 100 U of botulinum toxin type A into the masseter muscle of the fractured side. Patients were then operated on 12 to 48 h after the injection and EMG confirmation of muscle denervation. The temporary paralysis of the masseter muscles allowed for fewer miniplate and/or microplate insertions in all patients, and resulted in no complications related to either the botulinum toxin injections or surgical procedures. Kayikvioglu's group also found similar benefits of adjunct botulinum toxin treatment for surgical reduction of mandibular and condylar bone fractures.^[32,33]

1. Sialorrhea

This toxin also blocks the release of acetylcholine at the cholinergic synapses of the autonomic nervous system; thus, this toxin can block cholinergic parasympathetic secretomotor fibers of the salivary gland. Hence, botulinum toxin has been tested in some autonomic disease, such as achalasia, hyperhidrosis and gustatory sweating (Frey syndrome). Lim and Choi have reported that injection of botulinum toxin type A is a highly effective and relatively safe primary method of treatment for an acute postparotidectomy salivary fistula that, if treated with conventional pressure dressings, takes long to subside.^[34,35]

3. Retraining Muscles During Orthodontic Treatment

Botox can be used to prevent relapse of orthodontic treatment in case of patients with stronger muscle activity such as that of mentalis muscle. Botox can be used to reduce the

intensity of the muscle post treatment and over time, the muscle may be retrained to a more physiological movement.

4. Botox can be used in patients with a new denture especially if the patient has long history of edentulousness and has decreased vertical dimension.

5. Higher doses of botulinum toxin type A may potentially be used as a pharmaceutical splint, Limiting muscle contraction before resetting and during rehabilitation after fracture of a facial bone (e.g., fractured mandibular condyle).

6. Botulinum toxin type A can be used to verify whether the pain is muscular or pulpal (e.g., Complex toothache) in origin in patients with chronic intermittent toothache. For example, muscle pain from the anterior temporalis is often referred to the teeth. This should be treated before any major irreversible dental treatments are undertaken. In this context, the use of botulinum toxin type A is both prophylactic as well as diagnostic.^[4]

Drug interaction

The following drugs are seen to modify the effect of Botulinum toxin. Muscle relaxants, Aminoquinolones, Linosamide, Magnesium Sulphate, Quinidine, D-Penicillamine, Cyclosporin, and Aminoglycosides.^[36]

Side Effects

- 1) The muscles injected can be sore for a few days after the injections
- 2) Botox can cause temporary partial weakening of the muscles injected
- 3) When Botox is used for a long time, it may cause atrophy of the muscles injected. This atrophy is reversible if the therapy is discontinued
- 4) There have been reports of temporary side effects such as flu-like symptoms, palpitations, tingling sensations, or nausea. These side effects are rare and usually go away within 1-2 days.^[23]

Contraindications

The patients with the following conditions should not be treated with Botulinum toxin.^[37]

1. Patients with unrealistic expectations or psychologically unstable.
2. Patients with neuromuscular disorder.
3. Patients allergic to any component of BTX-A or BTX-B.
4. Actors, musicians, media personalities or singers who are more dependent on intact facial

movements and expressions.

5. Pregnancy and lactation

CONCLUSION

Botox has been introduced as an efficient treatment option to many dental conditions where surgical treatment was necessary. But still it is not wholly explored for dental use. It has important clinical uses as an adjunct therapy in temporomandibular joint (TMJ), bruxism cases and for patients of facial pain.

BOTOX is also used to harmonize aesthetic dentistry cases, as a minimally invasive alternate to surgically treating high lip-line cases, for denture patients who have difficulty adjusting to new dentures, periodontal cases, gummy smiles, lip augmentation and also for orthodontic cases where retraining of the facial muscles is required. However, much more is still to be discovered before its routine use in dentistry for various conditions. There are still a lot of dental conditions which require FDA approval to be treated by botulinum toxin. Botulinum toxin has no hesitation broadened the horizon of dentistry and is persuading dentists all over the world to bring it into their clinical practices.

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