

**BOTULINUM TOXIN IN DENTISTRY- A DEADLY POISON TO A REMARKABLY
RESOURCEFUL THERAPEUTIC AGENT**

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ABSTRACT-

Within the last 100 years, the perception of Botulinum neurotoxin (BTX) has evolved from that of a poison to a versatile clinical agent with various uses. BTX plays a key role in the management of many orofacial and dental disorders. Its indications are rapidly expanding, with ongoing trials for further applications. Over the past two decades the cosmetic and non - cosmetic uses of Botulinum toxin in the orofacial region has gained wide popularity. However, despite its clinical use, what BTX specifically does in each condition is still not clear. The main aim of this review is to describe some of the unclear aspects of this potentially useful agent, with a focus on the current research in dentistry.

KEYWORDS: Botulinum toxin; bruxism; trigeminal neuralgia; orofacial pain.**INTRODUCTION**

Botulinum neurotoxin (BTX) is a neurotoxic protein produced by the Gram-positive, rod-shaped, spore-forming, and strictly anaerobic bacterium *Clostridium Botulinum* and, rarely, by *Clostridium butyricum* and *Clostridium baratii*, commonly found on plants and in soil, water, and animal intestinal tracts. Although once considered lethal, BTX is now used as a therapeutic drug. BTX exhibits transient, nondestructive, dose dependent and localized actions, with minimal systemic side effects, underlying its wide use in various orofacial and dental disorders.^[1]

Botulinum toxin can be differentiated serologically into eight kinds of toxins named from A to G (A, B, C1, C2, D, E, F, and G).^[2,3] Neurotoxin strains A and B are antigenically different, but have similar functions and are commercially available for medical treatments.^[4,5]

“Botox” (BT) is the USA trade name for botulinum neurotoxin type A.^[6] BT is a high-molecular weight protein complex made of 3 different proteins: First, a 150-kDa toxin which itself is composed of a 100-kDa heavy chain and a 50-kDa light chain that are binded together with disulfide non-covalent bonds. This bond disrupts during toxin activation. Second, a non-toxin hemagglutinin protein, which protects the toxin from being destroyed by acids. Third, a non-toxin non - hemagglutinin protein.^[7] Although Botulinum toxin is a lethal, naturally occurring substance, it can be used as an

effective and powerful medication in the treatment of overactive oro- facial musculature. The purpose of this review is to provide insights into the current indications of BT, highlight its expanding use, and review recent advances in the use of BT in dentistry.

MECHANISM OF ACTION

BT mainly inhibits the release of acetyl choline at the neuromuscular junction resulting in paralysis of muscles. At therapeutic doses BT causes localized paralysis of target muscles. When it is injected to the muscle it causes proteolysis of proteins Synaptosomal associated protein SNAP-25 in the neuronal cytoplasm, which is very essential for the release of acetyl choline at the neuromuscular junction. Thus, there is loss of neuronal activity and ultimately localized paralysis of the isolated muscle.^[8] This therapeutic effect is reversible, which first appear in 1 to 3 days, peak in 1 to 4 weeks, and decline after 3 to 4 months.^[9]

Forms of BTX

There are several BT preparations in different countries. The most common available BT-A preparations are Botox, Dysport, Xeomin, Prosigne and PurTox. Myobloc is a BoNT-B preparation. The treatment dose varies for each brand of toxin and for different parts of the body.^[10]

Dosage

Each vial of Botulinum toxin (BT) contains-
 1.100 Units (U) of Clostridium Botulinum type A neurotoxin complex,
 2. 0.5 milligrams of Human albumin and 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative.
 Adding 4 ml of 0.9% preservative-free normal saline solution makes injections and the preparation should be used within 4 hours.^[11]

The potency of BT is expressed as mouse units. A unit of BOTOX is defined as the LD 50 for a colony of 20 gm Swiss-Webster mice, the usual maximum dose recommended for dental applications at an injection session is about 80-100 U.^[12]

Injection procedure

The BT dose should be tailored to the severity of the condition. Toxin is injected with a 1- to 1.5-inch, 25- to 30-gauge needle, with electromyography (EMG) monitoring. Subsequent injections can be given according to the response after 3 months.^[13]

Safety and Adverse Effects

In general, adverse reactions are uncommon and relatively mild and transient which are more common at or near the site of injection. These include dry mouth, dysphagia, dysphonia, transient muscle paralysis, headache, urticaria and nausea and these side effects are noted when the dose exceeds that recommended.^[14] The FDA revised the prescribing information for the commercially available botulinum toxin A products to include a "Boxed Warning" highlighting potentially adverse reactions related to distant spread of the toxin effect from the injection site. These highlight botulism like symptoms such as muscle weakness, hoarseness or dysphonia, dysarthria, loss of bladder control, difficulty breathing, difficulty swallowing, double or blurred vision and drooping eyelids. These effects can occur anywhere from a day to several weeks after treatment at unrelated sites.^[15, 16]

Patient Selection

BOTOX therapy is appropriate for patients in whom other preventive treatments and medications are poorly tolerated or contraindicated, patients who are refractory to other treatments, special patient populations, and patients who simply prefer this treatment.^[12]

Contraindications

Patients should not be treated or treated with extreme caution who are:^[17]

- Psychologically unstable or who have questionable motives and unrealistic expectations.
- Dependent on intact facial movements and expressions for their livelihood (e.g. actors, singers, musicians and other media personalities).
- Afflicted with a neuromuscular disorder (e.g. myasthenia gravis, Eaton-Lambert syndrome).

- Allergic to any of the components of BTX-A or BTX-B (i.e. BTX, • human albumin, saline, lactose and sodium succinate).
- Taking certain medications that can interfere with neuromuscular • impulse transmission and potentiate the effects of BTX (e.g. aminoglycosides, penicillamine, quinine, and calcium blockers).
- Pregnant or lactating (BTXs are classified as pregnancy category • C drugs).

Diagnostic Application of Botox

It can be used to verify whether the correct diagnosis has been established or not. The pain originating from the pulp will not be relieved when BOTOX is injected into the muscles. Hence, the patients will be certain about the muscular or pulpal origin of the toothache. The diagnostic applications are limited only for the elimination of pain originating from muscles and the pain originating from other structures are not relieved and can be clearly differentiated.

Applications of Botulinum toxin (BT) in dentistry**Cosmetic use of BT****1. Facial wrinkle**

The most common cosmetic indication of BT is in wrinkle therapy for glabella lines and platysmal bands, and in perioral cosmetic therapies such as gummy and asymmetry smile treatment.^[18,25,26] Wrinkles such as glabellar lines are a spontaneous facial animation that develops when the lower facial muscles pull the skin, and they develop mainly by the action of the procerus and corrugator supercilii muscles. In addition, this line becomes more obvious with aging and constant exercise.^[19] BT has been used to temporarily treat not only glabellar lines but also lateral cantonal lines called horizontal forehead lines, platysmal bands, perioral lines, and crow's feet. The efficacy of BTA in reducing facial wrinkles has been proven in randomized controlled trials.^[20-22]

Administering BT for wrinkle therapy is generally simple. An adequate dose is perpendicularly injected considering the anatomy of the region to be treated. BT is known to diffuse to approximately 10 mm and, therefore, is injected at that distance from major structures such as the bony orbit.^[18]

Successful results have been reported in the treatment of not only glabellar lines but also vertical lip rhytids, mentalist wrinkling, lower eyelid orbicularis hypertrophy, and excessive gingival exposure (gummy smile), which can be treated by injecting the toxin into the lip to elevate the muscle.^[18-26]

2. Correction of prominent mandible angle and facial asymmetry due to masseter muscle hypertrophy
 Although prominent mandible angle mainly develops skeletally, it can also develop by bilateral masseter muscle hypertrophy, and facial asymmetry develops with unilateral masseter muscle hypertrophy. In this case, a

satisfactory therapeutic effect can be obtained using intramuscular BTA injections. In addition, injecting BTA into the masseter or temporalis muscle is effective in the treatment of bruxism.^[18]

Current and expanding applications in oro-facial disorders.

1. Oro-facial pain conditions like trigeminal neuralgia, postherpetic neuralgia, migraine, headache and myofascial pain dysfunction.
2. Salivary gland disorders like sialorrhea, sialocele, Frey's syndrome etc.
3. Hypertrophy of masseter muscle.
4. TMJ disorders like dislocation, bruxism, and oromandibular dystonia and arthritis.
5. Trismus.
6. Gummy smile
7. Disorders of the facial nerve i.e. Facial nerve palsy/paresis.
8. Cancer therapy.
9. Botulinum toxin as a carrier for oral vaccines.
10. Preparation of oral cavity for microsurgical reconstruction.
11. During dental implant, jaw and periodontal surgeries.
12. In wound healing.
13. Treatment of hypertrophic scars.

Clinical conditions	Dosage
Headache, Migraine & Trigeminal Neuralgia	25-75 U injected into peri-cranial muscles
Myofascial and Neck Pain	Injection of muscles with BT - effective for myofascial pain caused by trigger points
Sialorrhea	Autonomic diseases such as achalasia, hyperhidrosis and gustatory sweating (Frey syndrome)
Masseteric Hypertrophy	5 U injected into the belly of the masseter below an imaginary line joining the tragus of the ear and the corner of the mouth
TMJ Disorders	Mild-moderate cases -Bilateral injections of 7.5 U into the anterior vertical fibres of each temporalis muscle. Severe cases -2.5 U are given into the middle and posterior third of the temporalis muscles. Tendonitis of temporalis -multiple injections of 2.5 U equidistantly spaced in the temple area outside the orbital rim
Recurrent Dislocation of the Mandibular Condyle	BT injections into the lateral pterygoid muscles.
Mandibular Spasm	35 units for each lateral pterygoid muscle & 30 units for the sub-mental complex
GummySmile	0.25 U 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.
Facial nerve palsy/paresis	10-80 U of BT in saline is given intramuscularly, with the precise dose being tailored to each patient and monitored by EMG.
Cancer therapy	Local administration of the toxin promotes tumor perfusion and oxygenation, and modulates the vasoreactivity of vessels. Greatest effects are seen when BT is injected 3 days before beginning anticancer treatment
Oral cavity reconstruction	3-4 injections are given to each gland, with a total dose of 80-100 U of BT.
Dental Implants	Prophylactic use of BT injections to the masticatory muscles for relaxation-better implant osseointegration
Oral Surgery	Low doses of BT - allow traumatized tissues to heal. High doses - "pharmaceutical splint," limiting muscle contraction before resetting and during rehabilitation after fracture of the facial bone e.g. fractured mandibular condyle
Diagnostic Applications	Injection of BT into the muscles aids in differentiation of muscular or pulpal origin of the toothache

CONCLUSION

An excellent therapeutic result of BT in medicine has drawn its course towards dentistry. Though off label BT

is a superior treatment modality than the conventional ones in many morbid conditions of orofacial region. BT provides a treatment that is reversible, conservative,

quick and painless in comparison to other surgical alternatives. Although there have been a number of preliminary studies on BT, most clinical studies have only reported the successful cases, and research studies showing a high level of scientific evidence have been very rare. To overcome this, a prospective, randomized, controlled study would be necessary.

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