Review Article

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A Review of Botulinum Toxins: The New Paradigm in Dentistry

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ABSTRACT

Background: Botulinum Toxin (BT) is the molecule produced naturally during growth and autolysis of bacterium called Clostridium botulinum. Use of BT in cosmetics has gained popularity over past few decades, and recently, other therapeutic uses of BT has been extensively studied and reviewed. BT is considered as an effective minimally invasive agent which can be used in the treatment of various orofacial disorders and improving the quality of life in such patients.[1] The objective of this article is to review the nature, mechanism of action of BT, and its application in various head and neck diseases.

Keywords: Botulinum Toxin, Clostridium botulinum, minimally invasive, orofacial disorders.

INTRODUCTION

A variety of factors, such as stress, hormones, diet, trauma, and certain neuromuscular diseases, can lead to an increase in sympathetic muscle tone, which results in masticatory muscle hypertonicity and parafunction.[2] Dentists have traditionally attempted to treat and prevent this transient disease with methods that are expensive, irreversible, and not evidence-based. There is a need for a conservative reversible noninvasive procedures that is quick, easy, relatively inexpensive, long acting, and effective.

Nature of toxin

Botulinum neurotoxins (BTXs) derive from the bacterium Clostridium botulinum and include seven distinct serotypes, identified as A, B, C, D, E, F, and G. Currently, two commercially available subtypes are BTX-A (Botox Cosmetic®, Vistabel®, Vistabex®, Dysport®, Reloxin®,CBTX-A, Prosigne®, Neuronox®, Xeomin®) and BTX-B (Myobloc®, Neurobloc®).[6] Both of these have 150-Kd dichain polypeptides.[2] BTA and BTB have light and a heavy chain connected with disulfide bond. Light chain of BTA bond with 5-Kd synaptosome-associated protein (SNAP-25), a protein which plays a major role in acetylcholine secretion from vesicle in the nerve ending. Light chain of BTB bond with synaptiobevin or vesicle-associated membrane protein (VAMP), which is less specific. For this reason, BTA is more effective as compared to BTB.[2]

Preparation

The toxin is harvested from a culture medium after fermentation of a toxin-producing strain of C. botulinum, which lyses and liberates the toxin into the culture. The toxin is then extracted, precipitated, purified, and finally crystallized with ammonium sulfate. BTX-A should be stored in a refrigerator but not frozen. BTX-A should be diluted with preservative free saline and the preparation used within 4 hours of reconstitution. Conditions for stability of the toxin in solution include pH 4.2–

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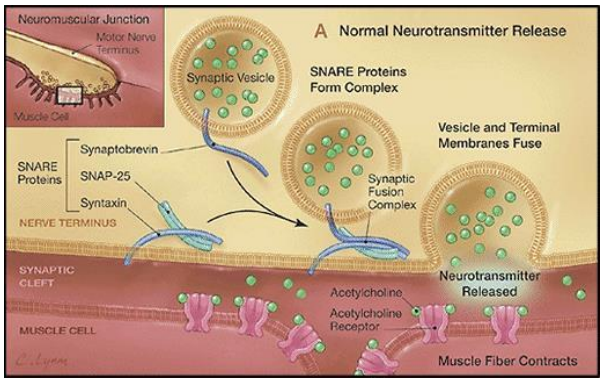

Fig 1: Mechanism of action of normal neurotransmitter release.

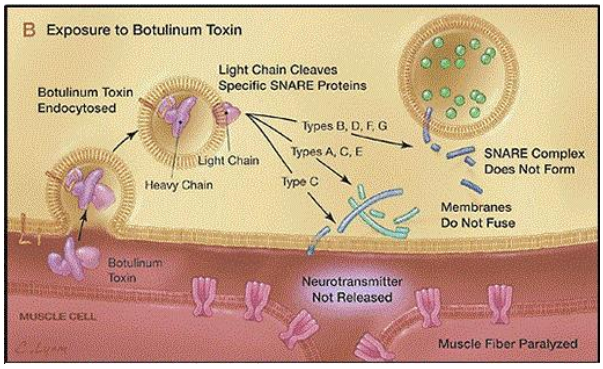

Fig 2: Mechanism of action on exposure to botulium toxin.

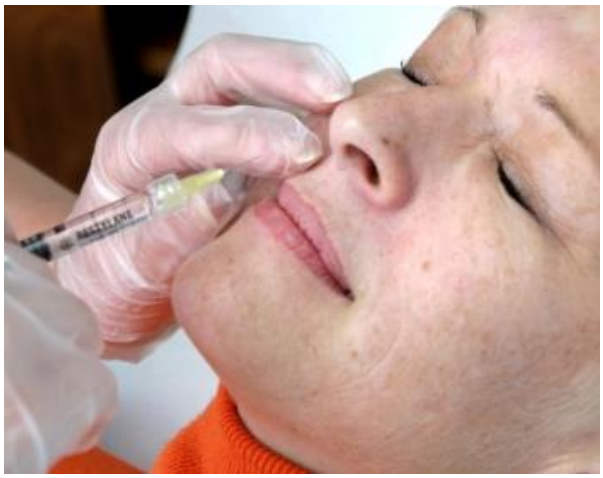

Fig 3: Toxin administration.

6.8 and temperature less than 20°C. The large molecule is very fragile and is inactivated easily in solution by shaking.[2]

Potency

The potency of BTX is expressed as mouse units, with 1 mouse unit equivalent to the median

Fig 4: tuberculin syringe.

Fig 2. Patient 1 – jaw-opening oromandibular dystonia. (A) pre-botulinum toxin injection; (B) post-botulinum toxin injection.

Fig 5: Oromandibular dystonia and correction with BT.

lethal dose (LD 50) for mice. Botox is dispensed in small vials containing 100 U, while a vial of Dysport® contains 500 U. The relative potency of Botox® units to Dysport® units is approximately 1:4. The lethal dose of Botox in humans is not known,although it has been estimated to be about 3,000 U. The usual maximum total recommended dose at an injection session is about 80–100 U. This means that the injector will have to inject 30 vials before a potentially lethal outcome. There is such a huge disproportion between the clinical dose and the lethal dose that a fatal overdose is almost impossible.[2]

Mechanism of action

The BT primarily acts on cholinergic receptors and prevents the release of neurotransmitter Acetyl choline, thus causing widespread paralysis of muscles, characteristic feature of botulism infection.[3] When therapeutic dose of BT is administered to isolated muscle, localized paralysis of target muscle ensues. It is believed that inhibitory action of BT first involves

Table 1: A summary of various applications in maxillofacial region.

Condition	Method of use of BT	Effect	Duration of effect
Hypersalivation	Intraglandular injection	Decreased production of saliva	1.5-6 months Variable,upto2years
Gustatory sweating	Interadermal injection into the affected area	Reduced local hyperhidrosis	5-12 months
TMD	Intramuscular injection into temporalis and masseter muscle	Relief from pain, improved mouth opening	
Oromandibular			Variable
Dystonia	Intramuscular injection into masseter and sub mentalis muscles Sub-mentalis muscle	Improved function of chewing and speaking	
Masseteric Hypertrophy	Intramuscular injection into masseter Muscle	Sustained reduction in gross masseteric size and hyperactivity	Upto 6 months
Prominent gingivae (Gummy smile)	Intramuscular injection into leavtor labii, superioris alaeque	improved smile	3-6 months –
Dental implants and maxillofacial	Nasi,and zygomaticus minor		
Fractures Orofacial pain	Intramuscular injection into masticatory muscle to achieve muscle relaxation injection into involved area	Better implant intergration ,stable environment for callous formation pain relief	–

BT: Botulinum toxin , TMD: Temeromandibuler disorder

binding of toxin to presynaptic nerve membranes followed by proteolysis of SNAP-25, a protein required for the successful docking and release of acetylcholine from vesicles located within nerve endings.[4] Intramuscular injection of BT results in local chemical denervation and the loss of neuronal activity in the target organ.[5] This localized weakness or paralysis (dose dependent) of skeletal muscle can last from three to six months, and the effect is reversed by neural sprouting with re-innervation of the muscle.(Fig 1,2,3,4.)

Application

Botox is used in various disorders asa treatment modality. Along with general applications it also has some specific dentofacial applications. Among the general applications, BT has been tried for treatment of overactive bladder, treatment of urinary incontinence due to detrusor over activity associated with a neurologic conditions, prophylaxis of headaches in adult patients with chronic migraine, treatment of upper limb spasticity in adult patients, treatment of cervical dystonia in adult patients, treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients, treatment of blepharospasm, treatment of strabismus. [6] A summary of the various applications in maxillofacial region is given in Table 1.

Hypersalivation

Hypersalivation or sialorrhea is excessive production of saliva.BT significantly decreased production of saliva when injected intragladularly

by blocking the release of Acetyle choline from nerve terminals.[7] Fuster-Torres MA and co-workers conducted a systematic Pubmed search, describing the usefulness of BT in sialorrhea. BT was injected into parotid, sub-mandibular gland or both, and doses of toxin varied from 10-100 units. The total doses of toxin injected varied from 10-100 units of Botox® or 30-450 units of Dysport®.[6]

The authors noted reduction in saliva production and effect lasted for 1.5 to 6 months. Adverse effects such as dysphagia, xerostomia, and chewing difficulties are reported with the use of BT injection into salivary glands. However, number of issues such as dose, site of injection, method of application is still open for discussion.[7,8]

Gustatory sweating

Gustatory sweating or Frey's syndrome or Auriculotemporal syndrome is a phenomenon of facial flushing and sweating after gustatory stimulus, usually secondary to surgical trauma of the parotid gland.

While medical therapies like systemic anti-cholinergics are not well-tolerated, surgical procedures seem disproportionate to symptomatology and ineffective. Recently, studies on the use of BT to the affected area in the treatment of Frey's syndrome have proven to be effective.[5,9] BT injected intradermally transiently blocks pre-synaptic acetyl choline release at neuromuscular junction, leading to chemical denervation and great improvement in patients suffering from gustatory sweating..

Pornprasit M injected 2 unit or 0.1 ml intradermal BT type A at every 1 cm^2 affected area determined using starch-iodine test as a diagnostic criterion.[9,10]. After toxin injection, duration of symptom-free periods is variable. Reduction in gustatory sweating after BT injection lasts for longer duration than those obtained when injecting BT to treat other illnesses, especially those of a muscular origin, where the effects only last three to six months.[1] Laccourreye et al., in a follow-up study of 33 Frey's syndrome patients treated with BT, found recurrence rates of 27% in the first year, 63% in the second, and 92% in the third year.[11]

Temporomandibular disorders

TMD is a broad term which may include true pathology of the temporomandibular joint as well as masticatory muscle dysfunction. TMD manifests with facial pain, joint sounds, headache, periauricular pain, neck pain, and/or decreased joint excursions. Muscular spasticity secondary to bruxism, external stresses, oromandibular dystonia, and psychomotor behaviors are common etiologic factors of TMD.[12,13] Excessive pathologic nocturnal clenching (excessive centric grinding of teeth) of the jaw which in severe cases may manifest as dystonic bruxism, contributes to TMJ dysfunction in additions to damage to teeth, bone, joints, and gums.[14] The treatment begins with a lower dose, because it is always possible to titrate up to a higher dose, if necessary.

Botox neurotoxins can be generally applied to a number of muscles of facial expressions and mastication, including the masseter, temporalis, pterygoids, frontalis, procerus, corrugator, orbicularis oculi, orbicularis oris, mentalis, and depressor anguli oris.[15]

The temporalis component of pain is treated with bilateral injections of 7.5 U into the anterior vertical fibers of each temporalis muscle. In more severe cases, 2.5 U are given into the middle and posterior third of the temporalis muscles. Pain relief for the tendon of temporalis is achieved with multiple injections of 2.5 U equidistantly spaced in the temple area outside the orbital rim.[14]

The masseter component of pain is treated with 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.[2]

Oromandibular dystonia

Oromandibular dystonia (OMD) is a focal dystonia affecting the trigeminal and oral-perioral musculature characterized by involuntary spasms of masticatory, lingual, and pharyngeal muscles.[1] Asynchronous spasm of the muscles involved in OMD results in distorted oral position and difficulty in speaking, swallowing, and eating. OMD can be seen in isolation (focal dystonia), as part of a more widespread segmental cranial dystonia, or as part of a multi-segmental or generalized dystonia.[16]There is no known cure for OMD at present, although BT injections have been the mainstay of treatment for

most focal dystonia. Denervation of motor endplates has been proposed as the leading mechanism of action of BTX in dystonia, including OMD.[17](Fig 5)

The literature on OMD has reported improvement of symptoms with the use of BT injections.[18,19] The study was conducted by Tan and Jankovic that treated 162 patients with OMD over a 10-year period. BT was injected into the masseters and/or the sub-mentalis complex, and improvement in function for chewing and speaking was reported in 67.9% of the patients.[19]

Masseteric hypertrophy

Patients who are chronic jaw clenchers frequently present with masseteric hypertrophy.[20] The increased size of these muscles is evident in the patient's facial appearance, which is often altered, e.g., the jaw can appear swollen and misshapen. To treat this, surgical resection was commonly resorted to which often resulted in substantial contracture. One of the treatment for masseteric hypertrophy is Botox being injected into the belly of the masseter muscle. This will cause a slenderizing of the face in addition to reducing the intensity of contractions of the masseter muscles, and like all other Botox treatments, repeat injections are required every few months.[21]

In a clinical trial, the injection of 30 U per side of BT into the masseter muscles resulted in a sustained reduction of gross masseter size (maximum reduction 35.4%).[22] The possible complications after BT injection into muscle include external scar and damage to the mandibular branch of the facial nerve, change in bite force, speech disturbance, muscle pain, facial asymmetry, and prominent zygoma.[23]

Prominent gingivae

The display of excessive gingival tissue in the maxilla upon smiling or the ''gummy smile'' is both an oral hygiene and aesthetic issue with no simple remedy. Several surgical techniques have been reported in the literature for the correction of hyper-functional upper lip elevator muscles, such as (a) Rubinstein and Kostianovsky, (b) Miskinyar (c) Rees and LaTrenta techniques. However, they are not routinely used to treat gummy smiles. In general, the most common surgical corrections currently used are the LeFort I maxillary osteotomies with impaction for skeletal vertical maxillary excess and gingivectomies for delayed passive dental eruption with excessive gingival display.[14]

Excessive gum exposure is frequently attributable to over contraction of the upper lip muscles, particularly the levator labii superioris alaeque nasi. When this is the case, a less invasive approach is to limit muscular over-contraction. If applied in small, carefully titrated doses, these muscles can be proportionately weakened with BOTOX, which will reduce exposure of the upper gums when smiling.[14]

Kayikvioglu and colleagues conducted a study to examine the use of BT 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. Patients with zygomatic bone fractures were injected with 100 U of BT into the masseter muscle of the fractured site. Patients were then operated on 12 to 48 hours after the injection, and the temporary paralysis of the masseter muscles allowed for fewer miniplate and/or microplate insertions in patients. Kayikvioglu's group also found no complications related to either the BT injections or surgical procedures.[24,25]

Polo conducted a study in which five patients with excessive gingival display due to hyper-functional upper lip elevator muscles were treated with BOTOX under electromyographic guidance. Patients received one 0.25 U injection per muscle bilaterally into the levator labii superioris, superioris labii alaeque nasi, and at the overlap areas of the levator labii superioris and zygomaticus minor muscles. All the patients were pleased with the results and the effective increase in upper lip length upon smiling averaged 124.2% and the duration of effect ranged from 3 to 6 months and no adverse effects were reported or observed. [26]

Dental implants and maxillofacial fractures

After implant placement, osseointegration can be impeded by excessive functional forces, especially in patients with para-functional habits. Thus, the overloading of implant results in its

failure.[1] Implant patients will benefit from pre-surgical BOTOX treatment. Over loading of the implants results in implant failure by loosening of the implant components or prevention of osseo-integration.[14] The muscular relaxation achieved with prophylactic use of BOTOX injections to the masticatory muscles can be beneficial by allowing implant structures better osseo-integrated. Maxillofacial fracture repair often requires multiple fixation sites and hardware to overcome the strong forces of masticatory musculature. Overloading of these muscles can prevent fracture callus formation. The muscular relaxation achieved with prophylactic use of BOTOX injections to the masticatory muscles can be beneficial by allowing fracture healing in a more stable environment.[27,28]

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Orofacial pain

The etiology of myofacial pain syndrome is incompletely understood. Some clinicians believe that it characteristically results from either an acute episode of muscle overload or from chronic and/or repetitive muscle overload. Active myofacial trigger points, which cause pain, exhibit marked localized tenderness and often refer pain to distant sites and disturb motor function. Injection of muscles with BOTOX has been reported to be effective for myofacial pain caused by trigger points.[29] Jennifer Warner, reported pain relief in 25 patients with chronic neck pain, after a single injection of Botox delivered to the affected neck muscle combined with standard physiotherapy.[30]

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.[13]

Dose

BT when administered in the appropriate doses by an experienced clinical specialist is a safe therapy. In general, 1 to 8 mL of saline is added to 1 vial, producing a concentration of 10 to 1.25 units per 0.1 mL, and once reconstituted, the effectiveness of BT begins to diminish. Therefore, it is recommended that BTA should be immediately administered once reconstituted. BT when administered in the appropriate doses by an experienced clinical specialist is a safe therapy.

Rao et al. recommends maximum dose for dental applications at an injection session about 80-100 U, which is much less than the lethal dose (estimated to be about 3000 U).[2,14] Depending upon the type of the product and its dilution, the prices of BT injections can vary in various countries. For example, prices for the newer products, Dysport and Xeomin, tend to be lower than Botox.

Contraindication and adverse effects

- The relative contraindications include pregnancy, lactation, neuromuscular diseases (myasthenia gravis, Eton-Lambert syndrome), motor-neuron diseases, concurrent usage of amino glycosides and sensitivity to toxin.
- The clear contraindications to the use of BT include known allergy to the drug, presence of inflammation or infection at the site of proposed injection.[1]
- Anatomic abnormalities like obesity or deformity can make the injections difficult or impossible. The patients who are on calcium channel blockers or those who suffer from coagulopathy (including therapeutic anti-coagulation) are also not appropriate candidates to receive BT injections. BT injections should be avoided in patients taking Aminoglycoside antibiotics, because aminoglycosides may interfere with

neuromuscular transmission and potentiate the effect of BT therapy.[26]

- The potential adverse effects of Botulinum toxin in oromandibular disorders include facial nerve palsy, pain at the injection site, flu-like symptoms, non-targeted muscle weakness, dysphagia, and hematoma. These complications are generally transient and resolve within a couple of weeks [12,14,31]

DISCUSSION

Research and studies have surely shown that Botox products are the viable treatment for various orofacial dysfunctions; when they are based on the musculature. Botox therapy is appropriate for patients in whom other preventive treatments and modifications are poorly tolerated or contraindicated, patients who are refractory to other treatments, special patient populations, and patients who simply prefer this treatment.[6]

Before injecting Botox into the muscle and/or joint and/or skin, the skin has to be cleaned with an alcohol/betadine/chlorhexidine swab. For muscle injections, the site to be injected should be determined by using a small electric recorder or a larger machine called an EMG machine, which helps in correctly locating the area of the muscle to be injected. Ultrasound-guided injections may also be used for deeper joints or muscles. BOTOX is injected using 1 ml tuberculin syringe and 0.30 gauge half inch needle. Injections of a small amount of this toxin into a muscle produces atrophy and weakness within one to twenty days and recovers over two to four months as new terminal axons sprout and restore transmission.Injections are spaced out for a minimum of three months to minimize the risk of antibody formation to the protein, which would prevent BOTOX from working the subsequent time.[14,32,33]

BOTOX produces partial chemical denervation of the muscle resulting in localized reduction in muscle activity. BOTOX can be used as a sole therapy or as an adjunct to oral medication. Adding 4 ml of 0.9% preservative-free normal saline solution makes injections and the preparation should be used within 4 h.[14] Injections are spaced out for a minimum of 3 months to minimize the risk of antibody formation to the protein,which would prevent BOTOX from working the subsequent time. Specialized equipment can be used for more accurate injections that include:

- EMG-guided injections (with the NeuroMax 1004).
- Peripheral nerve stimulator (NS 272).
- Ultrasound-guided injections (including the Canadian Centre for MSK ultrasound).
- MD injectors (Botox Therapeutic).[14,32]

The FDA approved Botulinum toxin type B for the treatment of cervical dystonia is marketed under the trade name ''Myobloc'' (Elan pharmaceuticals) in USA [2] and ''NeuroBloc'' (Solstice Neurosciences, Inc.) in Europe.[2]

CONCLUSION

The use of Botulinum toxin in the dental profession has a great potential as BOTOX paralyzes or weakens the injected muscle but leaves the other muscles unaffected. The injections block the extra muscular contractions but leave enough strength for normal use. The long duration of the positive effects of BT and limited systemic complications associated with its use are important pharmacological features of this therapeutic option. Intra muscular injections of BOTOX re-establishes the balance between masticatory closing and opening muscles, Its use relieves muscle pain, reverses masseteric hypotrophy with improvement of facial outlines, and restores normal kinetics of TMJ.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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