BOTULINUM TOXIN: FROM KILLER TO HEALER – A REVIEW

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ABSTRACT

Botulinum toxin (BT) which once created a chaos in the world of medicine due to its life threatening effects, is now been utilized for an array of cosmetic and therapeutic purposes. In addition to its well renowned cosmetic uses, BT has a very important role to play in disciplines like removable prosthodontics, orthodontics and implant therapy. It provides for a non-surgical and minimally invasive treatment of various disorders associated with the muscles of the head and neck and temporomandibular joint like myofascial pain dysfunction syndrome and bruxism. The purpose of this article is to review the molecular structure, mechanism of action and clinical uses of of BT in dentistry.

Key Words: Botulinium Toxin, Botox, Temporomandibular Muscle Disorders, Masticatory muscle Hypertrophy, Gummy smile

INTRODUCTION

Botulinum toxin (BT) which is renowned for its cosmetic uses,is also an invaluable tool in the treatment of various neurological and orofacial disorders. Clostridium botulinium which was once famous as a cause of fatal food poisoning produced by its deadly neurotoxins, nowadays, has been used as a therapeutic measure for many clinical situations when injected in minute quantities. There are eight different serotypes of botulinum toxin (A, B, CbC2, D, E, F, G) which occur both naturally and in-vitro culture; type A being the most potent and most commonly used clinically **(Table 1)**.[1, 2] The history of use of BT can be traced back to the early 1800's and has been used treat strabismus, blepharospasm, hemifacial spasm, various other muscle hyperactivity syndromes, exocrine gland hyperactivity syndromes and various orofacial disorders **(Table 2).**[3, 4]

Molecular structure and Mechanism of Action

BT is synthesised during growth of gram negative bacteria *Clostridium botulinium* and released in the surroundings during its autolysis.BT is synthesized as a large peptide comprising of a heavy chain (100kDa) and a light chain (50kDa) linked by a disulfide bond that acts at the neuromuscular junction where it exerts its effect by inhibiting the release of Acetylcholine (ACH) from the presynaptic nerve terminal.[5]ACH is a neurotransmitter contained in vesicles and requires several proteins (vesicle-associated membrane protein [VAMP], synaptosome-associated protein 25 kDA [SNAP-25] and syntaxin) for its release through the axon terminal membrane. BT binds to the presynaptic terminal via the heavy chains, gets internalized and separates the heavy and light chains. The light chains from Botulinum Toxin A (BT-A) cleaves *SNAP-25*, Botulinum Toxin (BT-B) and Botulinum Toxin F (BT-F) cleave VAMP and that from serotype C cleaves syntaxin. This disrupts theACH release and subsequent neuromuscular transmission, resulting in weakness or paralysis of the injected muscle **(Figure 1).** This localized dose-dependent weakness or paralysis of skeletal muscle can last from three to six months.[5, 6] BT may also exert an independent

action on peripheral nociceptors by blocking exocytosis of such neurotransmitters as substance P, glutamate and calcitonin gene–related peptide (CGRP). In addition, BT does not cross the blood–brain barrier and gets inactivated during its retrograde axonal transport, the effect is believed to be in the first-order sensory nerve and not centrally

Applications of Botox in Dentistry

BT can be used for a wide array of dental disorders **(Table 3).** Purified form of BT-A produces partial chemical denervation of the muscle resulting in localized reduction in muscle activity and therefore, has made its way for many therapeutic purposes. It is most potent and most commonly used amongst the various botulinum toxins for cosmetic and therapeutic purposes in dentistry. The site and the dose of injection of BT varies in

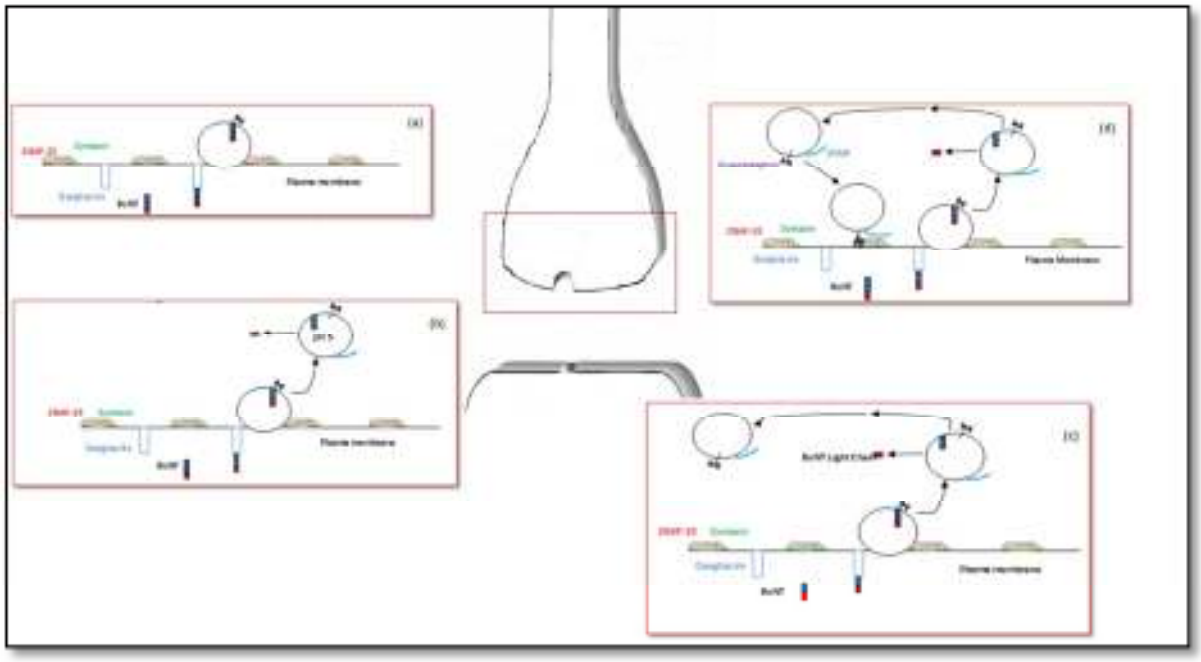

Figure 1: Mechanism of action of botulinum toxin

relation to the concerned disorder and its severity **(Figures 2 and 3).**

Temporomandibular Disorders

Temporomandibular disorders can be divided into two major groups namely those related to the muscles themselves (myofacial) and those related to the temporomandibular Joint (TMJ; arthrogenic).[8] Temporomandibular disorder is a collective term used to describe a number of diseases affecting masticatory function, which include true pathology of the temporomandibular joint as well as masticatory muscle dysfunction. The manifestations include orofacial pain, joint sounds, headache, ear pain, and joint hyper/hypomobility.[9]

A thorough knowledge of anatomy of the muscles involved in temporomandibular disorders is essential for diagnosis and treatment. First-line pharmacologic treatment for TMD includes anti-inflammatory agents, muscle relaxants and narcotics. Physical treatments such as orthodontic devices, physiotherapy, massage, acupuncture are also often used. The non-pharmacologic approaches include exercise, dietary adjustment and biofeedback therapy which play an important role in TMD management. Last resort is the surgical intervention such asarthrocentesis, intra-articular steroid injection, arthroscopy and open arthrotomy which if performed are often unsatisfying.[9, 10]

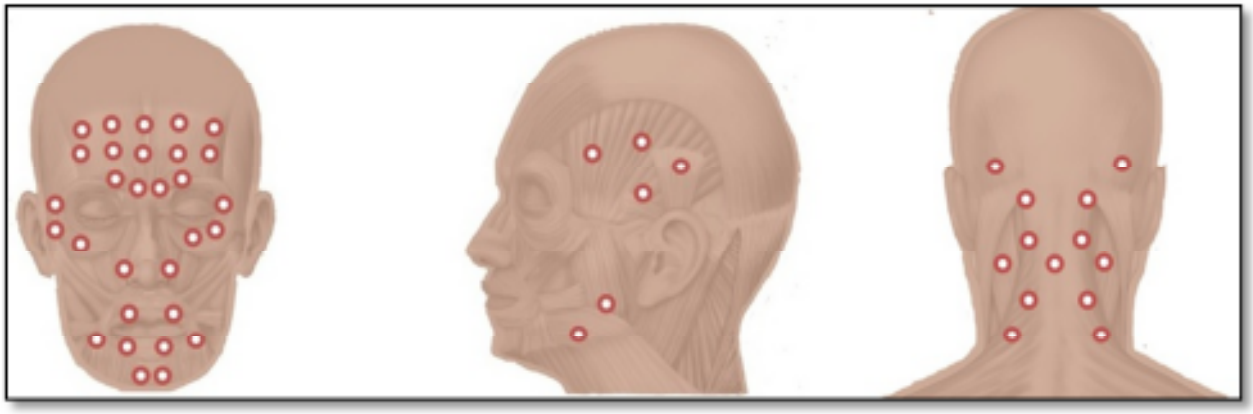

Figure 2: Injection Sites used during botulinium toxin therapy

T injections have emerged as a very potent, valuable and least invasive therapeutic measure of providing relief from intractable symptoms in TMD. The treatment must begin with a lower dose and then be titrated to a higher dose if necessary. 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. 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.[9, 11]

Freund et al[12] conducted a large clinical trial with 46 patients suffering from TMD and found that injections of BT to the temporalis and masseter muscles significantly decreased pain and tenderness and improved function and mouth opening. Lee et al[13] conducted a small open-label trial study and evaluated the effect of BT on pain in patients with limited mouth opening due to TMD. They concluded that all patients showed clinical remission of pain symptoms without any adverse effects during the 5-12 months follow-up period.

Chen et al[14] conducted a systematic review to assess the efficacy of BT in temporomandibular joint disorders (TMDs) which identified 5 relevant clinical trials involving 117 patients. The review could not bring a consensus on the therapeutic benefits of BT in TMDs.

Bruxism

Bruxism (excessive eccentric grinding of teeth) or excessive pathologic nocturnal clenching (excessive centric grinding of teeth) can affect the muscles solely and/or lead to the formation of TMD causing joint damage. Bruxism is strongly detrimental for all the stomatognathic structures, being responsible for tooth wear, periodontal tissue lesions, articular and/or muscular damage.[15,16]The current treatments available are neither ideal nor universally successful and muscular relaxation may pose a viable alternative. When muscle relaxants are used, the clenching reflex can be reduced or eliminated. A slight relaxation of muscle function reduces bruxing and is usually insufficient to affect chewing and swallowing.[17]

Occlusal covering appliances (mouthguards and nightguards) can be very effective in protecting the teeth against clenching and grinding damage

when worn during sleep or other activities that trigger the habit but they do little or nothing to stop the bruxism and offer only a brief respite from headaches and bruxism induced TMJ derangement or arthritis. Treating severe bruxism with BT helps limit the over-function of the muscles responsible for chewing. The treated muscles typically display a partial reduction in hyperfunction within 2-3 days with maximal reduction 1-2 weeks after treatment.[18]

Tan and Jankovic[19] conducted a long-term open-label trial on 18 patients with a history of severe bruxism wherein botox injections were given to the masseter muscle (range 25−100 U), which yielded a therapeutic response for 19 weeks.

Masseteric Hypertrophy

Patients who are chronic jaw clenchers frequently present with masseteric hypertrophy which becomes evident in the patient's facial appearance. Injecting small aliquots of Botox into the belly of masseter muscles resulted in reduced intensity of contractions of the masseter muscles and slenderization of the face.[20, 21]

Mandibular Spasm

Hemimasticatory spasm is a very rare disorder of the trigeminal nerve characterized by paroxysmal involuntary contractions of the unilateral jaw-closing muscles. It is a condition when the mandibular closing musculature remains semi- contracted or in spasm, resulting in restricted mouth opening thus limiting the basic oral hygiene necessary to prevent oral diseases. It usually occurs in association with progressive facial hemiatrophy or localized scleroderma, but may be seen without associated diseases.

There has been considerable speculation regarding the underlying mechanism that results in hemimasticatory spasm with localized muscle hypertrophy and subcutaneous tissue atrophy.

BT treatment to the masticatory musculature reduces the effects of hyper-functional or spastic muscles, resulting in improved mouth opening, decreased pain and tenderness to palpation.[22, 23]

Kim et al[22] suggested that local injection of botulinum toxin A into affected muscles may be the treatment of choice in mandibular spasms where all the patients respond positively to BT injections.

Headache, Migraine and Trigeminal Neuralgia

TMJ disorder and occlusal abnormalities lead to chronic headache by triggering chronic spasm in the muscles throughout the face, head, and neck. Standard medications used in the treatment of headache and migraine causes a number of side effects which has been overcome by BT. Injecting 25−75 U into pericranial muscles relieves headache by relaxing the over active muscles by blocking nerve impulses that trigger contractions. In migraine, BT acts by blocking the protein that carries the message of pain to the brain and the effect is seen 2−3 weeks after injection.[18, 24]

Elcio[25] found that excruciating pain associated with inflammation of the trigeminal nerve of the head and face was drastically relieved by injections of BT and concluded that treatment with BTA is not a cure for these types of headaches, but can provide significant relief.

Prominent Gingivae

Patients with a high lip line expose a broad zone of gingival tissue that poses both an oral hygiene and esthetic issue. Etiologic factors attributable to a gummy smile include skeletal, gingival, and over contraction of upper lip muscles that may occur alone or in combination. 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 passivedental eruption with excessive gingival display. A small titrated dose of BT injections into the muscles has emerged as a less invasive approach to limit muscular over-contraction which reduces exposure of the upper gums when smiling.[26]

Polo M[27] injected BT-A injections (2.5 units in both right and left levator labii superioris, superioris labii alaequenasi, and at the overlap areas of the levator labii superioris and zygomaticus minor) for the neuromuscular correction of excessive gingival display caused by hyperfunctional upper lip elevator muscles and found that the mean gingival exposure reduction was 5.2 mm with good patient satisfaction. Though the effect was transitory, the average gingival display still did not return to baseline values.

Facial Asymmetry

Facial asymmetries might be a result of genetics, physical trauma, previous facial surgeries, uneven skeletal growth of the

facial bones, nerve injury or muscle hypertrophy. BT can be used in certain and selected muscles which might be causing some of the asymmetry in order to balance the facial muscles thereby creating a more symmetrical appearance.[28]

Orthodontic Therapy

Orthodontic relapse has been a continual problem and there are a number of theories as to why this happens[7]. Most commonly, patients have a hyperactive mentalis muscle that disrupts the alignment of teeth leading to relapse. BT-A neurotoxins can reduce muscle contraction intensity, and over time, muscles can be trained to work normally. This could be used to deal with orthodontic relapse.[7]

Hypersalivation

Hypersalivation or sialorrhea is excessive production of saliva which negatively affects both quality of life and social interactions of the patient. There are a number of causes for sialorrhea which might include medical disorders like Parkinson's disease. BT has been used to treat sialorrhea by being injected into the parotid and submaxillary salivary glands to inhibit the stimulation of the cholingeric receptors.[29] Fuster-Torres MA and co-workers[30] 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 authors noted reduction in saliva production and effect lasted for 1.5 to 6 months.

Dental Implants and Surgery

Osseo-integration can be impeded by excessive functional forces in patients with para-functional habits after multiple implants or when immediate loaded implants are placed. Over loading of the implants results in implant failure by loosening of the implant components or prevention of osseo-integration[31]. The muscular relaxation achieved with prophylactic use of BT injections to the masticatory muscles can be beneficial by allowing implant structures better osseo-integrated. However, at present there are no studies that demonstrate any beneficial or adverse effects of BT use in dental implantology. Maxillofacial fracture repair often requires multiple fixation sites 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 BT injections to the masticatory muscles can be beneficial by allowing fracture healing in a more stable environment.[31, 32]

Kayikvioglu and colleagues[33] conducted a prospective study and examined the use of BT in five patients 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. Preoperatively 100 U of BT was injected into the masseter muscle of the fractured side. After 12−48 hours of injection, patients were operated and muscle denervation was confirmed by EMG. The temporary paralysis of the masseter muscle allowed for fewer miniplates and/or microplates inserted among the patients and resulted in no complications.

Miscellaneous

BT has been used as a minimally invasive procedure for the treatment of ranula which resolves with minimal complications.[34] Recurrent dislocation of the mandibular condyle can be minimized by injecting BT into the lateral pterygoid muscles.[35]Botulinum toxin type A has been used to smooth hyperkinetic lines (wrinkles) of the forehead and periocular areas in the upper third of the face. It has also been used to prevent the sun beam like wrinkles around the lips due to aging.[36]Habitual clenchers are more prone to snoring and sleepapnea. When BT is injected into the masticatory muscles that hold the jaw in a retruded position of habitual clenchers who are prone to snoring, it enables the patient's jaw to move slightly forward thereby opening the air way sufficiently to reducesnoring.[37]

Limitations of BT

The therapy using BT inhibits masticatory muscle function temporarily which will eventually return to previous levels (usually in 3-6 weeks) once the effect of the drug has subsided.

Discussion

Botox is a purified botulinum toxin type A isolated from the controlled fermentation of an anaerobic bacteria Clostridium botulinum. It produces partial chemical denervation of the muscle resulting in localized reduction in muscle activity and therefore has made its way for many therapeutic purposes.[36]It is dispensed in small vials containing 100 U or 500 U and is used after diluting with normal saline. The potency of BT is expressed as mouse

units. The lethal dose of BT in humans is not known although it has been estimated to be about 3000 U. The usual maximum dose recommended for dental applications at an injection session is about 80−100 U.[6,36] Antibody formation occurs more often with botulinum toxin type A injections of doses higher than 200 U, and for this reason the use of lowest dose with proven efficacy is recommended with a minimum of 3 months between procedures.[3]

Before injecting BT 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 an EMG 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. BT is injected using 1 ml tuberculin syringe and 0.30 gauge half inch needle.[10, 11]

BT is injected in different muscles of head and neck in certain concentrations depending on the existing disorder and the specific muscular involvement (Figure 2 and 3). After treatment, the patient should avoid lying down for the first 4 hours. Exercise, sun exposure and facials must be avoided for an additional 24 hours. Any other activities that manipulate the skin or can cause skin flushing like massage, heat packs, alcohol consumption, and make ups should also all be avoided during that time.[18]

Contraindications

The absolute contraindications include allergy to the drug (BT-A or BT-B) or its components (human albumin, saline, lactose and sodium succinate) infection at the site of injection, pregnancy (BTs are classified as pregnancy category C drugs) or lactation. Cosmetic treatment with BT is contraindicated in patients with unrealistic expectations.

It is relatively contraindicated in neuromuscular diseases (myasthenia gravis, Eton-Lambert syndrome), motor-neuron diseases, concurrent usage of medications that can interfere with neuromuscular impulse transmission and potentiate the effects of BT (e.g. aminoglycosides, penicillamine, quinine, and calcium blockers) and sensitivity totoxin.[37-41]

Side effects of Botulinium toxin therapy

The adverse-effects of BT are transient and relatively mild which get resolved

within a couple of weeks. The side-effects include nausea, pain and tenderness in the localized area, infection, inflammation, swelling, redness, dry mouth, transient muscle paralysis, headache, urticaria, and bleeding. In general, side effects are minimal and uncommon. These are especially manifested when the dose does not exceed that recommended or when a faulty injection technique is used by some inexperienced operator.[39, 41]

CONCLUSION

BT usage procedures are the fastest growing area of dentistry with the most significant, minimally invasive and promising results. It provides improved therapeutic and aesthetic outcomes for many clinical situations with ramifications in various branches of dentistry including restorative, aesthetic, periodontics, orthodontics and prosthodontics[42].BT paralyzes or weakens the injected muscle but leaves the other muscles unaffected thereby relieving muscle pain, reversing masseteric hypotrophy with improvement of facial outlines and restoring normal kinetics of temporomandibular joint.It is evident that the use of botulinum toxin in the dental profession has a great potential.

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