Review Article

Botulinum toxin: The Midas touch

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Abstract

Botulinum Toxin (BT) is a natural molecule produced during growth and autolysis of bacterium called *Clostridium botulinum*. Use of BT for cosmetic purposes has gained popularity over past two decades, and recently, other therapeutic uses of BT has been extensively studied. BT is considered as a minimally invasive agent that can be used in the treatment of various orofacial disorders and improving the quality of life in such patients. The objective of this article is to review the nature, mechanism of action of BT, and its application in various head and neck diseases.

Key words: Botulinum toxin, head and neck disease, temperomandibular diseases

INTRODUCTION

Botulism is a rare but serious illness caused by botulinum toxin (BT), which is metabolic waste produced under anaerobic conditions by the bacterium *Clostridium botulinum*, a condition first described by Justinus Kerner.[1,2] This is a life-threatening disease characterized by paralysis of muscles of face, limbs and in severe cases, paralysis of respiratory muscles leading to respiratory failure and death.[3] Although BT is a lethal toxin, it can be used as an effective and powerful medication by injecting in minute quantities of toxin into the overactive muscles. A.B Scott was first to use BT therapeutically to correct strabismus injecting the standardized toxin into external eye muscles.[4] Use of BT for cosmetic purposes has gained popularity over past two decades since it has been approved by the Food and Drug Administration (FDA) for therapeutic treatments of eye muscle problems (in 1989), neck problems (in 2000), and excessive sweating (in 2004). Recently, other therapeutic uses of BT have been extensively studied, and BT is considered as an agent that can be used in the treatment of various orofacial disorders.[5] The objective of this article is to review the nature, mechanism of action of BT, and its application in various head and neck diseases.

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NATURE OF TOXIN

BT is a natural molecule produced during growth and autolysis of anaerobic gram-positive bacterium called *Clostridium botulinum*. BT can be differentiated serologically into eight kinds of toxins named from A to G (A, B, Cb C2, D, E, F, and G).[6,7] These toxins occur both naturally and in *in vitro* culture.[8] Commercially available BT are botulinum toxin type A (BTA) and botulinum toxin type B (BTB), both of these have 150-Kd dichain polypeptides. 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.[9]

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.[8] 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 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.[2] Intramuscular injection of BT results in local chemical denervation and the loss of neuronal activity in the target organ [Figure 1].[10] This localized dose-dependent weakness or paralysis of skeletal muscle can last from three to six months, and the effect is reversed chiefly by neural sprouting with re-innervation of the muscle.

APPLICATIONS

The BT was initially approved for use in focal dystonia, primary axillary hyperhidrosis, blepharospasm, and strabismus. One of the most popular and successful applications of BT has been in the treatment of hyperkinetic facial lines. Recently, BT has been suggested as one of the treatment modalities of various orofacial conditions, and a considerable body of literature has been developed describing its efficacy and safety. Among the application in maxillofacial region, BT has been tried for movement disorders (such as blepharospasm, hemifacial spasm, and facial nerve palsy), hypersalivation, hyperlacrimation, gustatory sweating, temperomandibular joint disorders, muscle disorders, and orofacial pain.[2] A summary of the various applications is given in Table 1.

Hypersalivation

Hypersalivation or sialorrhea is excessive production of saliva.[11,12] Hypersalivation negatively affects both quality

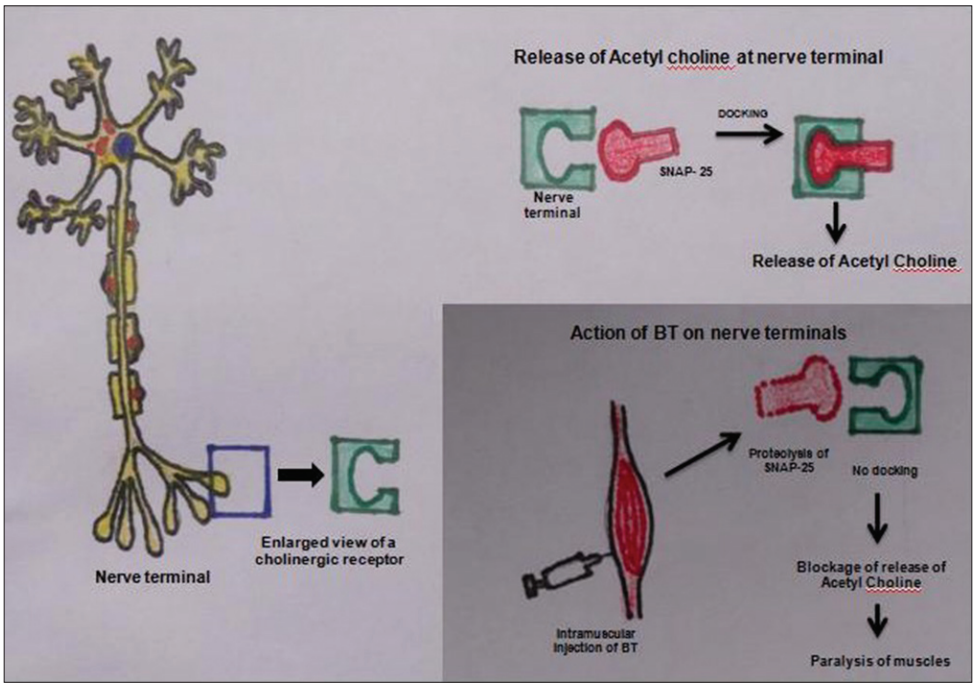

Figure 1: Mechanism of action of botulinum toxin

Table 1: Various applications of BT

Condition	Method of use of BT	Effect	Duration of effect
Hypersalivation	Intraglandular injection	Decreased production of saliva	1.5-6 months
Gustatory sweating	Intradermal injection into the affected area	Reduces local hyperhidrosis	Variable, upto 2 years
TMD	Intramuscular injection into temporalis and masseter muscles	Relief from pain, improved mouth opening	5-12 months
Oromandibular dystonia	Intramuscular injection into masseter and sub-mentalis muscles	Improved functions of chewing and speaking	Variable
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 levator labii superioris, levator labii superioris alaeque nasi, and zygomaticus minor	Improved smile	3-6 months
Dental implants and maxillofacial fractures	Intramuscular injection into masticatory muscles to achieve muscle relaxation	Better implant Integration, stable environment for callous formation	-
Orofacial pain	Injection into involved area	Pain relief	-

BT: Botulinum toxin, TMD: Temperomandibular disorder

of life and social interactions of the patient. This condition results from various neurological disorders such as Parkinson's disease or as an adverse effect of few drugs. Pharmacological therapy (i.e., anti-cholinergics) is the common modality of managing minor cases of hypersalivation, while more severe cases are eventually referred to surgery. Dryness of mouth encountered in patients with botulism has suggested the possibility of usage BT in the management of sialorrhea. BT significantly decreased production of saliva when injected intragladularly by blocking the release of Acetyle choline from nerve terminals.[13] 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 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.[11,13]

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. This local hyperhidrosis is an inappropriate response to cholinergic stimulus from the Auriculotemporal nerve after an aberrant regeneration of the parasympathetic endings of the nerve, which innervate the parotid gland. Due to trauma or gland resection, these nerve endings will grow anomalously towards the hypodermis, where the cholinergic receptors of the sweat glands are located. Consequently, gustatory stimulus will cause sweating of the skin in the pre-auricular area.[7,14] Many therapeutic approaches have been tried for managing Frey's syndrome including medical and surgical procedures. 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.[15,16] Intradermal injection of BT 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.[9,14] The author noted significant improvement in the symptoms and concluded that intradermal injection of botulinum toxin type A for patients with Frey's syndrome is not only effective with no side-effect but also minimally invasive. 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. Kyrmizakis DE noted complete absence of the symptoms as long as two years after injection.[15] Some authors reported that applying BT in the long term may produce complete atrophy of the parasympathetic nerve endings.[16] 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.[17] Guntinas-Lichius conducted a study to compare the duration of effect of two dosages regimes of BT to treat patients with Frey's syndrome. The study demonstrated that using a higher concentration of BT is more effective than a lower concentration in the treatment of FS.[18] Many other studies have also confirmed that BT is safe and efficacious treatment for gustatory sweating.[19-21]

Temperomandibular disorders

Temperomandibular disorder (TMD) is a broadly-defined term used to describe a group of conditions involving the temperomandibular joint (TMJ), masticatory muscles, and associated structure. Usual TMD symptoms can include jaw pain, difficulty with jaw opening, earaches, headaches, pain behind the eyes, jaw joint popping and clicking, dizziness, and difficulty chewing food or occluding the teeth. Treatment of TMD includes drugs such as narcotic analgesics, anti-inflammatory agents, and muscle relaxants, physiotherapy, orthodontic devices, and surgical interventions such as arthrocentesis, arthroscopy etc. None of these treatments has proved to be consistently effective and are associated with appreciable undesirable side-effects. Three-quarters of patients with TMD who are being treated with opioids do not achieve a reduction in pain or improvement in function.[6] In recent years, several reports have described the use of BT for several categories of TMD such as bruxism, masseteric hypertrophy, recurrent dislocation of the temperomandibular joint, oromandibular dystonias, and chronic myogenous orofacial pain.[22]

Propagation of pain in TMD occurs due to hypoxia evoking myofascial TMD pain secondary to local muscular contractures. Also, neuropeptides such as substance P and N-methyl-D-aspartate (NMDA) have been implicated in the induction of neuroplastic changes that alter the size and sensitivity of receptor fields to stimulation, thus propagating pain in TMD. There is no evidence that BT alters neuropeptide concentrations centrally despite its uptake into the central nervous system, but modulation of pain in TMD is due inhibition of muscle activity.[23] BT injection causes inhibition of the maximum contractile force of the injected muscles, and inhibition of efferents resulting in a reduction in the resting muscle tone.[6] Patients with TMD may have oral habits, so by reducing both the power and duration of effective contraction of the injected

muscles, BT may indirectly inhibit centrally motivated painful muscular activity. The overall reduction in muscle activity could also be indirectly responsible for altering the release of neuropeptides.

For patients who have failed to respond to conventional treatment approaches, BT injections can be the least invasive method of choice, which can provide relief of intractable symptoms. Freund *et al.* conducted an open-label trial with 46 patients suffering from TMD and found that 150 U injections of BT to the temporalis and masseter muscles significantly decreased pain and tenderness and improved function and mouth opening.[24] Another small open-label trial study conducted by Lee *et al.* to evaluate the effect of BT injections on pain in six patients with limited mouth opening due to TMD. All patients showed clinical remission of symptoms without any adverse effects during the 5-12 months follow-up period.[25]

Bruxism

The term bruxism is derived from the Greek word "brychein," which means "to grind or gnash the teeth" and is strongly detrimental for all the stomatognathic structures, being responsible for tooth wear, periodontal tissue lesions, articular and/or muscular damage. The reported prevalence is five to 96% in adult populations.[26] The etiology of bruxism is unclear. It has been suggested to be a multifactorial psychosomatic phenomenon. Bruxism has also been reported to occur secondary to the brain injury.[27] Muscular spasm caused by continuous contraction of the muscle fibers results in an altered nociceptive processing, leading to the perception of pain in the affected overactive muscles. BT has shown promise in alleviating the symptomatology of bruxism by blocking of cholinergic transmission and interruption of muscle contractions and normalization of muscle spindle activity. Van Zandijcke and Marchau described the successful treatment of a brain-injured patient with severe bruxism with 100 U of BT injections to the temporalis and masseter muscles.[28] Tan and Jankovic conducted an open-label trial on 18 patients with a history of severe bruxism and injected BT into the masseter muscle with mean dose of 61.7 U/side, which yielded a total duration of therapeutic response of 19 weeks.[29] Maaytah ME *et al.* reported that BT injection in the masseter muscles is an effective and safe means of intervention in cases of severe post-traumatic bruxism. It may be the only practical intervention available during the period of severe bruxism seen after brain injury when the patient is unable to co-operate.[27]

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. 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.[30] 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.[31] The literature on OMD has reported improvement of symptoms with the use of BT injections.[32-35] 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.[33]

Massetric hypertrophy

Masseteric hypertrophy is an asymptomatic enlargement of one or both masseter muscles. The etiology has been attributed to malocclusion, bruxism, emotional stress, microtrauma or temperomandibular disorders and in majority of cases, etiology is unclear. Although surgical partial excision of masseter muscle is the traditional treatment modality for this condition, often resulted in hematoma formation, facial nerve paralysis, infection, mouth opening limitation, and substantial contracture.[36] Smyth and Moore in 1994 introduced the technique of BT injection into the masseter muscle and considered BT as less invasive modality for cosmetic sculpting of the lower face.[37,38] BT when injected into a muscle causes interference with the neurotransmitter mechanism producing selective paralysis and subsequent atrophy of the muscle.[39] 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%).[40] Other clinical trials by Al-Ahmad, Al-Qudah, Mandel and Tharakan, and Rijsdijk and Vanes reported that injection of small aliquots of BT into the masseter muscles resulted in a sustained reduction of masseter hyperactivity.[41-43] 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.[39] Unlike surgical excision of muscle tissue that reduces the actual number of muscle cells, BT only reduces muscle volume temporarily, and the treatment effect wears away in six months. Therefore, patients have to be informed about the recurrence of the condition after the procedure.

Prominent gums

The display of excessive gingival tissue in the maxilla upon smiling, or "gummy smile," is often esthetically displeasing with no simple remedy. Several etiologic factors have

been proposed in the literature, which include skeletal, gingival, and muscular factors that may occur alone or in combination. The lip elevator muscles i.e., levator labii superioris, the levator labii superioris alaeque nasi, and the zygomaticus minor determine the amount of lip elevation that occurs during smiling, and overcontraction of these muscles results in gummy smile. The vertical maxillary dental and/or skeletal excess have been corrected by combination of surgical and orthodontic therapy. Several surgical procedures have been performed to correct gummy smiles caused by hyperfunctional muscles.[44] However, surgical procedures may lead to frequent relapse and undesirable side-effects such as scar contraction. Hence, minimally invasive treatment modality like BT would be advantageous when the gummy smile is due to hyper functional upper lip elevator muscles. BT limits muscular over-contraction when applied in small, carefully titrated doses. These muscles can be proportionately weakened with BT, which will reduce exposure of the upper gums when smiling.[45] Polo M conducted a study on five patients with excessive gingival display resulting from hyperfunctional upper-lip elevator muscles by injecting these patients with BT injections under electromyographic guidance. Patients received 0.25 U of BT per muscle bilaterally into the levator labii superioris, levator labii superioris alaeque nasi, and zygomaticus minor muscles. All of the patients were pleased with the results, and duration of effect ranged from three to six months, and no adverse effects were reported or observed.[44] According to Peck *et al.,* patients with a gummy smile had 20% or greater facial muscular capacity to raise the upper lip on smiling and suggested the need for reasonable guidelines for the application of BTX in orthodontic practice.[46]

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. Similarly, multiple fixation sites after maxillofacial fracture have to overcome the strong forces of masticatory musculature. Excessive forces from these muscles can prevent or impede fracture callus formation. The muscular relaxation achieved with BT injections to the masticatory muscles can be therapeutically beneficial by allowing better implant integration and more stable environment for fracture healing. 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.[6,47]

Orofacial pain

Chronic facial pain can be difficult to manage although various treatment modalities have been described in literature, but often associated with notable side-effects. Junghans *et al.* noted a improvement by injecting BT into the involved areas, thus achieving total or partial relief of symptoms without the necessity of systemic medication. Analgesic effect following BT injections in orofacial pain are due to direct analgesic and neuromodulating mechanisms of BT in the central nervous system, anti-inflammatory effects, and effects on the myofascial tender point.[48] The underlying mechanism of a chronic pain syndrome is that the disease of the trigeminal nerve causes increased firing as well as impaired the efficiency of the inhibitory mechanisms that control afferent activity in the trigeminal nucleus. The increased neuronal activity in the afferent nociceptive neurons results in the perception of pain.[49] Göbel *et al.* reported that BT causes normalization of increased muscle spindle activity, decompression of afferent nociceptive neurons of muscular and vascular tissue.[50] BT has also been shown to inhibit substance P, thus inhibiting neurogenic inflammatory processes from trigeminal nerve endings. When BT was given for treatment of migraine, protein that carries the message of pain to the brain is blocked and relief of pain occurs. Lawrence Robbins reported that excruciating pain associated with inflammation of the trigeminal nerve of the head and face can be substantially relieved by injections of BT. This is due to an anti-inflammatory substance, decreasing, or antagonizing the inflammatory effects.

DOSE

BTA is supplied in 100-unit vials, and one unit of BTA corresponds to the calculated median intra-peritoneal lethal dose (LD50) in mice. Unopened BTA must be stored in a refrigerator, and normal saline is used for reconstitution. 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).[51,52] 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.

SAFETY AND ADVERSE EFFECTS

In general, adverse effects with BT use are minimal and uncommon especially when the dose does not exceeds that recommended. Also, side-effects are relatively mild and transient and resolve within couple of weeks. These include nausea, localized pain and tenderness, infection, inflammation, swelling, redness, dry mouth, transient muscle paralysis, headache, urticaria, and bleeding.[44] In general, adverse reactions are minimal and uncommon especially when the dose does not exceeds that recommended. These include dry mouth, transient muscle paralysis, headache, urticaria, and nausea.

CONTRAINDICATIONS

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, during pregnancy and breast feeding, patients with some neuromuscular disorders such as amyotrophic lateral sclerosis, myasthenia gravis, Lambert-Eaton syndrome, muscular dystrophy, multiple sclerosis etc. 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.[44]

DISADVANTAGES

The effect of BT is reversed by motor endplate regeneration and generally leads to the re-establishment of symptoms. The treatment has to be repeated at intervals of two to three months once the symptoms re-appear.[53] Muscular relaxation may also fail for several other reasons such as insufficient concentration of active toxin in the vicinity of the motor end plate, the presence of antibodies to BT, or improper reconstitution and storage of the drug.[6] Asymmetrical or unnatural appearance of smile sometimes results due to improper injection technique.

CONCLUSION

The BT is a helpful and minimally invasive treatment option in treating challenging clinical problems improving the quality of life in patients with head and face disorders of different etiology. 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. Although more extensive confirmation of its use in multiple dental applications is needed, it is evident that the potential use of BT in the dental profession can be of great value.

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