Review Article

Applications of botulinum toxin in dentistry: A comprehensive review

Sanjeev Srivastava, Smriti Kharbanda[1], U. S. Pal[2], Vinit Shah[3]

Department of Conservative Dentistry and Endodontics, Sardar Patel Post Graduate Institute of Dental and Medical Sciences, Departments of [2]Oral and Maxillofacial Surgery and [3]Prosthodontics, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh, [1]Conservative Dentistry and Endodonitcs, Clove Dental, New Delhi, India

Address for correspondence:
Dr. Smriti Kharbanda, C2/115 (Back Side) Janakpuri, New Delhi - 110 058, India.
E-mail: smritikharbanda510@gmail.com

ABSTRACT

The horizons of treatment options in dentistry are broadening rapidly. In this scenario, applications of unconventional treatment options like use of botulinum toxin (BT) are gaining momentum. The use of BT has been popularly accepted in esthetic procedures like management of facial wrinkles; however, it has been documented to be successful in a variety of conditions. Of particular interest to this paper are applications of BT in the maxillofacial region, concerned to dentistry. BT offers a transient, reversible, relatively safe treatment option to many conditions of interest to a dental practitioner. Dental surgeons by their virtue of being extensively aware of the anatomy of faciomaxillary region are a potential pool of operators who can use BT in their armamentarium with minor skill enhancement and thus widen the perspective of alternative, minimally invasive options to refractory conditions or invasive protocols.

Key words: Botulinum toxin A, bruxism, gummy smile, temporomandibular joint disorders

Introduction

"Botulism" is a life-threatening disease first described by Kerner.[1] It is caused by botulinum toxin (BT) also known as botulinum neurotoxin produced under anaerobic conditions by *Clostridium Botulinum*. Botulinum is one of the most lethal toxins known and has found applications in bioterrorism as well.[2] However, botulinum toxin is a double-edged sword. Botulinum is the first toxin to be accepted for therapeutic uses. Since the first therapeutic use by Scott for strabismus[3] till today, the spectrum of therapeutic applications of BTs has widened. BTs can be differentiated into seven types from A to G. However, commercially available variants are purified exotoxin and only BT type A (BTA) and BT type B (BTB) are marketed by various brand names.

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BTA is marketed as follows:
- Botox® (Allergan, Irvine, CA) in the USA
- Dysport® (Speywood Pharmaceuticals, Maidenhead, UK) in Europe
- Xeomin® (Merz Pharmaceuticals, Germany) in Germany
- Prosigne® (Lanzhou Biological Products Institute, China) in China.

BTB is marketed as follows:
- Myobloc® (Elan Pharmaceuticals, San Diego, CA) and
- Neurobloc® (Elan Pharmaceuticals, Shannon, County Clare, Ireland).

Mechanism of Action

BT produces a transient dose-dependent weakening of muscle activity.[4] It is a neurotoxin and produces

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temporary chemical denervation of skeletal muscle by inhibiting the release of acetylcholine from nerve endings, which leads to flaccid paralysis. However, the neuromuscular transmission is re-established by sprouting of new axonal terminals and, therefore, the blockade is temporary. Thus, treatment with botulinum is actually a palliative approach rather than a curative option. The toxin has also been shown to prevent acetylcholine release at parasympathetic nerve terminals.

Preparation

Doses of BT used for the treatment of a particular condition depend on the particular brand/preparation as the unit of one product is not the same as the other. Instances of botulism have been reported in patients treated with intramuscular injections at therapeutic doses.[5,6] However, BTA has been in clinical use since 1967 now, and its safety has been well established.

The two most commonly available types of BTA are Botox® and Dysport®. About 20–25 units of Botox® are equipotent to 80 units of Dysport®. Botox® is marketed as single-use, sterile 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, preservative-free 0.9% sodium chloride injection USP prior to injection.[7] It is recommended that the reconstitution should be gentle as froth arising out of vigorous shaking can lead to surface denaturation of the toxin.

BT is stored in a frozen vial (2–4°C) until it is ready to use. Adding 4 ml of 0.9% preservative-free normal saline solution makes injections, and the preparation should be used within 4 h.[8] It is dispensed in small vials containing 100 U or 500 U. The preferred syringe is a calibrated 1.0 mL tuberculin syringe with a gauge preference of 26–30.[9,10]

Applications of Botulinum Toxin

BT is most commonly known for its cosmetic applications. Out of all the preparations available in the market, Botox® has received maximum approvals worldwide and is the most commonly used. While BTB has been accepted by US Food and Drug Administration (FDA) for cervical dystonia and hemifacial spasm (HFS),[11] its use is generally limited to patients developing antibodies to BTA. BTA finds wider approved spectrum of use. The uses of Botox® as accepted by FDA are as follows:

- Temporary improvement in the appearance of glabellar lines (wrinkles)
- Overactive bladder
- Urinary incontinence associated with a neurologic condition
- Prophylaxis of headaches in adult patients with chronic migraine
- Upper limb spasticity in adult patients
- Cervical dystonia in adult patients (severe neck muscle spasm)
- Severe axillary hyperhidrosis (excessive axillary sweating)
- Blepharospasm (spasm of the eyelids)
- Strabismus (squint).

BT has found widespread applications even beyond the FDA accepted uses. The basic spectrum of applications is dependent on the mechanism of action of the neurotoxin. Extensive reviews of the clinical applications have outlined uses such as HFS, oromandibular dystonia (OMD), bruxism, rhinitis, sialorrhea, crocodile tears (lacrimation), pain (most commonly neuralgic origin), hyperhidrosis, foot dystonia, axial dystonia, Writer's cramp (WC) and other occupational cramps, Tardive dyskinesia, tremor, spasticity, protective ptosis, spasmodic dysphonia, benign prostatic hyperplasia, as well as applications in parkinsonism.[12] Of particular, interest to this review are applications of BT in dentistry and head and neck region.

Applications of Botulinum Toxin in Maxillofacial Region

BT finds varied applications in head and neck region.[13,14] The uses of BTA in maxillofacial can be broadly divided into cosmetic and noncosmetic applications. Continuous research has paved the way for innovative uses of BTA in dentistry. BTA or Botox® offers substantial benefits as an adjunct to cosmetic dental procedures as well as a minimally invasive alternative to conditions which are refractory to routine medical management or require extensive surgical intervention.

Cosmetic applications

Facial wrinkles

- BTA has been most widely accepted for its use to temporarily treat hyperfunctional facial lines
- Forehead rhytids are managed by injecting 10–20 U of BTA injected at least 1 cm above the orbital rim with a general rule of avoiding injecting frontalis without injecting glabella to reduce the chances of brow ptosis. The injection site and pattern of injections vary depending on the desired brow position. It is preferred to inject lower doses away from the brow so as to avoid the frozen look
- Glabellar lines (frown lines) are generally managed by 20–40 U of BTA divided over five injection sites. The five injection sites correspond to the area of the procerus (between the eyebrows above the nasal bridge), paired injection sites that correspond to

the corrugator muscles (10 mm above the orbital rim on an imaginary vertical line running through the medial canthus) and a paired injection site for superior medial orbicularis (10 mm above the orbital rim approximately in the midpupillary line)
- Lateral canthal lines known as "crow's feet" (due to lateral orbicularis oculi) are generally managed by superficial injections of 8–16 U of BTA into the lateral orbicularis oculi about 10–15 mm away from the orbital rim so as to avoid diffusion into extraocular muscles
- Eyebrow lift by BTA injections can be managed by either injecting the glabella alone or injecting the vertical fibers of lateral orbicularis oculi in a dose of 20–40 U or 7–10 U respectively
- Perioral lines, wrinkles around the lips commonly called the "smokers wrinkles" are injected superficially at or above the vermillion border and sparing the corners of the mouth so as to avoid drooping of the corners. A side effect of these injections is difficult in pronouncing "b" and "p" and therefore, these injections are avoided in public speakers and singers. Doses are kept low so as to achieve esthetic results while maintaining function. Typical dose ranges in 5–6 U; however, doses as low as 1–2 U per injection point are advised
- Wrinkles on neck (due to platysma muscle) can be managed by injecting 2–4 U into six injection points evenly distributed along the jawline
- 5–6 U of BTA injected into mentalis muscle area can be used to manage cosmetic mentalis dimpling
- [Figure 1] shows a schematic representation of injection points of Botox® in the facial region.[15-18]

Temporalis and masseter muscle hypertrophy

The hypertrophy of temporalis and masseter muscles is generally associated with clenching or other parafunctional use of the jaws. The results of BT use in cases with masseter and temporalis muscle hypertrophy are very encouraging and appear to be safe and effective in treating chronic facial pain associated with masticatory hyperactivity.[17,19-22] Injection sites identified by palpation during clenching receive 12 U of BTA percutaneously in the thickest part of the muscle.[23]

Dentofacial esthetics and gummy smile

Recently, BT and derma fillers have been used to provide immediate volume to black triangles formed due to loss or inadequate interpapillary tissue.[24,25] Derma fillers along with BT act as volumizers injected into the interdental papilla to offer a minimally invasive treatment option as compared to the conventional therapies which include aggressive gingivectomy or orthognathic treatment approaches.[26,27] Use of BT is particularly effective in managing cases of excessive gingival display due to excessive contraction of upper

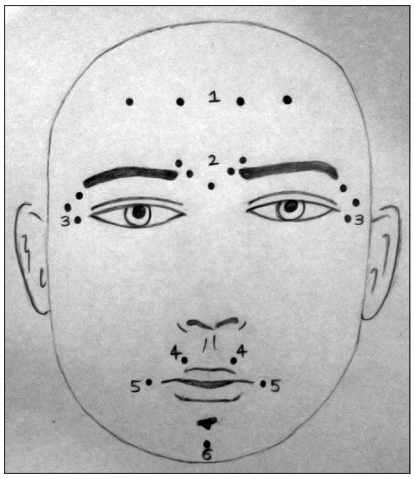

Figure 1: Schematic representation of botulinum toxin type A injection sites on the face. 1 - Forehead lines: Frontalis muscle, 2 - Glabellar/frown lines: Corrugator supercilii and procerus muscles, 3 - Crow's feet (lateral orbital lines): Orbicularis oculi, 4 - Perioral lines (smoker's lines), gummy smile: Orbicularis oris muscle, 5 - Marionette lines: Depressor anguli oris, 6 - Mentalis dysfunction: Mentalis muscle

lip muscles; primarily levator labii superioris alaeque nasi.[27,28] A dose of 3 U is recommended at an injection point known as "Yonsei point" for injection of BT.[26]

Drooping of corners of mouth

Hyperactivity of depressor anguli oris can lead to drooping of the corner of the mouth. Injection of BTA has shown to have positive results in such cases.[29] The site of injection is on the trajectory of nasolabial fold to the jaw line. Bilateral injections in doses of about 2–5 U is the norm.

Therapeutic applications

Temporomandibular disorders

Temporomandibular joint disorders (TMD) is a term suggested by Bell[30] and signifies not only disorders of the temporomandibular joint (TMJ) but also includes a spectrum of disturbances associated with the function of masticatory system, which are poorly understood and often intermingled with other chronic pain disorders. These set of disturbances have been previously termed as TMJ dysfunction syndrome, functional TMJ disturbances, myofascial pain dysfunction syndrome, and temporomandibular pain dysfunction syndrome.[31] TMDs may be myofascial (those related to muscles themselves) or arthrogenic (those related to TMJ), but majority of TMDs include a myogenic component[10,32] and muscular spasticity in relation to bruxism, external stressors, OMD, and psychomotor behaviors.[33] Conventional treatment approaches for TMDs include physiotherapy and exercise, anti-inflammatory and analgesic drugs, muscle relaxants, oral appliances (mostly stabilization splints), or a combination of these modalities. Surgery is sometimes indicated but is an expensive and invasive treatment option. BTA has been

found to be effective in resolving pain and tenderness in TMDs.[34,35] It has been proposed as an adjunct in managing TMDs, particularly in cases involving muscular hyperactivity. The diverse group of TMDs those are likely to be benefited by injection of BT includes the following:[21,36]

- Bruxism and clenching
- OMDs
- Myofascial Pain
- Trismus
- Hypermobility
- Masseter and temporalis hypertrophy
- Headaches.

Although no definite protocol has been proposed, various case reports have recorded significantly decreased pain and improved function and mouth opening at doses ranging from 25 to 150 U of Botox® injected intramuscularly into temporalis and masseter muscles.[37] Injection of BTA into lateral pterygoid muscle has been found effective in treatment of recurrent mandibular dislocation.[38-40] Potential sites for BTA injection into TMJ have been schematically shown in Figure 2.

Bruxism

Severe clenching or grinding of teeth is called bruxism and is often associated with generalized attrition, TMJ symptoms, headache, and muscular pain. BTA has been successfully used in cases of bruxism.[41] Injection of BTA bilaterally into masseter muscles (in a dose range of 25–100 MU per side) has been documented to significantly reduce the severity of symptoms for 6–78 weeks (mean 19 ± 17 weeks).[41] In comparison with oral splint, BTs are equally effective on bruxism and injections at a dosage of <100 U are safe for otherwise healthy patients.[42] Use of BTA in sleep bruxism is also encouraging,[43] and a single injection has been shown to be effective for at least a month.[44]

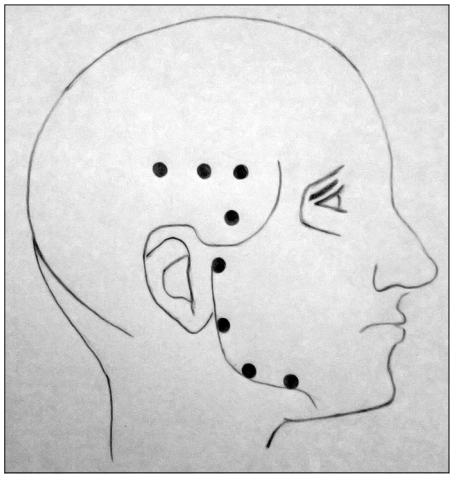

Figure 2: Schematic representation of sites for botulinum toxin type A injection in temporomandibular joint

Sialorrhea and salivary secretory disorders

Sialorrhea (excessive salivation/drooling) is a common problem caused by poor oral and facial muscle control. Treatment options may range from a conservative medical line to a more aggressive surgical approach. Effects of BTA on salivary glands have been studied.[45,46] The injection of BTA into the parotid and submandibular glands is effective in controlling drooling.[47-49] Botox® is administered in a dose range of 30–70 U into parotid gland with a significant reduction in salivary flow observed in 4 weeks. However, the effects fade in about 3 months, and repeat injections are often necessary.[48,50,51] BTA injections have also been shown to be effective in managing gustatory sweating (Frey's syndrome).[46,52] Repeated treatment improves on the results of primary treatment.[53]

Facial nerve palsy

BTA injection treatment was effective in reducing facial synkinesis, thus improving facial expression symmetry both at rest and in voluntary movements[54] One of the complications of facial nerve palsy is hyperlacrimation (crocodile tears) associated with salivation due to the aberrant connection between secretomotor fibers of salivary gland to lacrimal gland. Injection of BT into lacrimal gland has been successful in managing this condition.[55]

Facial pain and trigeminal neuralgia

BT has been found to be safe and effective in the management of pains in maxillofacial region, especially cervical dystonia and chronic facial pain associated with masticatory hyperactivity.[22] BTA has been found to be effective in case of trigeminal neuralgia without major adverse effects.[56,57] BT is fast becoming a minimally invasive method of choice in treating trigeminal neuralgia over other invasive therapies.[58]

Implantology

BT has been postulated to be therapeutically beneficial by allowing unimpeded osseointegration of implants. Stress due to any excessive functional force or any parafunctional habit may cause implant failure. Thus, injecting BTA relaxes the masticatory muscles, sparing the implant leading to unimpeded osseointegration.[59,60] However, the body of literature supporting the use of BT in implantology is scarce and warrants further research.[22]

Oral and maxillofacial trauma

The use of BT in treating injuries affecting the bones in the maxillofacial region including maxilla, mandible, zygoma, nasal bone, and orbital bone has shown astonishing results. In a study done by Kayikçioglu *et al*., temporary paralysis of masseter muscles allowed for fewer mini plates/microplates

in the treatment of zygomatic fractures.[61] Use of BTA in the management of condylar fracture has been strongly recommended in various reports.[62,63] Higher doses of BTA may potentially be used as a pharmaceutical splint during management of fractured facial bone. BTA injections in anterior belly digastric have been used successfully in the correction of posttraumatic anterior open bite.[64] BTA has also been proposed in the management of ranula as a minimally invasive therapy.[65]

Cancer and palliative care

The application of BTA can improve movement disorders like synkinesis following reconstructive surgery in patients with cancers of the parotid gland and as antispasticity agent in palliative care for severe pain[66,67] The application of BTA is a minimally invasive treatment option in various functional disorders, thus improving the quality of life in patients with head and neck cancers of different etiologies with minimal side effects.[68]

Denture wearers

Jaw muscles are able to adapt themselves to the changing functional demands by altering their size, cross-sectional areas, and properties.[69] BTA can be used in such patients struggling in getting used to a new set of dentures due to irregular and uncoordinated muscle activity, especially who have been edentulous for a long period of time by providing muscle relaxation.[69,70]

Adjunct to orthodontic treatment and to prevent relapse

In some cases, relapse following an orthodontic correction may occur in patients with strong muscle activity such as that of mentalis muscle. BTA can be used during treatment to reduce the intensity of muscle contractions and muscles can be slowly and gradually trained posttreatment to a more physiologic movement.[9,71,27]

Diagnostic application

In patients with chronic intermittent toothache, BTA can be used to verify the origin of pain (muscular or pulpal), for example in cases with referred pain from anterior temporalis. Thus, BTA in such cases can be used prophylactic as well as diagnostic.

General Guidelines

- Preparation has to be used within 4 h
- The area of the injection has to be covered with a topical anesthetic cream or can be anesthetized using ice
- Start with a lower dose
- Muscles should not be paralyzed completely
- Males generally require higher dose due to larger muscle masses.

The treatment with BT is based on palliative rather than curative approach as the blockade is temporary. Blockade lasts for three to 4 months after which there is sprouting of new axon terminals resulting in return of neuromuscular function.[72] The general latency for BTA is 1 week, and it is recommended that injection is done no more than once every 12 weeks to avoid development of antibodies against the toxin. Following application, the clinical effect occurs within approximately 3–7 days, followed by 1–2 weeks of maximum effect, which then levels off to a moderate plateau until full nerve recovery within 3–6 months.[73]

Depending on the target muscle, injection dose is 10–50 U of Botox® per site (total of 200 U in the masticatory system). Maximum of 400 U can be used if other sites in the head and neck are included in the protocol.

Adverse Effects

In general, adverse reactions are uncommon and localized. The results from a systematic review with meta-analysis have concluded that BTX-A has favorable safety across wide spectrum of therapeutic uses.[74] Botox® is administered by injection and dosing depends on the condition that it is used for. Side effects of Botox® include allergic reactions, rash, itching, headache, neck or back pain, muscle stiffness, difficulty in swallowing, and shortness of breath. This can also be accompanied by nausea, diarrhea, stomach pain, loss of appetite, injection site reactions, sore throat, runny nose, ringing in ears, and increased sweating in areas other than the underarms.[75,76] The two most common medication-related side effects from BT orofacial injections are alterations in salivary consistency and inadvertent weakness of the swallowing, speech, and facial muscles. These complications are injection site-specific (e.g., more common with lateral pterygoid injections and palatal and tongue muscle injections) and dose-dependent problems.

In some cases, BT effects may be observed at sites beyond the site of local application, known as the "Spread of toxin effect." The symptoms of such a presentation are consistent with the actions of BT and include generalized muscle weakness manifesting as diplopia, dysphagia, dysphonia, ptosis, and urinary incontinence or even breathing difficulties. The probability of this spread of toxin effect is even more in the face as well as head and neck region due to facial planes and spaces.

BT is classified as category C for use in pregnancy, and its use is warranted only if the potential benefit outweighs the potential risk to the fetus. Similarly, use in nursing mothers is also not recommended routinely. Use of BT in pediatric age groups should also be restrained, and FDA guidelines for its use were followed.

The lethal dose of Botox® in humans is not known. Although it has been estimated to be about 3000 U.[77] The maximum dose recommended for dental applications at an injection session is about 80–100 U. It means that 30 vials of Botox® injected would have a potentially lethal outcome.

Contraindications

- In any known hypersensitive reaction to any of the botulinum preparations
- Allergy to any of the constituents of BTX-A or BTX-B[9]
- Presence of active infection at the proposed injection site[78]
- Pregnancy and lactation[77]
- Patients receiving treatment with aminoglycosides, anticholinergic drugs or other agents interfering with neuromuscular transmission or muscle relaxants should be observed closely because the effect of Botox® may be potentiated
- Patients suffering from peripheral motor neuropathic diseases, sclerosis, or any neuromuscular junction disorders like myasthenia gravis are at increased risk for clinically significant adverse reactions and should be closely monitored
- Psychologically unstable patients.[9]

Future Perspective

Although plenty of reports on the use of botulinum in maxillofacial region are published, quality literature is scarce.[22,79-81] Most of the published reports are case reports of series and actual randomized control trials are lacking. While dental surgeons are well placed by their virtue of knowledge of facial anatomy, further skill enhancement training is warranted to prepare them to administer botulinum toxin for therapeutic uses. Many regulatory bodies in the United States have already started additional licensure procedures for practicing Botox® in dentistry. The interest among dental practitioners to practice botulinum is growing, mostly for esthetic dental reason; however, a majority still reject the idea due to lack of knowledge and experience.[82]

Conclusion

The journey of BT from a deadly poison to a remarkably resourceful therapeutic agent has broadened the horizon of dentistry. BT has certainly been demonstrated to have significant value in the management of cases where the patient is unresponsive to less invasive treatment modalities or in conjunction with them. It offers a minimally invasive approach to manage and treat selected suitable cases with minimum complications. However, the practicing dentist must ensure that the treatment is within his/her scope of practice and has appropriate training not just to administer but also to deal with its potential adverse effects.

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Conflicts of interest
There are no conflicts of interest.

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