

THE EMERGING ROLE OF BOTULINUM TOXIN IN THE TREATMENT OF OROFACIAL DISORDERS: LITERATURE UPDATE

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ABSTRACT

Botulinum toxin (BTX) is a lethal neurotoxin produced by Gram-positive anaerobic bacterium called *Clostridium botulinum*. It is the first toxin used for therapeutic purposes since 1989. BTX treatment is relatively safe and efficacious, less invasive, conservative, and the effects are faster and reversible. The purpose of this article is to review the literature regarding the applications of BTX in the treatment of various orofacial disorders, their mechanism of action, contraindications, and complications. From the recently published literature, it is clear that the role of BTX as a therapeutic agent for several conditions is expanding. With the training of BTX-A injection techniques and adequate knowledge about treatment protocols, general dentists can safely administer BTX injections. The ability to use Botox as an adjuvant and primary mode of the treatment for various maxillofacial disorders offers exciting treatment options for dentists and patients in the future.

Keywords: Botulinum toxin, Botulinum toxin A, Botox, Orofacial disorders, Temporomandibular disorders, Dentistry, Myofascial pain

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INTRODUCTION

Botulinum toxin (BTX) is a deadly neurotoxin produced by Gram-positive anaerobic bacterium called *Clostridium botulinum*. Ingestion of contaminated food (canned or preserved) or wound infection releases bacterial toxin into the blood stream, eventually leading to severe symptoms of botulism such as vomiting, slurred speech, respiratory arrest, paralysis, and even death [1,2]. Botulinum, a natural protein and lethal neurotoxin is one of the most potent biological substances known which is used in bioterrorism as well [3]. It is the first toxin used for therapeutic purposes.

Justinus Kerner (1786-1862) gave the first complete description of clinical botulism, a life-threatening disease and called the toxin a "sausage poison," because it was observed that illness occurred after ingestion of spoiled sausage. In 1870, John Muller coined the term "botulism" (which means "sausage"). In 1949, Burgern was the first to discover that the toxin was able to block neuromuscular transmission. There are seven different toxin serotypes, namely, A, B, C, D, E, F and G, which differ in their potency, duration of action, and cellular target sites [4]. In human beings, botulism is mainly caused by types A, B, E, and rarely F, whereas in animals it is caused by types C and D. Commercially available variants are BTX-A and BTX-B, where BTX-A is the most commonly used toxin in medicine and dentistry. BTX-B is used in cases of resistance to BTX-A. BTX-E and BTX-F are used only for those individuals who do not respond to A and B due to clinical resistance or antibody formation. BTX-A is marketed worldwide under the name Botox (onabotulinum toxin A), Dysport in Europe, Xeomin in Germany, and Prosigne in China. BTX-B is marketed as Myobloc in the USA and Neurobloc in Europe.

Since 1989, BTX has been used for medical treatments but has recently become a popular innovative dental treatment option. Botox was approved by the US Food and Drug Administration (FDA) for the treatment of strabismus, blepharospasm, hemifacial spasm, facial glabellar lines, cervical dystonia, and axillary hyperhidrosis [5]. BTX-B has been approved by the FDA for the treatment of cervical dystonia. Since then BTX-A has been used for the treatment of various disorders in the orofacial region [6].

CHEMICAL STRUCTURE

BTX is synthesized as a single chain (150 kDa) and subsequently cleaved by host proteolytic enzymes into a di-chain molecule consisting of a 100 kDa binding subunit and a 50 kDa toxic subunit linked by a disulphide bond (Fig. 1). The light chain acts as a zinc endopeptidase with proteolytic activity located at the N-terminal end. The heavy chain provides cholinergic specificity and binding of the toxin to presynaptic receptors. This promotes translocation of the toxin across the endosomal membrane [7].

PREPARATION OF BTX

BTX is prepared by laboratory fermentation of the bacteria *C. botulinum*, which lyses and liberates the toxin into the culture. The toxin is then harvested, purified, crystallized with ammonium sulfate, diluted with human serum albumin, lyophilized, bottled in vials (sterile, vacuum dried powder form), and sealed for single use. Optimal pH of the solution is between 4.2 and 6.8, and vials should be stored in a freezer at or below -5°C. Preparations should be reconstituted with 1-5 mL of saline without preservatives just before use. Because Botox is easily denatured via bubbling or agitation, the diluent should be gently injected onto the inside of the wall of the vial. The reconstituted solution should be refrigerated at 2-8°C and used within 4 h. The preferred syringe for injection is a 1.0 mL tuberculin syringe with a gauge of 26-30 [8].

The potency of BTX is expressed as mouse units, with 1 mouse unit equivalent to the median lethal dose (LD 50) for a colony of 20 g Swiss Webster mice. Botox is dispensed in vials containing 100 U, while Dysport in vials containing 500 U. The relative potency of Botox units to Dysport units is approximately 1:4. BTX-B (Myobloc/Neurobloc) is available in vials of 2500 U/0.5 mL, 5000 U/mL, or 10,000 U/2.0 mL. Its relative potency to Botox is 50-125 U of Myobloc to 1 U of Botox. This product does not require reconstitution and is stable for up to 21 months in a refrigerator. Botox produces dose-dependant paralysis. When compared with BTX-B, BTX-A causes less pain during injection, longer duration of action, and more predictable diffusion patterns. The usual maximum total recommended therapeutic dose at an injection session in the dental office is about 80-100 U. Cosmetic dosages are less

than the therapeutic dose. The human lethal dose is estimated to be approximately 3000 U. Thus, clinical dose can be given safely without a fatal overdose complication. The treatment dose varies for each brand of toxin and different parts of the body.

ADMINISTRATION OF BTX

It is injected either intramuscular, intradermal, intraglandular or into the affected area depending on the condition to be treated. Intramuscular

BTX injections are accomplished via a single-point or a skewered method with the needle inserted parallel to the plane of the muscle, and the injection is performed while the needle is carefully withdrawn. Care should be taken to space injections about 1-2 cm apart and to avoid injecting into muscles where paralysis is not desired [9]. BTX diffuses up to 10 mm into the adjoining areas, so a thorough knowledge of related anatomy is necessary to prevent undesirable effects. Gently pinching the muscle during injection may help reduce pain and ensure superficial placement of the drug. Topical anesthetic or ice may also be used to reduce pain during injection. Pressure with gauze immediately after injection is advisable to prevent bleeding and bruising and massaging the area after the injection is not recommended to prevent the unwanted diffusion of the toxin into adjacent muscles [10]. Strenuous physical activity should be avoided for 1 day after treatment. Injections are spaced out for a minimum of 3 months to minimize the risk of antibody formation to the protein, which would prevent BTX from working the subsequent time. Injections can administered with the help of electromyography (EMG) or ultrasound guidance for deeper muscles and joints. Topical formulations of BTX-A are also used for treating axillary hyperhidrosis with promising results.

MECHANISM OF ACTION

In the blood, the toxin targets peripheral neurons of the central nervous system (CNS) and binds to ganglioside receptors on the neuronal surface via the large subunit. Changes in pH at the neuronal surface mediate penetration of the membrane and passage of the small subunit into the neuron. The small subunit of the protein possesses a

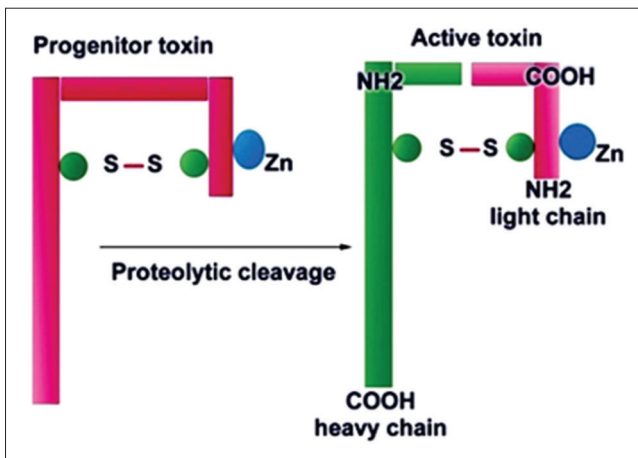


Fig. 1: Chemical structure of botulinum toxin

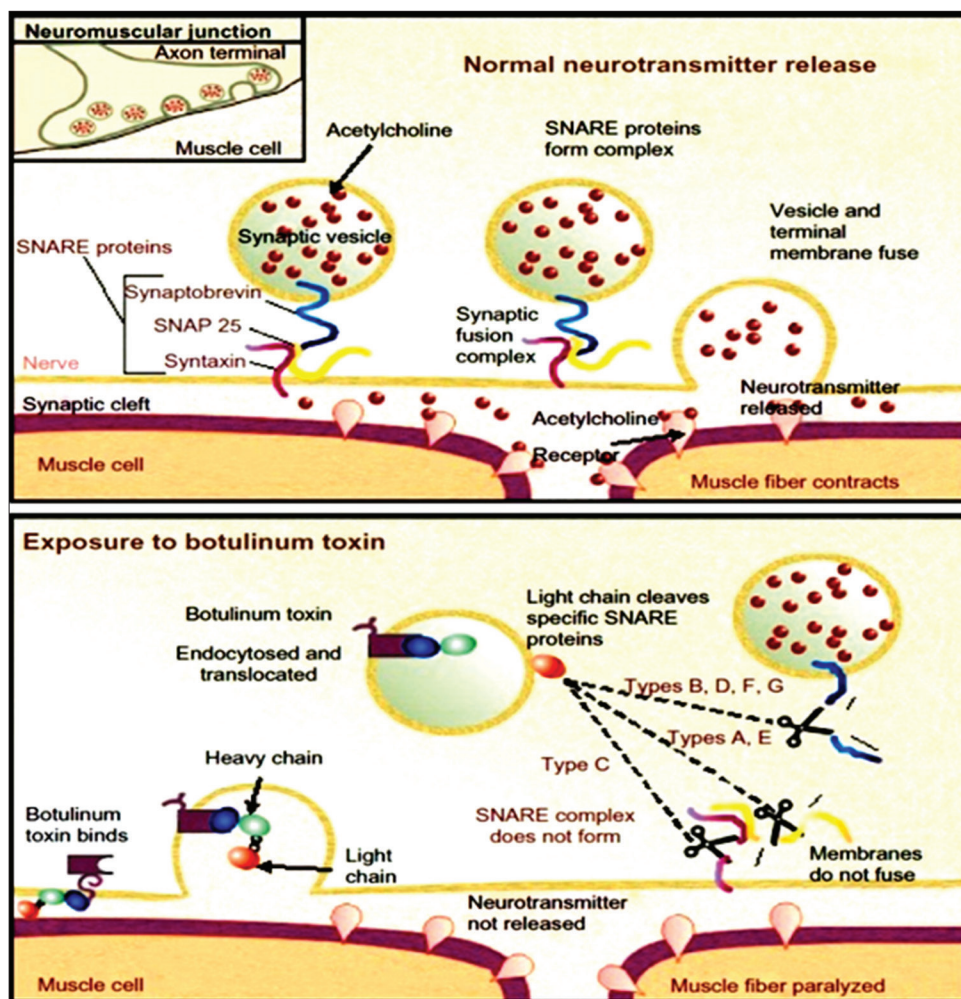


Fig. 2: Mechanism of action of botulinum toxin

metalloprotease activity which cleaves components of the neuronal SNARE complex (Fig. 2). This complex is implicated in releasing neurotransmitter, acetylcholine when released depolarizes the motor end plates of the muscle thereby causing muscle contraction. Inhibition of this release leads to abolition of stimulatory activity of the neuron. This lack of stimulatory activity can cause paralysis, a major side effect of BTX administration.

Thus, BTX inhibits the release of acetylcholine from the presynaptic nerve terminal effectively and will either reduce the intensity of the contraction of the muscle or will eliminate the contraction altogether, depending on the dosage used. Thus, Botox causes a temporary muscle paralysis which lasts up to 3 months. Gradually, the muscle returns to its full function with no side effects as the muscle initiates new acetylcholine receptors, and the growth of branches from the neurons to form new synaptic contacts [11]. The toxin has also been shown to block acetylcholine release at parasympathetic nerve terminals. The clinical effects appear between 1 and 3 days after administration of BTX, and the maximum effects occur after 1-2 weeks, which then stabilizes to a moderate level until complete recovery of the nerve in approximately 3 months [12]. BTX does not inhibit the production of acetylcholine, and therefore, motor function is recovered by subsequent motor axon outgrowth [13].

Repeated treatments and increasing dosage with Botox have been shown to cause atrophy of the underlying muscles, usually leading to longer resolution of the problem. The antinociceptive and analgesic properties of BTX-A are also much discussed in the literature and have suggested that the BTX-A can play an independent role in peripheral nociceptors by blocking the release of certain neurotransmitters such as substance P, glutamate, and calcitonin gene-related peptide [14]. Resistance is most likely associated with increased doses and frequency of treatment sessions [15,16]. Repeat doses of 300 U and above have been associated with resistance [17]. Hence, treatment should be started with the minimal dose required and can be gradually increased. 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. The use of other serotypes (F or B) may benefit those who have developed antibody resistance [18].

CLINICAL APPLICATIONS OF BTX IN THE OROFACIAL REGION

Cosmetic applications

Facial wrinkles occur naturally with due to pull off the skin by the underlying musculature, but becomes more prominent with aging and are unesthetic [19]. Botox has been approved for treating these hyperfunctional facial lines. When injected, it weakens the underlying muscles and is used worldwide successfully for treating glabellar (frown) lines, frontalis and lateral canthal lines (crow's feet), platysma bands, perioral lines, mentalis wrinkling, lower eyelid orbicularis hypertrophy, and vertical lip rhytids (lipstick lines) [20,21]. It is also used to treat hypertrophic scars and keloid with good results. Botox used in conjunction with dermal fillers have proved to be very beneficial for the correction of facial wrinkles [22,23]. BTX-A and dermal fillers have been used to provide immediate volume to black triangles formed due to loss or inadequate interpapillary tissue in the oral cavity [24,25].

Therapeutic applications

Gummy smile

The gummy smile is characterized by a marked gingival exposure on smiling of more than 3 mm. In the gummy smile caused by muscle hyperfunction, the BTX is injected into the lip elevator muscles thereby causing paralysis of them and resulting in less gingival display. It is the first preferred method in such cases due to ease and safety of applications, rapid effect, and more conservative method compared to surgical procedures (myectomy or Le Fort I osteotomy). Irineu presented a case of gummy smile successfully treated with BTX and showed that better results could be obtained with BTX either alone or as an adjuvant therapy to gingival resection surgery [26]. Several authors

have demonstrated that BTX-A injections can be used successfully for treating gummy smiles [27-32].

Temporomandibular disorders (TMD)

TMD is a term which includes not only disorders of the temporomandibular joint (TMJ) but also includes a wide range of disturbances associated with the function of the masticatory system. TMDs may be myofascial (those related to muscles themselves) or arthrogenic (those related to TMJ) or both of them, but the majority of TMDs include a myogenic component, in which hyperactivity of the masticatory muscles are present [33]. Hence by directing treatment at the muscular component of TMD, therapeutic gains can be achieved. TMD symptoms can include jaw pain, neck pain, facial 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. TMD are considered the major cause of pain in the orofacial region [34]. It has been shown that BTX injections can be the least invasive mode, which can provide relief of intractable symptoms in patients who have failed to show any improvement with the conventional modalities of treatment [35,36]. Injecting measured doses of BTX into specific sites (3-5 sites/muscle) in the major muscles of mastication can achieve sufficient masticatory muscle relaxation [37,38]. 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 for treating TMD [39].

In a study conducted by Freund *et al.* on 46 patients suffering from TMD, it was found that with 150 U injections of BTX to the temporalis and masseter muscles; there was a remarkable improvement in mouth opening as there was a reduction in pain over masticatory muscles [40]. Lee *et al.* evaluated the effect of BTX injections on pain in six patients with limited mouth opening due to TMD. In all of their patient's symptoms subsided without any adverse effects during the 5-12 months follow-up period [41]. BTX injections have been used effectively for the treatment of masticatory muscle hypertonicity and parafunction [42]. The treatment protocol according to Katz included one injection of BTX 7.5 U bilaterally into the anterior fibers of each temporalis muscle, and additional injections of 2.5 U are given into the middle and posterior third of the temporalis muscles in the most severe cases. Masseter muscle is treated with 5 U injections. [42]. Zhang *et al.* in their study concluded that BTX-A has obvious advantages for the treatment of TMD in terms of reducing the occlusal forces, but psychological intervention plays an important part of the treatment [43]. Park *et al.* found that Masseter muscle activity as measured by EMG was immediately decreased after a BTX-A injection [44]. There is strong evidence that BTX is a valuable clinical tool in the management of the myofascial component of temporomandibular disorders. The temporalis and masseter muscles are always treated bilaterally even if only one side of the face is involved.

Bruxism

Bruxism refers to both clenching and grinding of the teeth. Etiology is multifactorial and has a psychologic component involved. Bruxism can affect both TMJ and masticatory muscles. Bruxism destroys healthy dentition, exacerbates periodontal disease, causes TMD and ultimately leading to headaches and facial pain. Patients with chronic bruxism can have difficulty in speaking, chewing, swallowing and restricted mouth opening. BTX-A injections have been used to treat patients with parafunctional habits like bruxism by injecting into the flexor muscles of mandible which resulted in the relaxation of muscles in most of the cases. Bilateral injections of BTX-A in the dose range of 25-100 U per side into the masseter and temporalis muscles have provided resolutions of the symptoms of bruxism. BTX-A injections by removing bruxism element reduce facial pain, TMD symptoms and can significantly help the other associated treatments of periodontal disease [45]. This has also been proven useful in sleep bruxism [46,47].

Van Zandijcke and Marchau [48] described the successful treatment of a brain-injured patient with severe bruxism with 100 U of BTX-A injections to the temporalis and masseter muscles and reported marked reduction in bruxism during the recovery period from coma. Tan and Jankovic [49] treated 18 patients with a history of severe bruxism by injecting BTX into the masseter muscle with mean dose of 61.7 U/side (range 25-100 U) and obtained a total duration of therapeutic response of 19 weeks. Maaytah *et al.* [50] reported that BTX 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 cooperate. Ivanhoe *et al.* reported success with a 200 U dose of BTX-A for severe bruxism in a patient with brain injury [51].

Masseter muscle hypertrophy

It is the unilateral or bilateral enlargement of the masseter muscles, which is mostly associated with clenching and bruxism. Other causes are anatomical asymmetry of the jaw, habitual asymmetric use of the jaw, or congenital malformations. This condition is commonly treated with Botox injections into masseter muscle [52], which thins the muscle and reduces the intensity of contraction of masseter muscle unlike surgical excision in which muscle bulk is reduced permanently. Recurrence of this condition is common in 6 months with BTX, as it reduces muscle volume only temporarily thereby making repeat injections necessary [53]. In a clinical trial, the injection of 30 U per side of BTX into the masseter muscles resulted in a sustained reduction of gross masseter size (maximum reduction 35.4%) [54]. Various clinical trials [55-57] reported that injections of BTX into the masseter muscles resulted in a sustained reduction of masseter hyperactivity. With BTX-A injections good, facial contour was achieved [58,59] and several cases were treated successfully [60]. Similarly, temporalis muscle hypertrophy can be treated with BTX injections [61].

Myofascial pain

TMD are considered a subgroup of musculoskeletal and rheumatologic disorders and represent the main cause of nondental pain in the orofacial region. For facial pain and TMD cases, BTX-A can be generally applied to a number of muscles of facial expression and mastication [62]. The FDA has approved BTX-A as a primary treatment for migraine and facial pain using a treatment protocol involving the muscles. BTX-A injections resulted in relief of pain in facial muscles in 90 percent of patients who did not respond to traditional treatments [63]. EMG evaluations were also used to evaluate the effects of BTX-A on muscle activity of patients with myofascial pain, with or without disc displacement. The results showed a decrease of muscle potential action of the masseter in the evaluation after 14 days and an increase in potential 28 days after the procedure. It was also found that the reduction of pain and improvement in psychological indices persisted at reassessment 28 days after the intervention [64].

BTX appears relatively safe and effective in treating cervical dystonia and chronic facial pain associated with masticatory hyperactivity [65]. Several studies have shown BTX-A injections to be effective in cases of chronic facial pain associated with muscle hyperactivity/bruxism [66-68]. Machado *et al.* [69], in their study, concluded further randomized controlled clinical trials, with representative samples and longer follow-up time, are required to assess the real effectiveness of BTX injections in the management of masticatory myofascial pain and muscular TMD. Injection of muscles with Botox has been reported to be effective for myofascial pain caused by trigger points [70]. Research has certainly shown that Botox and Dysport achieve successful treatment for many facial, TMD and oral dysfunctions which originate from the musculature [71]. Sidebottom *et al.* in their prospective study concluded that BTX is a valuable alternative second line treatment for masticatory myofascial pain when conservative measures have failed [72].

Mandibular spasm

It is a condition in which the elevator muscles of mandible are in a spasmodic condition resulting in restriction of mouth opening and pain during mandibular movements. Intramuscular Botox injections have resulted in relaxation of muscles, reducing inflammation of muscles and TMJ and the guarding response to pain thereby improving mouth opening. Several case reports have been published [73-76] describing the effectiveness of BTX-A in patients with hemimasticatory spasm, where all the patients responded positively to intramuscular Botox injections.

Oromandibular dystonia (OMD)

OMD is characterized by involuntary contraction of the masticatory and lower facial muscles causing unintentional opening and closing of the mouth in vertical, lateral, and protrusive directions. This will also result involuntarily chewing of the soft tissue inside the mouth often interfering with regular chewing and speaking. Although there is no cure for OMD, BTX 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. Masseteric injection of Botox has been used for OMD as well as for plethora spasm which is often related conditions [77]. Literature on OMD treatment has reported improvement of symptoms with the use of BTX injections [78-82]. Over a 10-year period, Tan and Jankovic treated 162 patients with OMD by injecting BTX-A into the masseter muscles and/or the sub-mentalis complex, and improvement in chewing and speaking was reported in 67.9% of the patients [79].

TMJ dislocation

Recurrent dislocation of TMJ can occur due to OMD, epilepsy, stroke, and dyskinesias. BTX injection is specially indicated in patients in which conservative treatment has failed and surgery carries major risks. BTX-A has been used to treat recurrent TMJ dislocation by injecting into lateral pterygoid muscle in most of the cases and masseter muscle in some of the cases [83-86]. Bhogal *et al.* [87], in their review article, stated that mandibular dislocation when treated with BTX injection into lateral pterygoid muscles; the results lasted for a minimum of 3 months. Intramuscular BTX injection in lateral pterygoid muscle as an adjunct to arthrocentesis in the treatment of internal derangement of TMJ gave a good improvement of symptoms suggesting synergy between the two procedures [88].

Salivary secretory disorders

Sialorrhea

Excessive saliva production or the inability to hold saliva in the mouth can result in sialorrhea or drooling. Xerostomia is one of the manifestations of botulism, which led to the introduction of BTX to treat sialorrhea and drooling. BTX-A treated for sialorrhea associated with Parkinson's disease had a very favorable outcome when injected into parotids or both parotid and submandibular glands to inhibit the stimulation of cholinergic receptors [89-92]. Fuster *et al.* injected BTX into parotid submandibular gland or both with doses varying from 10 TO 100 units, which resulted in reduction in saliva production which lasted for 6 months [93]. This has to be done carefully, as too much will result in chewing difficulties, dysphagia and xerostomia. Botox is administered mostly only into parotid gland in a dose range of 30-70 U with a significant reduction in salivary flow observed in a month. However, the effects last only up to 3 months, and repeat injections are often necessary. BTX-A also had been treated with success for sialorrhea in patients with amyotrophic lateral sclerosis, cerebral palsy, and other neurological disorders which are caused by muscarinic type cholinergic hyperactivity [94-97].

It has also been used successfully in patients with post-traumatic and iatrogenic salivary sialoceles [98] and acute postparotidectomy salivary fistula [99]. Botox is useful in cases of drooling or salivary fistulas after oropharyngeal cancer surgery where temporary stopping of glandular secretory action is needed to promote healing [100]. Bartolo corradino

et al. [101], in their study, injected 80-100 U of BTX -A preoperatively into major salivary glands for 43 oral cancer patients who underwent surgery and found that there was a considerable, temporary reduction of salivary secretion thereby avoiding the postoperative complications due to saliva stagnation and also helped in better healing and outcome of the surgery.

Frey's syndrome

Other uses of BTX are to treat auriculotemporal (Frey's) syndrome. However, its transient effectiveness (3-4 months) requires multiple injections. Intradermal injection of BTX into the affected area resulted in greater improvements in patients suffering from gustatory sweating, and the effects were long-lasting than intramuscular injections. [102]. Laccourreye *et al.*, in a follow-up study of 33 Frey's syndrome patients treated with BTX, found recurrence rates of 27% in the 1st year, 63% in the second, and 92% in the 3rd year [103]. Guntinas-Lichius in his study demonstrated that using a higher concentration of BTX is more effective than a lower concentration in the treatment of Frey's syndrome [104]. Several other studies have also confirmed that BT is safe and efficacious treatment for gustatory sweating [105,106].

Facial nerve palsy

Facial nerve palsy is a disfiguring condition for the patient and has been treated successfully with BTX. In patients with facial asymmetry, BTX injections into the normal side have been reported to result in an apparent symmetrical function of the face [107-109]. BTX-A is commonly used to treat facial synkinesis with marked improvement of facial symmetry at rest and during voluntary movements [110,111]. Hyperlacrimation (crocodile tears) which may occur after a facial palsy has been successfully treated by injecting BTX into lacrimal glands [112]. It has also been used to intentionally induce ptosis to protect cornea in facial palsy patients by injecting into the levator palpebrae superioris muscle [113]. There are also reports of BTX injections into lateral rectus and medial rectus muscles for treating third and sixth cranial nerve palsies with varied improvements.

Pain in head and neck region

BTX-A was found very effective in the management of various facial pain conditions such as tension headache, migraine, myofascial pain, trigeminal neuralgia and in post-operative wound pain including TMJ surgery, blowout fracture repair and reconstructive facial surgery. Botox 25-75 U injected into pericranial muscles relieves a headache by relaxing the overactive muscles by blocking nerve impulses that trigger contractions. For migraines Botox works by blocking the protein that carries the message of pain to the brain and relief typically takes effect in 2-3 weeks after injection and the longer the treatment duration, the better the pain relief [114]. 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 [115]. BTX inhibits substance P and is used in relieving excruciating pain associated with inflammation of trigeminal nerve, as it is an anti-inflammatory agent. Analgesic effect following BTX injections in orofacial pain are due to direct analgesic and neuromodulating mechanisms of BTX in the CNS, anti-inflammatory effects, and effects on the myofascial tender point [116]. Botox is also very useful in treating chronic pain syndrome [117]. Another study reported that BTX causes normalization of increased muscle spindle activity, decompression of afferent nociceptive neurons of muscular and vascular tissue [118].

Trigeminal neuralgia

Trigeminal neuralgia is frequently confused with dental pain and needs to be considered more often as a possible diagnosis when all other dental and muscle pathologies have been eliminated as the source of dental and facial pain. BTX-A use is increasing for trigeminal neuralgia cases and while the mechanism of action has not been well established, it has been a useful adjunct to treating these patients as primary or secondary treatment [119-121]. Ngeow and Nair described a persistent case of trigeminal neuralgia, when treated with 100 U BTX-A injection responded well immediately and the patient was completely relieved

of pain for 5 months. Pain recurred later for which BTX injection was repeated and underwent neurosurgery after 1 year [122].

Other uses

Oral and maxillofacial trauma

In the treatment of various facial bone injuries, such as condylar, zygoma fractures, and BTX injections has proven to be useful in assisting post-operative wound healing by weakening/relaxing muscles, thereby reducing displacing forces on the fracture ends and obtain good immobilization if rigid fixation is not possible [123-126]. It also helps in reducing the number of plates required for stabilizing the bones. Facial laceration wound healing was better with BTX [127,128].

Implantology

Parafunctional habits like bruxism or stress due to any excessive functional forces during osseointegration stage of implants can cause implant failure. Application of BTX relaxes masticatory muscles and helps in unimpeded osseointegration of implants especially in immediate load implant protocols [129]. However, not many studies demonstrate the beneficial effects of BTX use in dental implantology. Further randomized controlled trials are needed to evaluate their use in dental implantology [130]. Relapse is a problem after orthodontic treatment and/or orthognathic surgery and the root cause are the hyperactive muscles, e.g., mentalis muscle. BTX-A can reduce muscle contraction intensity, and over time, muscles can be trained to work normally. Similarly, in a patient receiving complete dentures BTX injections into muscles such as masseter, medial, and lateral pterygoid can be done for muscle training, thus enhancing in gradual adaptation of the orofacial musculature to the denture. In addition, according to Seok *et al.*, the injection of BTX-A into the digastric muscle corrected the post-traumatic anterior open bite [131]. Chow *et al.* used BTX-A injections for treating ranula in 3 patients and achieved good results [132].

Contraindications

There are no absolute contraindications for BTX use. Relative contraindications include pregnancy, lactation, neuromuscular diseases (e.g., myasthenia gravis, amyotrophic lateral sclerosis, Eaton-Lambert syndrome, and Charcot disease), motor neuron disease, drug interactions (aminoglycosides, muscle relaxants, quinidine, calcium channel blockers, magnesium sulfate and polymyxin), allergy to any of the components of BTX-A or BTX-B (i.e. BTX, human albumin, saline, lactose, and sodium succinate), infection at injection site and psychologically unstable patients.

Complications

Local side effects are mild and include Pain, edema, headache, erythema, ecchymosis, blepharoptosis, and perioral muscular palsy. Other complications during therapeutic applications are dry eyes, mouth droop, lid edema, xerostomia, transient dysphagia, trismus, nasal regurgitation, nasal speech, blurred vision, dizziness, upset stomach, infection, neck weakness, voice changes, difficulty in chewing and breathing, risk of aspiration, recurrent jaw dislocation, dysarthria, salivary duct calculi, injury to branches of the facial nerve, facial muscle weakness, and facial asymmetry during movements. Systemic side effects are nausea, fatigue, headache, facial pain, flu-like symptoms, anxiety, itching, and transient weakness [1].

According to Cote *et al.* [133] in 2005, the adverse event reported to the FDA (1989-2003) after therapeutic and cosmetic use of BTX was 1437 cases. 217 serious adverse events were reported including 28 reported deaths; respiratory arrest, myocardial infarction, cerebrovascular accident, pulmonary embolism, and others [21]. All of them were related to therapeutic application rather than cosmetic purpose of the BTX. FDA issued a Black Box warning in 2009 because of the ability of BTX to migrate from injection site (systemic toxicity), that could lead to life-threatening symptoms of botulism (dysphagia and breathing difficulties) which is more likely to occur after intramuscular injections even with therapeutic doses. Botulism-like symptoms are

muscle weakness, hoarseness or dysphonia, dysarthria, loss of bladder control, difficulty breathing, difficulty swallowing, double or blurred vision, and drooping eyelids which can occur anywhere from a day to several weeks after treatment at unrelated sites. However, safety of BTX-A in clinical uses has been well established [134]. Most of the adverse effects are linked to local tissue diffusion of BTX. Careful attention to drug dose, dilution, handling, storage, and site of injection are required for optimal treatment outcome and to minimize adverse effects.

SUMMARY

BTX is increasingly being used in medicine and dentistry and is associated with a few reversible adverse effects [128]. It is used in the field of oral and maxillofacial surgery for more than two decades. Botox applications are expanding in the treatment of various orofacial disorders. Its applications range from cosmetic to various therapeutic purposes such as temporomandibular disorders, salivary secretory disorders, hyperhidrosis, facial paralysis, orofacial pain, and implantology [135-139]. Even though numerous publications have reported successful outcomes after BTX application, they are mostly case reports and case series. There are only a few scientific reports with the high level of scientific evidence. Hence, more good quality clinical research needs to be carried out with randomized, controlled, blinded settings to understand the properties, clinical efficacy, and any associated long-term adverse effects. Treatment with BTX cannot be considered curative but a simple, safe, palliative, and symptomatic approach to the management of a problem. BTX treatments have shown to have a low risk of side effects and contraindications, are comparably cost effective, reversible and relatively safe, which makes this treatment choice popular among patients and dentists.

Dentists are highly knowledgeable regarding oral and facial anatomy, which seems reasonable for them to be at the forefront in providing these services, understanding limitations of treatment and having the ability to recognize and manage complications. As Botox treatment is technique, sensitive appropriate training is essential not only to administer the drug but also to deal with potential adverse effects. Benninger *et al.* [140] concluded from their study that BTX-A is an effective treatment for oral pathologies and dentists should be allowed to inject BTX-A based on their didactic and clinical anatomy courses and clinical curriculum. This study revealed the training of a general dentist appears to satisfy the basic science knowledge and clinical skills one would need to administer BTX-A injections to the head and neck region. Dentists worldwide are now treating patients with BTX-A for various oral and maxillofacial aesthetic and therapeutic purposes, and Botox injections are being integrated into dental treatment plans routinely [141,142]. But according to Al Hamdam *et al.*, dentists in Saudi Arabia were hesitant in using BTX injections and derma fillers as they were lacking in knowledge and confidence regarding BTX injections and were worried about complications of BTX injections, which emphasizes the need for adequate training programs regarding BTX injections for the dentists [143].

CONCLUSION

BTX treatment is relatively safe and efficacious, less invasive, conservative and the effects are faster and reversible. It is used for both cosmetic and therapeutic purposes. The role of BTX as a therapeutic agent for several conditions is expanding. With training of BTX-A injection techniques and adequate knowledge about treatment protocols, general dentists can safely administer BTX injections. The ability to use Botox as an adjuvant and primary mode of treatment for various maxillofacial disorders offers exciting treatment options for dentists and patients in the future.

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