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# Botulinum Toxin: Dentistry Insight

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***Authors' contributions***

*This work was carried out in collaboration between all authors. The study was designed by authors SM and GS. Collection of data (manual and online) and the protocol was written by author AG. Data analysis and the first draft of the manuscript were written by author SM. Final drafting and proof reading was done by author GS. All authors read and approved the final manuscript.*

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## ABSTRACT

Botulinum toxin is the first biologic toxin to be used in the treatment of human diseases. It is a minimally invasive, revolutionary and a novel approach to treat several orofacial disorders. It is produced by autolysis of gram positive anaerobic bacterium called *Clostridium botulinum*. Botulinum toxin is lethal and is well known for its lingering threat of bioterrorism which is associated with it. On the other hand it has a therapeutic potential when injected in minute quantities in hyperactive muscles. Over the past two decades the cosmetic and non - cosmetic uses of botulinum toxin in the orofacial region has gained wide popularity. The purpose of this article is to overview the tortuous course of botulinum toxin from its discovery as a lethal toxin to its cosmetic and non- cosmetic enhancement roles in the perioral region and to determine its usefulness and effectiveness in wide range of orofacial disorders.

*Keywords: Botulinum toxin; myofascial pain; bruxism; trigeminal neuralgia; orofacial pain.*

## 1. INTRODUCTION

Long perceived as lethal causing a deadly disease Botulism, Botulinum Toxin (BT) in therapeutic dosage has revolutionized the treatment approach for cosmetic enhancement and pain management in chronic oro-facial disorders. In this revolutionary era of dentistry

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the advent of botulinum toxin therapy in oral and maxillofacial region has sprouted interest in many clinicians worldwide to investigate the efficacy of this novel treatment approach in various chronic orofacial ailments. Futuristic scope of botulinum treatment in the perioral region is expanding unabated not only because of high acceptance of this therapy in medicine but also because of the definite advantages owed by it.

For an explicit presentation this paper has been divided into two halves. The first halve provides general information, biochemical properties, mechanism of action and on label uses of BT. The second half deals with the contemporary orofacial application of the drug highlighting its advantages, disadvantages and contraindication. Though this treatment modality is gaining popularity in dentistry both amongst the clinicians and distressed patients extensive confirmation regarding its effectiveness and long term usage is required.

The purpose of this article is to overview the tortuous course of botulinum toxin from its discovery as a lethal toxin to its cosmetic and non- cosmetic enhancement roles in the perioral region and to determine its usefulness and effectiveness in wide range of orofacial disorders.

## 2. HISTORY

In medieval times, sausage production was controlled as it was the major source of botulism. Botulism is aptly derived from the greek word “Botulus” which means sausage. Botulism was originally called ‘sausage poisoning’ as it occurred after ingestion of poorly prepared sausage. It is a life threatening disease characterized by paralysis of muscles of face, limbs and respiration ultimately leading to respiratory failure and death. The credit for the description of clinical features of botulism with a precision still unsurpassed goes to a German physician Justinus Kerner in 1820s [1]. In 1895, Emile P. Van Ermengem first isolated this evil microbe *Clostridium botulinum* from food and post mortem tissues of victims who died in Belgium after consumption of raw and salted pork [2]. His landmark publication made a platform for research on botulism that led to food preservation measures we follow today. In 1946 the toxin produced by this organism was first isolated in crystalline form by Edward J Scantz in Maryland [2]. In 1950s its mechanism of action was proposed suggesting that it blocked acetycholine (Ach) release from motor endplates thus causing muscle paresis [3]. It was first used in humans in 1973 [4]. In 1970s Botulinum toxin was also used as a research tool to study spinal cord physiology [5]. In 1980s perception about this toxin was suddenly changed when its therapeutic potential suddenly became apparent.

## 3. BIOCHEMICAL NATURE OF BT

Botulinum Toxin (BT) currently called Onabotulinum Toxin by Food and Drug Administration [6] is produced by *Clostridium botulinum*. The bacterium , was initially classified in eight different serotypes namely A, B, C alpha, C beta, D, E, F, G that produce seven serologically different exotoxins. Currently this old classification of 8 strains of the bacterium is no more considered satisfactory. Now the bacterium is divided into 4 physiologic groups which include *C. botulinum*, *C. argentinense*, *C. butyricum*, *C. baratii* strains [7]. All the serotypes inhibit Ach release from nerve terminals and cause muscle paresis of target tissues by chemical denervation. Recently BT-B has become commercially available. This unique action of BT has been exploited by the clinicians and researchers to achieve the desired therapeutic effect.

Despite this typical and unique mode of action of all the serotypes their intracellular target proteins, potencies and characteristics of action vary substantially. BT-A is the most potent and most widely studied serotype for therapeutic purpose [1]. BT is produced as pretoxin consisting of a 100-kDa heavy chain and 50-kDa light chain linked together by a single disulphide bond. Light chain has an endopeptidase activity. Disulphide bond is cleaved to generate an active neuroparalytic toxin i.e. when the bond is intact BT has no catalytic activity

## 4. MECHANISM OF ACTION

The cellular mechanism for neuroparalytic action of BT can be categorized into Binding, Internalization and Intraneuronal action. BT inhibits the exocytosis of Ach vesicle on cholinergic nerve endings of motor nerves [8]. Autonomic nerves in the glands and smooth muscles are also affected [9]. As BT does not cross blood brain barrier and since it gets deactivated during retrograde axonal transport, the effect is seen in first order sensory nerve and not centrally [1].

### 4.1 Binding

When BT is injected into target tissue, heavy chain binds to glycoprotein structures specific to cholinergic nerve terminals thus showing high selectivity for cholinergic synapses.

### 4.2 Internalization

This specific docking of BT and cholinergic nerve terminal internalizes the toxin via receptor mediated endocytosis. Once endocytosed, the toxin can no longer be neutralized by antisera.

### 4.3 Intraneuronal Action

After internalization the light chain of BT binds specifically to the SNARE protein complex. SNARE proteins form complex to allow synaptic vesicles to fuse with plasma membrane for the release of Ach. Light chain in the cytosol cleaves SNAREs. SNARE complex is non functional and Acetycholine is not released as the docking of Acetycholine vesicle and vesicle fusion is blocked. SNARE proteins are of three types- SNAP-25, VAMP, Syntaxin. The target proteins vary amongst the BT serotypes. SNAP-25 is cleaved by BT-A whereas BT-B cleaves vesicle associated membrane protein (VAMP), also known as synaptobrevin-II [1]. If the target tissue is a muscle, paresis is seen due to chemical denervation. When the target tissue is an exocrine gland, the glandular secretion is blocked.

### 4.4 Antinociceptive Action of BT

Patients being treated with BT for focal dystonias and other spastic conditions reported a marked analgesic effect [10]. Initially it was thought that the pain relief was due to direct muscle relaxation. However very soon direct analgesic effects of BT were apparent based on its inhibition on neurotransmitters other than Ach [11]. However various studies and observations suggest that BT exerts an independent action on peripheral nociceptors by blocking the exocytosis of neurotransmitters like substance P [12-14], glutamate [11,15], noradrenaline [16] and calcitonin gene-related peptide (CGRP) [17]. Amongst all the serotypes BT-A produced strongest susbstance P suppression [14].

## 5. MEDICAL APPLICATIONS

BT is the first biological toxin to be used in the treatment of human diseases. Dr Allan Scott has played a pivotal role in the history of Botulinum therapy. Dr Scott's union with Schantz and his purified toxin made him the first to non- surgically treat strabismus by injecting BT into external eye muscles [18]. Use in fine muscles paved its path for the use in larger group muscles. Soon its role in the treatment of dystonias, the disordered tension of skeletal muscle was recognized. The explosive cosmetic application of BT was the result of a seminal observation of a doctor couple in 1987 who observed that the frown line disappeared following the use of botox for the treatment of blepharospasm [2].

Such clinically significant findings and a long research set a platform for Food and Drug Administration to finally approve BT-A for the treatment of strabismus and blepharospasm in 1989, cervical dystonia in 2000, cosmetic use to reduce severe glabellar lines in 2002 and for primary axillary hyperhidrosis in 2004 [19]. In 2000 the FDA approved BT-B for the treatment of cervical dystonia in patients who developed antibodies towards BT-A. BT-A was approved by the FDA for the treatment of chronic migraines in 2010. It is the only prophylactic treatment for chronic migraines [20]. These are on label uses of BT.

Educational efforts, research and investigations coupled from multiple disciplines of medicine has made apparent that BT can be used in various hyperkinetic facial lines, crow's feet, nasal flare, eyebrow elevation, chin dimpling [2]. Other than the cosmetic use botulinum therapy holds great promise in other medical conditions like Parkinson's [21], achalasia, dysphonia, cerebral palsy and chronic anal fissures [2]. It is also widely being used to manage pain [22].

## 6. DENTAL APPLICATIONS

After years of testification of powerful and dramatic action, BT has carved its way into dentistry. Collected scientific evidence and reported cases support the application of BT in the following oro-facial disorders.

### 6.1 Bruxism

It is a non functional jaw movement incorporating gnashing, grinding, clicking and clenching of teeth. It is derived from the greek word 'brychein' meaning 'to gnash or grind the teeth'. Reported prevalence of sleep bruxism varies from 5% to 21% of population [23,24]. It is estimated to be as high as 96% in adult population [25].

Pathophysiology of bruxism is unclear. It is supposed to be a multifactorial psycho-neuromotor dysregulation. An example of neuromotor disease that exhibits bruxism as a feature is cerebral palsy. Bruxism can be secondary to brain injury [26] . The management of bruxism is a full arch occlusal appliance that does not suppress excessive motor activity but mitigates dental damage [27]. Continuous and uncontrolled muscle spasm results in altered nociceptive mechanism, leading to pain perception in the affected muscles. This is in addition to other signs of bruxism that includes progressive attrition, teeth fracture, unstable occlusion, bruxism induced pulpitis, cheek biting etc.

BT, a motor suppressive medication has shown to play a promising role in alleviating the damaging consequences of bruxism. It blocks the cholinergic transmission, interrupts muscle contraction and normalises muscle spindle activity. One of the first reported cases in support of this concept was in 1990 wherein severe bruxism in a brain injured patient was controlled by BT [28]. This was followed by many practical interventions wherein bruxism was partly or completely treated by BT injections in temporalis and masseter muscles [26,29-31]. Ample evidence exists supporting the use of BT as a successful interventional treatment modality for severe bruxism especially in uncooperative patients after brain injury. Still the reported cases do not make a strong platform for its routine use in managing bruxism.

### 6.2 Oromandibular Dystonia

Oromandibular Dystonia (OMD) is involuntary, intermittent short but sustained asynchronous muscle contraction producing twisting, repetitive movements or abnormal posture [32]. Dystonias can be generalized or focal. Focal form is 10 times more common than generalized systemic form [33]. OMD is a type of focal dystonia of orofacial region involving jaw openers, tongue muscles, facial muscles (orbicularis oris & buccinator) and platysma. When it occurs in association with blepharospasm it is called Miege's syndrome [34]. Dystonias can be primary (idiopathic) or can be more widespread secondary to any CNS disease, trauma, vascular lesion or drug use [35]. Pathophysiology is unclear and various mechanisms have been proposed to explain dystonia e.g. basal ganglia dysfunction and hyper-excitability of neurons involved in motor signaling [36].

Asynchronous muscle spasm in OMD presents itself as distorted oral position, galloping tongue, difficulty in speaking, swallowing and eating. Typical of dystonia is 'Geste Antagonistque' [37] i.e. suppressive effect can be made on involuntary muscle movement in dystonia by tactile inhibition, for example touching the chin in case of OMD prevents dystonic behavior of the jaw. Dystonias are more common during waking period and disappears entirely during sleep.

Treatment involves use of several motor suppressive medications such as Benzotropine, a cholinergic antagonist. Mainstay in the treatment of OMD is chemodenervation using BT. Early reports in support of this concept was in 1989 suppressing OMD by injecting in masseter & temporalis [38] and in 1991 lingual dystonia was treated by injecting BT in genioglossus muscle [39]. These initial trials indicating successful application of BT in treating OMD were confirmed by its effective usage in several other patients [40-42]. Charles et al. [43] treated 9 patients of Meige's syndrome with BT. A meta-analysis reviewing the motor suppressive medications indicated in dystonias summarized that BT shows obvious benefits in the treatment of focal dystonias [44] .

### 6.3 Sialorrhoea

Sialorrhoea also known as hypersalivation can be primary or secondary. Drooling is unintentional loss of saliva from the mouth. Drooling if associated with disorders of the coordinated activity and paralysis of orofacial and palatolingual muscles with normal salivary secretion is called secondary sialorrhoea. Excessive salivary secretion is called primary sialorrhoea [45]. Drooling is associated with social impediment and the condition is distressful and embarrassing both for the patient and the care givers. Neurodegenerative diseases such as amylotrophic lateral sclerosis, Parkinson's, cerebral palsy and post-stroke often cause secondary sialorrhoea. Minor cases can be treated by anticholinergic drugs whereas severe cases mandate surgery.

In 1822 Justinus Kerner after noting the severe dryness of mouth in patients with botulism first suggested that the toxic substance causing botulism might be useful in treating hypersalivation. BT when injected intra - glandularly in the treatment of drooling demonstrates promising efficacy [46,47,48]. In 2007 a systematic review was done to check the

usefulness of BT in sialorrhoea [49]. Transient reduction in saliva was observed for an average period of 1.5-6 months after intra-glandular injection of 10-100 units of BT. Impressive data in the literature shows that BT has a promising role in treatment of hypersalivation [50]. Randomised controlled trials have demonstrated the effectiveness of BT in the management of sialorrhoea with a duration of 2-7 months [51,52]. However adverse effects like xerostomia, dysphagia, weak mastication, dental caries and parotid gland infection can be seen. Moller et al. [53] conducted a prospective study on 12 patients of amyotrophic lateral sclerosis and 3 patients of Parkinson's disease. BT-A were given into the parotids (25-40 U) and submandibular glands (15-30 U) under ultrasonographic guidance. Follow up was done every two weeks for 2 months. The study showed that the maximal reduction during observation period was 40% for drooling and 30% for flow. Clearly, there exists a scope to explore issues such as dose, site and technique of injecting BT in the treatment of sialorrhoea.

### 6.4 Massetric Hypertrophy

It is an asymptomatic enlargement of one or more commonly both masseter muscles. Etiology is unclear but malocclusion, bruxism, emotional stress, microtrauma or temporomandibular derangements can be attributed as the predisposing factors. It can be unilateral or bilateral and acquired or congenital. Unilateral occurrence is common when the patients chew primarily on a single particular side [54]. Conventional approach for treating this primarily cosmetic disorder has been surgical partial excision of masseter. But the surgery is often associated with complications like hematoma formation, facial nerve paralysis, trismus, infection etc [55]. The concept of less invasive cosmetic sculpting of lower face with BT injections into masseter muscle was introduced by Smyth and Moore in 1994 [56,57]. BT when injected causes muscle atrophy following muscle paresis.

A clinical trial showed a sustained reduction of gross masseter size upto 35.4% post BT injection [58]. Many other studies have attained similar results, thus confirming the efficacy of BT in massetric hypertrophy [59,60]. Possible accompanied complications include prominent zygoma, speech disturbance, facial asymmetry, altered bite force, external scar and damage to the mandibular branch of facial nerve [54]. Xie et al. [61] in 2014 proposed an objective classification method for customized BT-A injection protocol. The study was conducted on 504 masseters to provide a scientific basis to reduce the injection dosage and complication rates without compromising with the eventual esthetic advantage [61].

### 6.5 Myofascial Pain

Myofascial Pain (MFP) is the most common muscle pain disorder [62]. It is acute to chronic, local and referred muscle pain which is dull or achy, diffuse in nature and characterized by the presence of trigger points expressed as taut bands in muscles, fascia or tendon. It is a common cause of persistent regional pain in subcutaneous tissues in the region of trigger points or can be referred to distant areas as in neck, temporal region, shoulder etc. [63]. A trigger point may be active or latent. Active trigger points are hypersensitive and demonstrate continuous pain in the zone of reference where as latent trigger points display only tenderness to palpation without continuous pain referral. Reproducible duplication of pain symptoms with specific palpation of tender taut areas is often diagnostic.

Myofascial trigger point is said to be the result of abnormal motor end plate activity releasing excessive amount of the neurotransmitter Ach [64]. Management of MFP is directed both peripherally and centrally. Theoretically using neuromuscular blocking agents like BT can be used as a trigger based therapy to eliminate end-plate dysfunction by inhibiting the release of Ach and there by alleviating pain. This idea promoted the use of BT in treating MFP. There are many repeated studies examining the effectiveness of BT in MFP. However, it is difficult to draw any definite conclusion about the effectiveness of BT in MFP.

An open-label case series on 77 patients published in 2003 reported reduced visual analog scale (VAS) pain levels and reduction in motor end plate activity after using BT-A for trigger points in MFP patients [65]. In stark contrast to this case series a clinical study published in 2006 concluded that BT had no better effect on pain when compared with isotonic saline [66]. There are other studies that negate the anti-nociceptive action of BT in MFP [67,68]. A study concluded equal and effective usefulness of BTA and bupivacaine as trigger point therapy in reducing pain in MF patients [69]. No significant difference between the injected agents in the duration or

magnitude of pain relief, function or satisfaction of patients was seen. A systematic review addressing BT to treat jaw muscles myofascial pain from 2000 to April 2012 concluded that BTA is not more effective than established conventional treatment to treat MFP [6]. Overall evidence suggests that BT is no better than is placebo or other standard trigger based therapy.

### 6.6 Frey's Syndrome

Auriculotemporal syndrome or Frey's Syndrome (FS) is named after Lucia Frey, a neurologist who first described this syndrome in her landmark publication on 'syndrome du nerf auriculotemporal' in 1923. It is characterized by facial flushing and sweating of skin during gustatory stimulus. It can be an unavoidable sequelae of parotidectomy. The postulated etiology is that parasympathetic fibers normally innervating parotids when sectioned, aberrantly dysregenerate to innervate the vessels and sweat glands of the overlying skin. Because of penetrating trauma or parotid surgery these parasympathetic nerve endings grow anomalously towards the hypodermis of preauricular region. The activation following aberrant regeneration produces an activation of new targets during meals, resulting in local vasodialation 'gustatory flushing' and localized sweating, 'gustatory sweating' [70,71]. Proposed treatment modalities for FS are: 1) External radiotherapy. 2) Anticholinergic drug. 3) Surgical partial section of efferent neural arch. 4) Interposition of subcutaneous barrier (fat or muscle). 5) Intra cutaneous BT-A injection.

Injecting BT-A intradermally as a treatment of gustatory sweating was proposed in 1995 by Drobik et al. [72]. Many studies on the effective and efficacious use of BT for FS have been published [71,73,74]. It is seen that intracutaneous injection of BT in patients of FS is not only an effective and minimally invasive technique but its effect is longer lasting compared to when administered for other disorders. A case reported complete absence of symptoms for 2 years after injection [75]. Some authors believe that administered BT in due course may cause complete atrophy of the parasympathetic nerve ending [76]. A study demonstrated that higher concentration of BT is more effective than a lower concentration in the treatment of FS [77]. A follow up study on 33 FS patients treated with BT-A found recurrence rates of 27% in the first year, 63% in the second and 92% in the third year [78].

### 6.7 Gummy Smile

Gummy smile designates a problem with the dynamic relationship of lips to teeth. It can be defined as gingival exposure of more than 3mm upon smiling [79]. Excessive gingival display can be attributed to skeletal, gingival, muscular or dental factors. Gummy smile due to vertical maxillary excess is treated by orthognathic surgery whereas the one of dental origin is successfully corrected by orthodontic intrusion mechanics. Gummy smile due to hyperactive lip elevators has been conventionally treated by surgery [19,80]. These surgical approaches are invariably associated with morbidity, scar contracture and are cost and time consuming.

Peck et al. [81] stated that patients with gummy smile had 20% or more facial muscular capacity to raise the upper lip on smiling. BTA injection at preselected sites has emerged as a novel minimally invasive approach for transitory improvement of gummy smile caused by hyperfunctional lip elevators. Two classic articles that have revolutionized the approach of muscular gummy smile with BT-A are by Polo M in 2008 and Hwanga et al. in 2009. After a pilot study on 5 patients in 2005 [82] Maria polo successfully treated 30 patients with neuro-muscular gummy smile by injecting 2.5 units in all subjects at two sites per side (a total of four sides per patient). The toxin was injected at the overlapping points of levator labii superioris alequae nasii (LLSAN) and levator labii superioris (LLS) and the LLS and zygomaticus minor (ZM) muscle. The mean gingival exposure reduction was 5.2 mm and 24 weeks post treatment the average gingival display had not returned to the base line values [19]. Hwanga et al. [83] identified a safe reliable, reproducible and effective injection point for BT-A toxin called Yonsei Point. It is a point around the converging area of the three muscles namely LLS, LLSAN and ZM on the area lateral to the ala of nose. Many authors have proposed subtle differences in dose, sites and treatment protocol for gummy smile treatment with BT [82,84,85]. It is therefore crucial to have long term clinical trials and further research substantiated by empirical outcomes for this treatment to emerge as a regular approach of smile enhancement in muscular gummy smile patients.

### 6.8 Trigeminal Neuralgia

Trigeminal Neuralgia (TN) also called tic douloureux owing to the facial expression or

flinch that often accompanies the neuralgic attack. It is neuropathic oro-facial pain, typically unilateral and accompanied by phases of remission. It is equally seen in maxillary and mandibular divisions and less commonly in ophthalmic division. It can be idiopathic or secondary to trauma or demyelinating diseases (eg. Multiple sclerosis). The incidence has been reported to be 2-27 individuals per 100000 of population [86,87]. It is more common in women and above 50 years of age group. Pain is typically sharp, shooting, lancinating, electric-shock type lasting from a few seconds to two minutes. It is often associated with intra-oral or extra-oral trigger points. Conventional treatment modality for TN is pharmacological (carbamazepine, baclofen) or surgical (microvascular decompression, glycerol rhizo-tomy and stereotactic radiosurgery).

Use of BT has been proposed in the treatment of TN to paralyze the trigger points. Many uncontrolled open label reports are available that show substantial pain reduction after BT injections in TN [88,89,90,91]. Two randomized clinical trials show that BT injections were as efficacious as local anaesthetics (bupivacaine .5%, lidocaine .5%) in terms of duration and magnitude of pain relief and quality of life with BT being less cost effective [92,93].

These results emphasize the need for further research and well designed randomized control clinical trials to provide quality data to make any definite comment about the efficacy of BT injections in TN and MFP.

### 6.9 First Bite Syndrome

First Bite Syndrome (FBS) was first described by Haubrich in 1986 [94]. The name is ideally derived since the patient reports excrutiating pain typically after first bite of meal. Pain decreases in intensity with subsequent masticatory cycles only to recur to the same excruciating level at the first bite of next meal [95]. Etiology of FBS is unclear but it is hypothesized that it is due to loss of sympathetic innervation to the parotids with subsequent hypersensitivity of myoepithelial cells to parasympathetic neurotransmitters [96]. The concept that pain is elicited by myoepithelial contraction led to the proposal that paralysis of myoepithelial filament with BT-A may relieve FBS symptoms.

First documented use of BT in the treatment of FBS was reported in 2008 [97] thus adding to the list one more application of BT. However, due to rarity of such cases and unavailability of substantial data to support or refute this potential use of BT, nothing much can be concluded with certainty about the efficacy of BT in FBS.

### 6.10 Implants and Maxillofacial Surgery

Botox can be potentially used to hasten osseointegration by deprogramming the muscles responsible for excessive occlusal forces. Osseointegration can be impeded by excessive functional forces following implant placement. Muscle relaxation owing to prophylactic use of intramuscular injections of BT in muscles of mastication can be beneficial in achieving uneventful osseointegration of implants [98,99].

Maxillofacial fracture stabilization and fixation often requires multiple fixation sites to overcome strong muscular forces. Muscular overloading can cause impaired callus formation. BT injection when prophylactically used can provide a more stable environment for fracture healing with reduction in number of hardware used thus reducing the cost and post-operative morbidity. Higher doses of BT can be used as ‘pharmaceutical splint’ limiting muscle contraction before fracture healing and during rehabilitation.

Kayikviaglu et al. [100] conducted an open label prospective study to examine the use of BT-A in 5 patients as an adjunct to zygomatic fracture fixation surgery in an attempt to reduce the number of fixation sites. Pre operatively 100 U of BT-A was injected into masseter muscle of the fractured side. Patients were operated 12-48 hours following chemical denervation of muscle (as confirmed by EMG). Muscle paresis allowed for fewer plates insertion among the patients and resulted in no complication.

BT can be a boon for patients suffering from recurrent TMJ dislocation. Even with good patient compliance conservative treatment is not sufficient. Surgery has also been indicated in chronic recurrent cases but with its obvious disadvantages. BT injections in lateral pterygoid muscle, though a technique sensitive procedure offers a prolonged and predictable solution to condylar dislocation [101].

## 7. SUMMARY

The purpose of this review was to determine the efficacy and usefulness of BT in various disorders of the perioral region. Substantial

scientific evidence supported many applications of BT in oro-mandibular disorders. Still, the available evidence and reported cases do not make a compelling story for its routine use and high level of efficacy in dentistry. The potential use and effectiveness and a number of other issues such as dose, site of injection, etc of BT in orofacial disorders is still open for discussion. Since the use is not labelled or approved yet by FDA, patient's consent is mandatory prior to its administration for oro-dental purpose. Off label drug use bears a legal liability on the clinician but FDA does not recognize the use of such drugs as inappropriate. If the practitioners best possible judgement believes that off label use of BT in orofacial disorders is outweighed by the potential benefits to the patient, it can be administered to the patient in context to that particular disease. In such cases the limitations, risks, benefits should be explained to the patient and a consent form should be signed by the patient prior to commencing the treatment. Clinician should also be familiar with reasonable body of scientific evidence supporting BT application specifically for the disorder under treatment. Patients should as well be informed that its effect is transitory and the treatment needs to be repeated to have an ongoing effect. The national institutes of health consensus conference of 1990 has included it as a safe and effective therapy for non-labeled uses [102].

As explained earlier the therapeutic action of BT is partial chemical denervation of the muscle resulting in muscle paresis. Onset of paralysis is seen within 6 hrs of drug administration and the clinical effects are apparent within 24-72 hrs [103]. Recovery is in response to the growth factor secreted by the paralysed muscle which cause the sprouting from poisoned pre synaptic axon and regeneration of new neuromuscular junctions. The process of recovery takes about 90 days after BT injection. However, with repeated exposure to BT, the process of recovery takes progressively longer time. When BT is given over a period of time actual muscle atrophy can occur [1].

Botulinum toxin cannot be considered curative but a palliative and symptomatic approach to treat a disorder. It can be used as a sole therapy or as an adjunct to medication or surgery. Till date most of the reports relate to BT-A with few well controlled and planned randomized controlled trials. BT-A is available in vials in lyophilized form. Each vial contains 100 units (U) of botulinum neurotoxin and .5 mg of human albumin in sterile vacuum dried form without preservatives. One unit corresponds to the calculated median intra peritoneal lethal dose required to kill 50% (LD 50) of a group of 18-20 g female Swiss- Webster mice. In humans, LD 50 is estimated to be 40 U/kg i.e. about 2800 U in a 70 kg adult [104]. Maximal dose recommended for a dental application is not more than 100 U. It means at least 28 vials of Botox have to be injected to achieve a potentially lethal outcome in humans. Lethal dose and clinical dose has a huge disproportion, thus a fatal outcome is next to impossible.

The typical date of expiry is one year when stored at -5 to -20℃. Adding preservative free .9% saline solution under manufacturer's guidelines makes the injection and it has to be consumed within 4 hours when stored at 2-8℃. 1.0 ml tuberculin syringe with needle between 26-30 gauge is the preferred syringe. In contrast BT-B does not require reconstitution before use. It retains the potency for 9 months at 25℃ and for 3 years at refrigerated temperatures(2-8℃) [105] .BT is marketed worldwide in the name of Botox (Allergan, Inc. Irvine, CA, USA.) and in Europe as Dysport (Speywood Pharmaceuticals Ltd. Maidenhead, U.K.). Another BT-A is marketed from Germany in the name of Xeomin which is equipotent to Botox. BT-B is marketed under the trade name of Myobloc (Elan Pharmaceuticals, U.S.A.) and NeuroBloc (Soltice Neurosciences Inc., Europe).

Localised side effects upon BT injections include edema, pain and ecchymosis at the site of injection, headache, malaise and dry mouth [105,106]. Other side effects reported are hoarseness of voice, dysphagia, transient unintended muscle paralysis, slurred speech (in case of patients who had injection in palatal muscles or lateral pterygoid). There are no reports of severe life threatening complications after use in head and neck region. BT is a category C drug as its reported use in pregnant and lactating woman is scant. About 1% of patients who receive BT therapy experience severe debilitating headache which may persist for two to four weeks before fading away [107]. Upon receiving higher doses especially at frequent intervals about 5-10% of patients may develop antibodies which contributes to resistance [108]. Therefore FDA recommends using as lowest effective dose as possible, no more frequently than once in three months.

BT has potential drug interactions with medications. Drugs which interfere with neuromuscular transmission such as, amino-

glycosides, succinylcholine chloride, cyclosporine, polymixins, anticholinesterase, quinidine and curare-like non depolarizing blockers can potentiate the effect of BT [106,109-111]. It should not be used in pregnant and lactating mothers, patients with known sensitivity to albumin or any other ingredient in the formulation and patients with neuromuscular junction disorders e.g. myasthenia gravis. BT therapy is contraindicated in the presence of infection.

## 8. CONCLUSION

Potential applications of BT extend beyond cosmesis. Excellent therapeutic results of BT in medicine has drawn its course towards dentistry. Though off label BT is a superior treatment modality than the conventional ones in many morbid conditions of orofacial region. In this era of evidence based dentistry a skilled clinician must not diagnose and treat any disease based on anecdotal lore or frivolous experimentation but on the firm understanding of pathophysiology of disease, underlying anatomy, pharmacology of drug and substantial literature supporting the treatment protocol. BT injections in the predetermined sites is a novel, transitory and minimally invasive approach in treating many orofacial maladies which are refractory to conventional pharmacological and surgical interventions.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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