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Botulinum toxin, a new Paradigm in maxillofacial disorders – a review

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Abstract

In this era of passion to look beautiful, various new technologies are emerging to enhance and improve the physical appearance of people. Botox has emerged as one such popular treatment to improve various facial anomalies. Unquestionably the Botox and dermal fillers are recognized for their esthetic results with regard to smooth skin and replacing lost volume in face, particularly the oral and perioral areas. The Botox is a minimal invasive technique and may prove out to be an attractive alternative to Surgery in some cases.

A variety of factors, such as stress, hormones, diet, drugs, trauma, and certain neuromuscular diseases, can lead to an increase in sympathetic muscle tone, which results in masticatory muscle hypertonicity and parafunction. Dentists have traditionally attempted to treat and prevent these diseases with methods that are expensive, risky, irreversible, and not evidence-based. There is an absolute need for a noninvasive, reversible, conservative treatment which is quick, easy, relatively inexpensive, long acting, and effective. Botulinum toxin is a natural protein that is one of the most efficacious biological substances which is commonly used. Masticatory muscle relaxation can be

reliably achieved by injecting measured doses of botulinum toxin into specific sites in the major muscles of mastication. A reduction in dystonia and pain with optimization of function is easily achievable with a site- and dose-specific injection protocol. This review focuses on the application of Botox in dentistry. The aim of this paper is to discuss the healing aspect of this dangerous toxin.

Keywords: Botulinum toxin, Maxillofacial disorders, dentistry.

Introduction

The botulinum toxin (BOTOX) was conceived for medical and therapeutic uses for the first time by a German physician Justinus Kerner (1786-1862). Later in 1895 the bacterium was isolated by Emile Van Ermengem. Finally the toxin was isolated in 1944. There are seven reported serotypes (A-G) of the toxin and each responds to a specific antibody.[1] The seven distinct serotypes namely A, B, C, D, E, F and G, all these vary in their potency, plasma half life, and cellular target sites.[2,3] Alan B. Scott, in 1973 found its clinical use in the management of temporary paralysis of musculature and located its mechanism that lead to its development for therapeutic use.[1]

BTX-A is marketed worldwide under the name Botox (Allergan Inc, Irvine, CA, USA), and in

Europe as Dysport® (Speywood Pharmaceuticals Ltd, Maidenhead, UK). It has been approved by the US Food and Drug Administration (FDA) for therapeutic use in the treatment of strabismus, blepharospasm,[4] focal spasms including hemifacial spasm,[5] cosmetic correction for the facial glabellar lines.[6] Recently in 2000, BTX-B (Myobloc) was approved by the FDA for the treatment of cervical dystonia. BTX-E and BTX-F is used Particularly for those patients who are resistant to A and B secondary to clinical resistance or antibody formation.[1]

Botox was most commonly used as a therapeutic modality for achieving cosmetic results, but recently the therapeutic uses have been globalized far beyond cosmetic applications, including facial dystonias, spasticity, salivary flow, nondystonic disorder of involuntary muscle activity, smooth muscle hyperactive disorders, sweating disorders, fistula treatment and temporomandibular disorders.[7,8,9,10,11,12,13,14,15]

Mechanism of Action

The exocytosis of acetyl choline (Ach) on the cholinergic nerve endings of motor nerves is inhibited by the Botulinum toxin (BoNTA). It also affects the autonomic nerves by inhibiting the release at neural junction in the glands and smooth muscle. This activity of botulinum toxin is achieved by its endopeptidase activity against Snare proteins, which are 25-kd synaptosomal-associated proteins, which are required for the docking of the Ach vesicle to the presynaptic membrane.[16]

On intramuscular administration of Botox at therapeutic doses, it results in limited extent of chemical denervation of the muscle leading to localized decrease in muscle activity. In addition to this, the muscle atrophy may be observed; it may also result in axonal sprouting, and development of extrajunctional acetylcholine receptors. It has also been evidenced that the reinnervation of the muscle may occur, thus gradually reversing muscle denervation produced by Botox. On intradermal administration, Botox produces a reduction in sweating in a local area secondary to transient chemical denervation of the sweat gland.[17]

Preparation

The botulinum toxin is produced by the Gram-negative anaerobic bacterium Clostridium botulinum. Usually it is harvested from the culture medium after fermentation where the toxin producing strain of C. Botulinum undergoes lysis and liberates the toxin. Then the toxin is

extracted, precipitated, purified, and thereafter crystallized with ammonium sulfate. In the present form, BTX-A should be preserved in a refrigerator but in an unfrozen form. BTX-A should be diluted with saline that should be free of preservatives and the reconstituted preparation should be used within 4 hours. In solution the toxin is stable at a pH of 4.2–6.8 and temperature less than 20°C. The larger molecules of the toxin is very fragile and is easily inactivated in solution by shaking.[18]

General Applications of Botulinum toxin

Botulinum toxin has been effectively used in the Treatment of overactive bladder, urinary incontinence due to detrusor over activity associated with a neurologic conditions, as a prophylactic drug in the treatment of chronic migraine, cervical dystonia, upper limb spasticity affecting adult patients, inadequately managed severe cases of axillary hyperhidrosis by topical agents in adult patients, blepharospasm, and in strabismus.[11,17,19]

Applications of Botulinum toxin in Dentistry

Sialorrhoea

Sialorrhea or excessive salivation, and drooling are common and disabling manifestations in different neurological disorders such as Parkinson's disease and cerebral palsy. A handful of Randomized controlled studies have proved the effectiveness of Botox injections to the salivary glands in patients with Sialorrhoea.[20,21,22] It has been reported by Jongerius *et al*. that 51-63% reduction in salivary flow rate from the combined sublingual and submandibular glands in three of the four cases.[23]

Temporomandibular joint disorders

Most of the time the lateral pterygoid muscle spasm may affect temporomandibular joint (TMJ) by displacing the articular disc anteriorly which results in severe pain and clicking. Many RCTs have proved the effectiveness of Botox in the treatment of such TMJ disorders.[24,25,26]

A "fixed smile" has been observed following administration of the Botox to lateral pterygoid muscles because of the diffusion of the Botox in the superficial facial muscles. [12]

BT can be a useful adjunct in treating TMDs particularly in cases involving muscular hyperactivity when other modalities have failed to provide adequate relief. The route of administration can be through intraoral or transcutaneous route, depending upon the anatomic location of the targeted muscle. In case of superficial muscles, masseter and temporalis can be palpated extraorally and injected externally based on the anatomic landmarks. The dose of Botox Type A varies from 10-50 U per site with a maximum of 200 U being injected in the masticatory system. This dose can be increased up to a maximum of 400 U when other sites in the head and neck are considered in the injection protocol.[27,28]

Gummy smile

Gummy smile or gingival smile can be defined as the excess of gingival tissue that is displayed superior to the maxillary front teeth upon full smile. Many terminologies are used to describe it which includes – Gummy smile, high lip line and full denture smile.[29] This can be treated by keeping the levator labii superioris aleque nasi muscle as target sites. This muscle may be identified by asking the patient to move the tip of his nose. Injection of between 1 and 3 units of botox at superior medial naso-labial fold result in relaxation of this muscle. Without a proper elevation of this muscle, the upper lip position is lowered sufficiently to cover the crown portion of the teeth during smile.

Improvement of the affected area may be augmented with materials like fillers which reduces the prominent superior naso-labial folds. The "downturned smile" can misinterpret emotions, presenting a sad or concerned appearance. This may be corrected with injecting BT into

posterior aspect of the depressor anguli oris muscle. The zygomaticus muscle will be allowed to act unopposed by elevating the corners of the mouth in a favourable, horizontal position by the Botox injection.[30]

The affected muscle is selected for injecting by palpating the jaw line as the patient frowns or pulls down the corners of the mouth and the average dose of botox is between 3 and 5 units per side.

Myofacial Pain and Neck Pain

The myofacial pain syndrome is a complex disorder the etiology of which is incompletely understood. It was believed that it can be a result of a micro trauma or a macro trauma causing muscle overload. The pain can get aggravated on touching the trigger points which is characterized by localized tenderness and often may result in referred pain to distant sites and disturb motor function. The injection of Botox to these muscles have been proved to be effective for myofacial pain caused by trigger points.[31] Jennifer Warner, conducted a study involving patients who reported with chronic neck pain, and found that the injection to be effective after administering Botox at the affected site in the neck muscle in combination with regular physiotherapy.[32]

Bruxism

Bruxism is a condition characterized by a diurnal or nocturnal activity that consists of clenching, grinding, bracing and gnashing of the teeth.[33] Bruxism can be described as a nocturnal non-functional contact of the mandibular and maxillary teeth that result in clenching or tooth grinding secondary to repetitive, unconscious contraction of masticatory muscles particularly the masseter and temporalis muscles.[34] The definite prevalence is not known, but it is probably much more common than thought. It is believed that vast majority of patients who have bruxism probably never seek medical attention and the disorder is often misdiagnosed as TMJ (temporomandibular joint) syndrome, Even though the TMJ disorder may occur as a secondary complication of bruxism.[33]

A RCT involving 30 patients has proved the efficacy of Botox injection in relieving the symptoms of myofacial pain in chronic bruxer patients in comparison with control patients receiving saline placebo injections[24] with a second one currently underway.[35] In an open trial, Tan and Jankovic[36] studied 18 subjects with severe bruxism and were administered with a total number of 241 BTX-A injections in the masseter muscles during subsequent 123 treatment visits.

On a single side the Botox A dose ranged from 25-100 MU with a mean dose of 61.7± 11.1 U per masseter muscle. The mean value of total duration of response was 19.1 ± 17.0 weeks (range 6 – 78), and the peak effect ranged from scale of 0 to 4 (where 4 indicates total abolishment of grinding) with a mean peak effect of 3.4 ± 0.9.

Masseteric Hypertrophy

Masseter muscle hypertrophy can be described as an asymptomatic perpetual enlargement involving unilateral or bilateral masseter muscles, secondary to clenching teeth, bruxing, substantial gum chewing and frequently seen in younger individuals. With the advancing age with resultant dental deterioration, pre-existing Masseter muscle hypertrophy tends to recede as there is an inability to fully activate the masseters. With Masseter muscle hypertrophy, the patient's face takes a typical rectangular configuration.[37,38]

Injection of botulinum toxin type A in to the masseter muscle is an alternative treatment modality used other than surgery, since the Botulinum toxin type A injection is reported to be safe and effective treatment modality. By virtue of its interference with the neurotransmitter

mechanism it results in selective paralysis and subsequent atrophy of muscle.[39,40,41,42,43,43,44]

Oromandibular dystonia

Oromandibular dystonia (OMD) can be defined as an involuntary spasms of masticatory, lingual and pharyngeal muscles.The Oromandibular Dystinia can be of six types of: jaw closing dystonia (JCD), jaw opening dystonia (JOD), jaw deviation dystonia (JDD), lip and perioral dystonia, lingual dystonia, pharyngeal dystonia, and combination OMD. This condition is characterized by unconditioned, action-induced, tonic or clonic spasms of the muscles of mastication, tongue and the pharynx. Symptoms include dysphagia, dysarthria, bruxism and tempomandibular joint subluxation. There are case series and case reports[45,46,47] proved the favorable effects of Botox injections into muscles of mastication particularly the lateral pterygoid, anterior belly of digastric, masseter and temporalis muscles.

Brin et al.[48] conducted a study with 96 patients having OMD. Onset of OMD was in the 4th decade. In over 70% of patients the cause was found to be idiopathic. Response of the treatment was rated by a subjective “linear” scale, where, the subjects were asked to assess their percent normal function from 0 – 100%. All muscles associated with jaw motion were considered for injection. In all muscle movement categories, patient’s function improved by 30% of normal function to about 74% following BTX-A treatment.

Tongue protrusion dystonia (TPD)

TPD usually results in defective speech and chewing. It is most commonly observed in patients with tardive dystonia and in primary (idiopathic) cranial dystonia. The lingual dystonia is also typically present in patients with neuroacanthocytosis.[49] Gelb et al. conducted a study involving 13 patients with TPD[50] and they injected Botox to genioglossus and hypoglossus with an average dose of 18.3 U (range 10 – 27) and it was observed that there was an improvement in function from 32 to 76% of normal function and the effect lasted 11.2 ± 1.9 weeks. The injection of botox was associated with certain adverse effects observed in 38.5% of patients. Five patients developed dysarthria and dysphagia, which required a change in routine diet; one patient had aspiration pneumonia.

Palatal and stapedius myoclonus

Palatal myoclonus is a condition characterized by involuntary contraction of the soft palate muscles over the membranous Eustachian tube, causing clicking tinnitus. Similarly, contraction of stapedius muscle can cause clicking tinnitus and the condition is termed as stapedius myoclonus. It has been reported in two case reports consisted of each type of myoclonus, it was found that the Botox injections were effective in reducing the symptoms.[45] The site of injection for palatal myoclonus was in the soft palate done under EMG guidance[51] and for stapedius myoclonus, Botox can be administered trans-tympanically into the middle ear with a piece of gelfoam.[52] In the latter case, the favorable effects of Botox lasted for about four months.

Hemifacial spasm

It can be described as involuntary movements involving muscles of facial expression supplied by facial nerve which is unilateral in occurrence. The most common cause is compression of the facial nerve near its origin by an aberrant branch of the posterior inferior cerebellar Artery.[53] It was studied for the first time in 1986 to assess the effect of Botox in hemifacial spasm.[54] Since then, there have been several studies which have proved Botox as an effective and safe treatment option.[55]

Facial nerve paresis

Botox may be used to induce therapeutic ptosis in acute stages of facial nerve paresis to protect the cornea. This is

achieved by transcutaneous injection into the levator palpebrae superioris and Mueller's muscle. There are two case series reported in the literature, of which one case series comprised of 3 patients and another case series composed of 10 patients who were administered with Botox which showed beneficial effects in preventing damage and improving healing of the cornea.[56,57,45] In addition, there is another series of cases involving 30 patients showed the effectiveness of Botox in reducing synkinesis in divergent facial nerve regeneration succeeding facial nerve paresis.[58] Among these 30 patients, botox injection was administered to multiple synkinetic muscles in patients having facial nerve paresis showed marked improvement following treatment. [45]

Blepharospasm

Blepharospasm can be defined as an Involuntary contraction involving eyelid muscles commonly occurs bilaterally involving patients in the age group of 60 years and above. The orbicularis oculi muscle is most frequently affected, followed by the upper facial muscles. The therapeutic application of Botox injection in blepharospasm was described for the first of its kind in 1985[59] and since then it has become the treatment of choice.[60] It was observed in a Cochrane systematic review that the use of placebo (saline) to prove the efficacy of Botox was considered unethical because of the high effectiveness and advantages of Botox in managing Blepharospasm.[61]

Maxillofacial fracture treatment

The maxillofacial fracture management requires multiple fixation sites with arch bars, wiring, plates and screws. These are placed to stabilize the fractured fragments to overcome the strong forces of masticatory musculature. These masticatory muscle forces can hinder the formation of the callus formation. The prophylactic injection of the Botox to the muscles of mastication can be used to allow the fractured bones to heal in a more stable condition. The intensity of the para functional clenching can be potentially limited by a low dose of Botox which allows the traumatized structures to heal. High doses of Botox can be used as a ''pharmaceutical splint,'' limiting muscle contraction prior to resetting and at the time of rehabilitation after in treating fractured facial bone, e.g., fractured mandibular condyle.[62,63,64]

Dental Implants

It has been proved that the Implant patients have been benefited from pre surgical Botox treatment. Following placement of multiple implants or immediate implants the osseo-integration is hindered by the excessive function and parafunctional forces. These forces results in loosening of the implants by impeding osseo-integration resulting in implant failure. In such cases, prophylactic injection of the Botox may cause relaxation of the muscles of mastication and allowing the implants for better osseo-integration.[62,63]

First bite syndrome

The development of pain in the facial region soon after the first bite of each meal commonly seen following surgical procedures involving the parapharyngeal space, particulary deep lobe parotidectomy is referred to as First bite syndrome.[65] This occurs secondary to autonomic dysfunction of salivary myoepithelial cells. Intraparotid injection of Botox injection was found to be very effective in significantly reducing the symptom severity in a case series as reported by Ali MJ et al in five patients.[66]

Tetanus induced rigidity and spasms

Trismus and dysphagia are commonly seen early symptoms of tetanus. The symptoms of tetanus might be generalized and cephalic. This may result in major hazards to the patient, notwithstanding of the threats of either respiratory failure or autonomic dysfunction. In these patients who cannot swallow normally, normal salivation

can result in aspiration and results in pneumonia.[67] Many case series have been reported about the use of botulinum toxin in the treatment of symptoms of tetanus. Treating trismus using Botox is reasonably a safe procedure if it is administered to masseter and temporalis muscles without jeopardizing the adjacent vital structures. Otherwise these injections can result in compliations secondary to spread of these toxins locally. In comparison to the tetanus toxin, botox has limited axonal and transsynaptic transport. Thus the botox effects are limited to the lower motor neuron terminals which inhibit acetyl choline release and voluntary muscle activation. This action of botox play a major role in lowering the hyperactivity of the muscle in tetanus patients.[68] Along with the above function, botox also reduces the need for muscle relaxant drugs that effect consciousness,[69] and also reduces long lasting effect of botox (>3 months).[70]

In Nasal Aesthetic Procedures

With the invention of numerous safe materials, many esthetic areas in facial region are manages with minimal invasive procedures. Among these esthetic areas Nose has been an area of interest from the ancient times.[71]. The rhinoplasty procedure with little or minimum invasive technique that depends on two basic things,

1. By controlling the depressor septi nasi and levator labii alaeque nasi muscle activity that results in rotation and dropping of the nose by Administration of botulinum toxin A (BTxA) along the muscle insertion superior to columella and in the nasal spine. For this 2–4 U Vistabel/Bocouture or 10 U Azzalure was injected by Redaelli A et in their case and advised to inject
2. Use of absorbable fillers that improves the profile of the nose and aging.
3. It was also suggested that, for proper results it is better to wait for 7 to 15 days and if further improvement is required a second injection can be administered after 15 days.[72]

Conclusion

Botox is an emerging attractive treatment option in comparison to many surgical alternatives in the maxillofacial pathologies. This treatment modality can be used as an effective, non invasive tool to wadd the armamentarium in the management of conditions like masticatory and other pericranial muscular disorders. The effectiveness of the botulinum toxin in restoring function, esthetics and controlling the symptoms of masticatory muscle hypertonicity has been proved by many studies. If used carefully by taking proper training and safety measures this treatment modality will surely take dental profession to one step ahead in the field of progress.

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