

Review Article

The Varied Therapeutic Use of Botulinum Toxin in Oral and Maxillofacial Surgery

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ABSTRACT

It is astonishing that Botulinum toxin (BTX), one of the most lethal biological toxins known to man is proving to have escalating therapeutic worth. It has a wide range of remedial and cosmetic application and is a minimally invasive technique.

Its mechanism of inhibiting acetylcholine release at neuromuscular junctions following local injection is distinctive for the treatment of facial wrinkles. Other dose-dependent anti-neuroinflammatory effects and vascular modulating properties have expanded its spectrum of applications. Conditions such as temporomandibular joint disorders, headache, sialorrhea, neuropathic facial pain, muscle movement disorders, and facial nerve palsy could also be treated with this drug. Further applications of BTX are likely to be developed.

This paper reviews the established and emerging applications of BTX in the field of oral and maxillofacial surgery and its usage in non-cosmetic conditions .It intends to dispel some myths on Botox and increase awareness of its usefulness, considering its journey as the most dreaded toxin to a miraculous drug.

Introduction

Purified botulinum toxin (BTX), a potent neurotoxin produced by the bacterium Clostridium botulinum has been established as the first bacterial toxin widely studied and successfully used for therapeutic purposes. Botulinum toxin was known as a "sausage poison" and "fatty poison", because the bacterium that produces the toxin often caused poisoning by growing in improperly handled or prepared meat products. Botox was considered one of the most potent naturally occurring biological poisons and in the past has been

responsible for many accidental deaths prior to its discovery in medicine It was Kerner, a physician, who first conceived a possible therapeutic use of botulinum toxin.¹

1. BTX has gained widespread popularity as an alternative to cosmetic surgery .This drug is now the treatment of choice for hyperkinetic lines in the upper and lower face as well as in the aesthetic management of patients with asymmetry from stroke and Bell's palsy. BTX is, however, also quickly becoming recognized as a valuable diagnostic and therapeutic

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tool for pain and dysfunction. The exponential expansion of its use in wide range of medical and surgical conditions has been aided by understanding of its physiology along with improved efficacy and safety.

Mechanism of action

BTX induces temporary chemical denervation of skeletal muscle by blocking the Ca²⁺-mediated release of acetylcholine from nerve endings of alpha and gamma motor neurons (myoneural junction), producing a transient dose dependent weakening of the muscle activity rendering it nonfunctional without systemic effects.² This property of producing profound but reversible muscular relaxation has made it a unique tool for the diagnosis and treatment of muscle-related disorders. The inhibition of muscular contraction is believed to be followed by the sprouting of new axon terminals, which results in synaptic regeneration and the reestablishment of neuromuscular transmission. Clinical effect lasts about 2-6 months and then resolve. Recovery occurs through formation of new nerve terminals and regeneration of the original neuromuscular junction takes place.³ Recovery of inactivated terminals appears to be the basis of the loss of clinical effect several months after injection.

There are seven distinct serotypes, A, B, C, D, E, F and G, which differ in their potency, duration of action, and cellular target sites. Three forms of botulinum toxin type A (Botox, Dysport and Xeomin) and one form of botulinum toxin type B (MyoBloc) are available commercially for various cosmetic and medical procedures. Studies contrasting the cosmetic efficacies of BTX-A and BTX-B account that the latter causes more pain during injection, has shorter action and probably a less predictable diffusion pattern.^{4,5}

BTX-B could be useful in situations in which rapid onset is desirable or in which there are concerns about antibody production to BTX-A.^{6,7,8}

Cosmetic use of BTX for facial rhytids and dynamic lines in maxillofacial surgical practice, was first reported by Niamtu in 1999⁶. This was followed by its extensive use for lateral canthal lines (crow's feet), orbicularis oris injection, masseter muscle injection and the treatment of temporomandibular disorders (TMDs). The use of BTX in cosmetic facial procedures has already been established as a reliable way to enhance aesthetics in the upper and lower face comprising the treatment of glabellar lines, the frontalis muscle, peri-orbital lines, gummy smile and masseter muscle hypertrophy.^{9,10,11} Its use in non-surgical facial cosmetic procedures produces high rates of improvement with rapid onset and long duration of action (longer than 4 months for some patients) with widespread acceptance of the technique.^{12,13}

BTX has gradually evolved from venom to a versatile clinical tool for various conditions resulting from muscular hyperfunction. Most recently, it has been increasingly employed as a therapeutic remedy for head and neck region, including focal dystonias, vocal tics and stuttering, cricopharyngeal achalasia, various manifestations of tremor, hemifacial spasm, sialorrhea, hyperhidrosis, headache, temporomandibular joint dysfunction, bruxism, and masticatory myalgias.^{14,15} It is also used in dental implantology aiming at the prophylactic reduction of masseter and temporalis muscle strength after implantation in immediate load protocols¹⁶

Temporomandibular disorders

Numerous reports on BTX-A treatment for TMJ disorders have dealt with TMJ and masticatory muscle pain^{17,18}, reduced jaw opening capacity^{19,20}, masticatory hyperactivity and recurrent TMJ dislocations^{21,22,23}

Temporomandibular disorders (TMDs) are considered the chief cause of pain in Orofacial region and may be divided into those related to the muscles acting on the joint (myofascial) and those related to the joint itself (arthrogenic)²⁴. Frequent symptoms of TMD include Joint noise, pain and a restricted range of mandibular motion²⁵. Focusing treatment towards the muscular component of TMD, which in some patients can be acknowledged as non-spastic clenching or bruxism, could deliver significant therapeutic gains.

Studies have cited that displacement of the articular disc may be attributable to lateral pterygoid activity or friction between the articular surfaces of the disc and condyle causing clicking.^{26, 27} BTX injection into the lateral pterygoid muscle has effectively reduced the clicking associated with TMD along with distinctive positional improvement in the disc-condyle relationship.²⁸

Bruxism is severe, rhythmic grinding often allied with headache, masseter hypertrophy, dysarthria, TMJ destruction and dental wear. Various studies have illustrated the treatment of bruxism with BTX. Injections of BTX-A into the flexor muscles of the mandible have been found to produce subjective and objective reductions in muscular voluntary contraction in most subjects. Studies have revealed BTX as efficacious in relieving myofascial pain symptoms in bruxers when contrasted with control patients who received saline placebo injections²⁹

When used as an adjunct to arthrocentesis of TMJ in chronic cases of internal derangement, intramuscular injection of BTX have given encouraging results with marked relief in discomfort and dysfunction.¹⁷

The anterior displacement of condyle beyond the articular eminence leads to TMJ dislocation. Several anecdotal reports are suggestive of the use of BTX-A as treatment for TMJ dislocation, but a controlled clinical trial is yet to prove evidence of its efficacy.³⁰ It is specifically indicated in patients for whom conservative treatment of recurrent dislocation of the TMJ has failed and for whom surgery carries major risks. Though the muscle selected varies with each case, but the lateral pterygoid has been commonly reported. Treating the lateral pterygoid muscle seems to be sufficient to prevent temporarily recurrent dislocation of the TMJ, but, in some reports, the superficial part of the masseter at the angle of the mandible was also injected. An increase in verbalization, mastication and improved quality of life has been reported with BTX treatment in cases of protracted TMJ dislocation following medical conditions such as anoxic encephalopathy and stroke or cerebrovascular event.^{27,30}

Peripheral and central mechanisms may be variably involved in the propagation of chronic myofascial pain in TMD³¹. Abridged subjective pain and tenderness has been observed with injection of BTX-A into the masseter and temporalis muscles of patients with TMD. BTX is believed to have a presumed action on nociceptors and restrains specific protein-receptor binding within the intracellular compartment on the release of neuropeptides and inflammatory molecules including calcitonin gene-related peptide, and glutamate.³² Some degree of improvement in the maximal range of vertical motion owing to muscular

relaxation and reduction of inflammation after BTX therapy has been experienced in patients with restricted mouth opening.³³

Random clinical trials have documented BTX to be more effectual than placebo (saline) in reducing masticatory myalgia. Masticatory myalgia can be explicated by chronic nociceptive irritation of the tendons and fascias of the temporalis ,masseter, and medial pterygoid muscle. Evaluation with EMG the action potentials of the masseter and temporalis muscles demonstrated that these decreased by nearly 80% on day 14, and by 25% on day 28 following Botox injection³⁴. Disuse atrophy of the affected muscle is caused by injections of BTX leading to relief in tension, along with improvement in aerobic metabolism. This facilitates decompression of afferent nociceptive neurons with diminution of substance P-mediated neurogenic inflammation.^{34,35}

Salivary secretory disorders

BTX has an inhibitory action on cholinergic receptors of salivary gland cells, hence making it effectively therapeutic in salivary secretory disorders. Transient efficacy for about 3-4 months has been observed with Topical injection of BTX-A for the treatment of drooling in neurological diseases and sialorrhea.^{36,37,38}

Pilot studies have reported promising and favourable outcomes of BTX-A in the treatment of drooling in upto two-thirds of patients after the treatment of both parotid and submandibular glands.^{36,37}

BTX has been effectual for sialorrhea in Parkinson's disease, cerebral palsy and carcinoma of the upper digestive tract. Its applicability can be appreciated in accumulated saliva and drooling caused by swallowing disorders after tumor operations of the upper aero

digestive tract. It has been strongly recommended for use where the temporary stopping of glandular secretory action is imperative to promote healing.^{36,37,38}

Intracutaneous injection of BTX-A has been a highly reliable treatment modality for auriculotemporal (Frey's) syndrome. It markedly diminishes the skin area affected by gustatory sweating as it inhibits the sweat glands that are abnormally re-innervated by the cholinergic pathway. A single course of injection is believed to produce symptomatic relief with long lasting therapeutic effects.³⁹

Facial nerve palsy (FNP)

Studies have relieved successful use of BTX in various aspects of FNP. It serves as a good means of inducing a protective ptosis ,though an orbital or skin crease by temporarily paralyzing the levator palpebrae superioris and Mueller's muscle . This prevents desiccation of cornea in intensive care patients. Chemo-denervation of the normal side of the face can be attempted in patients with facial asymmetry. BTX reduces the relative hyperkinesis of the contralateral side and thus serves as a disguising tool with a more symmetrical function of the face.⁴⁰

Subsequent to aberrant regeneration, Synkinesis occurs which is an involuntary uncoordinated muscle movement associated with voluntary movement of the muscle. BTX-A is frequently used to relieve the symptoms of synkinesis with marked improvement.^{41,42}

Consequent to facial palsy an anomalous connection may occur in between salivary motor fibres and fibres of the lacrimal gland causing hyperlacrimation whenever the

patient salivates (crocodile tears). Injection of BTX-A in lacrimal gland serves as a remedial means in such cases.

Other nerve palsies

There have been reports of proficient use of BTX in third-nerve palsy in adults and children following trauma. It is injected to the lateral rectus muscle, lessening its probability of contracture, thus allowing return of medial rectus muscle function.⁴³

Muscle movement disorders

BTX-A injections have been accepted as a minimally invasive and effective local treatment for muscle spasms and dystonia. Dystonia is a neurologic disorder postulated to be a condition of central motor processing disorder characterised by abnormal and involuntary muscle movements. Dystonia's can affect many different parts of the body and may include symptoms such as muscle weakness, abnormal or involuntary movements, cramps, dysphasia, tremor, and shortened muscle/tendon lengths. Diverse studies cite its usefulness in the treatment of oromandibular dystonia^{44,45}, cervical dystonia^{46,47} (spasmodic torticollis) and hemifacial spasms.⁴⁸ Oromandibular dystonia is characterized by involuntary, tonic or clonic spasms of the masticatory, lingual and pharyngeal musculature. Symptoms include dysarthria, dysphagia, bruxism and temporomandibular joint subluxation. Owing to encouraging effects of BTX injections into the lateral pterygoid, anterior belly of digastric, masseter and temporalis muscles, favourable results have been associated with this disorder.^{44,45} BTX also serves as a flattering therapeutic option in hyperkinesias of the platysma.

Orofacial Pain

Botox can be used as a prophylactic therapy for migraine and trigeminal neuralgia as supported by numerous multicentre double-blind placebo-controlled trials. The technique involves injections into muscles innervated by the facial or trigeminal nerves (e.g. procerus, corrugator, frontalis, temporalis and suboccipital), specific sites of pain distribution or a combination of both. Considerable diminutions from baseline were observed in patients in the Botox trial arm with regard to headache and migraine days, cumulative hours of headache and frequency of moderate/severe headache days. While in trigeminal neuralgia, prior to considering more invasive therapies such as surgery or gamma knife radiosurgery, BTX was found to be effective in combination with pharmacotherapy.^{49,50}

First bite syndrome which is basically development of facial pain after the first bite of each meal usually seen after surgery in the parapharyngeal space, involving deep lobe parotidectomy. The likely cause of it is the autonomic dysfunction of salivary myoepithelial cells. Intraparotid Botox injection have been found to radically decrease symptom severity and improve the patients' quality of life.⁵¹

Perioperative use of botulinum toxins

In maxillofacial surgery, where rigid fixation is not desirable, BTX-A can be used to immobilize muscles following a jaw fracture, thereby reducing the displacing forces on the fracture ends⁵².

Although experimental, some authors have found it effective in reducing the strength of masseter and temporalis muscle in immediate loading protocols of implantation. Henceforth making BTX-A advantageous in osseointegration of dental implants.⁵³

Postoperative involuntary movements in patients with movement disorders may be unfavourable for healing. Improved post operative healing and recovery can be achieved by BTX induced muscle weakening.

Complications

BTX has a wide safety margin with few complications.. Allergy, immunogenicity and local complications have chiefly been associated with cosmetic application of BTX. Owing to high estimated clinical resistance of BTX-A which accounts to 7 per cent , investigations for the use of BTX-B as an alternative therapeutic agent are now being attempted. There have been reports of pain , oedema, ecchymosis and erythema , along with short term hypoesthesia following injections of BTX-A.⁵⁴

Mostly local and relatively mild, complications have been associated with its therapeutic applications. This comprises of pain, erythema, ecchymosis of the region injected, dry eyes, ptosis and lid edema, facial muscle weakness, xerostomia, dizziness, upset stomach, infection etc. There have been rare reports of systemic side effects which include transient weakness, nausea and pruritis and fatigue. Flu-like syndromes for a very brief duration have been reported as well⁵⁵

Potential Therapeutic Uses

Topical formulations of BTX are being considered by investigators for axillary hyperhidrosis

Intradermal BTX injection for treating focal hyperhidrosis of the palms, soles, axillae and facial areas have been proven beneficial.⁵⁶

Vocal tics which produces embarrassing speech is caused by repetitive dyskinetic movements of the laryngeal musculature and it is usually seen in Gille de la Tourette syndrome. Injections of BTX into the

thyroarytenoid muscles intend to reduce the frequency and urge of vocal and motor tics .The efficacy of BTX is promising in this aspect and further research is mandated to assess its ability for its use in vocal tics .⁵⁷ Disorder of speech-motor control is often referred as stuttering or stammering. In such cases, the flow of speech gets interrupted by involuntary repetitions and continuances of words, sounds, syllables along with intermittent involuntary silent pauses. This is ascribed to poor coordination between laryngeal, respiratory, lingual, labial muscles. The application of Intralaryngeal Botox injection aimed at fluency in speech therapy and treating this disorder is still questionable and necessitates further research.⁵⁸

Evidences sustaining the potential use of BTX in improving the appearance of hypertrophic scar have been documented by researchers. It is believed to have the ability to thwart excessive muscle contraction of skin adjacent to keloid. Reports suggestive of its influence on cellular apoptosis and proliferation of cells have been acknowledged⁵⁹.

Conclusion

Botulinum toxin also has several advantages including relatively rare systemic side effects, lack of tissue destruction, graded therapeutic response by dosage adjustment and, above all, high patient acceptance. With ongoing research and extremely gratifying clinical benefits, the spectrum of clinical applications and number of people receiving Botox will definitely enhance.

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