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Research Paper

Use of Botulinum Toxins in Oral and Maxillofacial Surgery

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ABSTRACT *– Botulinum Toxin is a bacterial toxin that can be used as medicine. Clinical applications of BTX have been expanding over the last 30 years .The mechanism of inhibition of acetylcholine release at neuromuscular junctions following local anesthesia injections is specific for the treatment for facial wrinkles. Various conditions such as TMJ disorders , sialorrhea , headache , muscle mobility disorders and various neuropathies can be treated with this drug. Further applications of BTX in the field of oral and maxillofacial surgery are likely to be developed . This article reviews the various applications and provides an overview of the pharmacology , toxicity and preparations of the agent.*

KEYWORDS *- BTX, Temporomandibular Disorders (TMDs)*

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I. INTRODUCTION

Purified botulinum toxin BTX is the first bacterial toxin which was used as medicine. It became quite a significant and versatile drug in the field of medicine after its introduction. BTX is widely used in various cosmetic procedures such as the treatment of facial wrinkles after local injections , but conditions such as TMDs , sialorrhea , facial neuropathy , muscle mobility disorders and facial nerve palsy could also be treated with this drug. Many other indications are under investigation and further applications for BTX are likely to be developed .[1] In the maxillofacial region , most of the studies on BTX are of low quality (noncomparative , non-randomized trials) , but the overall results are promising .In this review , pharmacology , toxicity and different preparations of the agent are given .

HISTORY – The idea of a possible therapeutic use for BTX was first developed by German physician and poet Justinus Kerner (1786-1862) which he named ‘ *SAUSAGE POISON* ‘ . In 1870 , Muller , another German physician , coined the name botulism . The Latin form is *botulus* , which means *sausage* [2] . BTX was firstly manufactured as a biological weapon by many countries in the 20th century.[3] A therapeutic use for botulinum toxin type-A was first studied in primates by Scott et al in 1978.[4] BTX was later introduced for the treatment of strabismus in the 1970s.[5] BTX was used in the treatment of facial wrinkles and aging skin in 1988, but its use on a large scale did not occur until the mid 1990s.[6] During the mid and late 1990s , BTX was used widely for crow’s feet (lateral canthal lines) , platysmal banding, orbicularis oris injections, masseter muscle injections and the treatment of TMDs.Later there were many attempts to use BTX on a widespread scale in treating different conditions in oral and maxillofacial surgery .

BACTERIOLOGY –

Clostridium species bacteria are sporulating , obligate anerobic , Gram positive bacilli. The spores of *C.botulinum* are omnipresent , that are present in huge numbers in the soil and marine sediments globally and are often present in the intestinal tract of domestic grazing animals .[7,8] C.botulinum grows and produces neurotoxin in the anerobic conditions that are frequently involved in the canning or preservation of foods .[9.10] Seven different strains of Clostridium have been described (A , B ,C (1 and 2) , D , E , F and G) and each produces a specific neurotoxin identified by the corresponding letter of the bacterial strain producing it namely BTX –A, -B, -C, -D, -E , -F and –G.[11] Humans can be affected by the toxins of 5 strains (A,B,E,F and G) and are not affected by the toxins of strains C and D . [11] All 7 toxins may potentially cause botulism in humans when they are exposed to high levels. [12] All seven neurotoxins are structurally similar but are immunologically different .[13] There is some serum cross-reactivity among the serotypes , because they share some sequence homology with one another as well as with tetanus toxin.[14]

STRUCTURE AND TOXICITY

The toxins that are produced by clostridia bacteria belong to the category of high molecular weight protein complexes that include 3 key proteins : a 150 kDa toxin , a non-toxin hemagglutinin protein and non toxin non-hemagglutinin protein . The 150 –kDa toxin is composed of a 100-kDa heavy chain and a 50 kDa light chain . Disulfide and noncovalent bonds are present between the heavy and the light chains and both the chains are responsible for neurotoxicity .[11] BTX is the most toxic material known which is 100 x 10^{10} more lethal than sodium cyanide . The estimated human dose of type A toxin lethal to 50 % of an exposed population (the LD 50) is estimated , to be approximately 0.09 – 0.15 µg by IV administration , 0,7-0.9 µg by inhalation and 70 µg by oral administration.[15,16]

MECHANISM OF ACTION

BTX is essentially a protease enzyme that causes transient denervation of skeletal muscle by blocking the calcium mediated release of Acetylcholine from the nerve endings of alpha and gamma motor neurons , producing a temporary dose dependent weakening of the muscle activity rendering it non-functional without systemic effects .[17] This inhibition of muscular contraction is believed to be followed by the sprouting of new axon terminals , which results in synaptic regeneration and the re-establishment of neuromuscular transmission.[18]

The 7 neurotoxins have different specific toxicities [19] , different durations of persistence in nerve cells and different potencies. [20] All serotypes of BTX essentially inhibit acetylcholine release .

The area of flaccidity that is produced may be larger than the area of muscle denervated as a result of postulated paralysis of gamma motor neurons , so the output of the muscle spindles is reduced leading to decreased contraction of the muscles and surrounding sites within the injected muscle .[21] Animal studies have demonstrated that BTX-A diffuses across the fascial planes into the surrounding muscles .[22] The clinical effect occurs approximately within 3-7 days after administration , followed by 1-2 weeks of maximum effect , which then levels off to a moderate plateau until the full nerve recovers within 3 – 6 months.[23]

PREPARATIONS :

BTX-A – The first use of Botox in humans dates back to 1968 when it was used to treat strabismus.[4] In 1991, several batches of BTX –A were purchased by Allergan Inc. and then the agent was given the name BOTOX .[24] Botox has been approved for the management of strabismus , cervical dystonia , blepharospasm and axillary hyperhidrosis. In some of the studies , there are reports of Botox improving the patients' self-perception.[25,26,27] Each vial of Botox contains 5ng of air dried toxin , with 1 unit equal to the median amount required to kill 50 % of female Swiss –Webster mice weighing 18-20 g each after intra-peritoneal injections (LD50)[28,23,24] Each vial contains 500µg of albumin and 900 µg of sodium chloride.[28]

Dysport is another BTX -A product which has been approved for use in cosmetics , which is marketed and sold in many European countries as well as Russia , New Zealand , Mexico, Brazil , Argentina and Vietnam .[25] Each vial contains 12.5ng (500 U) of air dried toxin , 125 µg of albumin and 2.5 mg of lactose .[28] Xeomin , packaged as a freeze dried powder , is a purified BTX-A that is free of accessory complexing proteins found in other BTX-A products.[29] Many studies have found that Botox and Xeomin have similar dose-dependent paralytic effects and minimal diffusion effects on surrounding musculature .[29]PurTox is a purified BTX-A that is undergoing trials to approve its efficacy in some therapeutic uses .[30]

BTX-B – BTX-B is available as Myobloc (Solstice Pharmaceuticals , South San Francisco, CA , USA) and is marketed as Nuerobloc (County Clare , Ireland)[28] Myobloc has shown efficacy in clinical trials for the treatment of various movement disorders since 1995 and was provided by approval by FDA for the management of cervical dystonia and hemifacial spasm in 2001.[31] Myobloc has not received approval for cosmetic purposes in any country .It appears to offer versatility in cosmetic neuroblockade by exhibiting action in patients resistant

to BTX-A products .[32,33] Treatment of patients with cervical dystonia with Botox and Myobloc led to various attempts at equivalency doses in many cosmetic studies but the optimal ratio has not been established .[30]
Studies comparing the cosmetic efficacies of BTX –A and BTX –B report that latter causes more pain during injection , has shorter action and probably a less predictable diffusion pattern .[34,35]

COSMETIC USES – Intra muscular injection of BTX to reduce wrinkles on the face is the most commonly performed procedure in many countries .Used subsequently with the fillers , BTXs allow the practitioner to modify the face through alterations in the dynamics of the facial musculature .The uses of these drugs for hyperkinetic forehead wrinkles and brow furrows belie its range of cosmetic applications .

FACIAL WRINKLES – Glabellar lines , also called *Frown lines* , occur naturally with facial animation , as a result of the pulling of the skin by the underlying musculature , predominantly the procerus muscle and the corrugator supercilii. With aging and chronic activity of the facial musculature , these lines become more prominent.[36] Since the discovery of the cosmetic potential of BTX – A in the 1980's , it has been used temporarily to treat glabellar lines and other hyperfunctional facial lines such as horizontal forehead lines , lateral canthal lines , 'crow's feet ', platysmal banding and perioral lines .[37,38] The technique for injecting BTX is generally simple and most patients tolerate injections without anesthesia quite well , although topical anesthetics are used by practitioners .Many patients treated with topical anesthesia elected not to use it for subsequent treatments.[39]
Multiple injection techniques have been described .Some authors describe a method based on brow position .Others describe a method based on needle angulation and measurements .[40] Botox has only been approved officially for the treatment of glabellar lines , but other uses have shown the same degree of improvement for frontalis and lateral canthal lines region. It has also been used to reduce platysmal banding .[41] Several patients with mentalis wrinkling and lower eyelid orbicularis hypertrophy were treated successfully with Botox injections .[42,6] Some authors have described an improvement in patients with excessive gingival exposure .By weakening the lip elevators , the amount of movement decreases and the patient shows less gingiva on smiling .[43]

MASSETERIC AND TEMPORALIS MUSCLE HYPERTROPHY –
Masseteric hypertrophy usually results from anatomical asymmetry of the jaw, habitual asymmetric use of the jaw , clenching during exercise or sleep , excessive chewing of gum or congenital malformations . The early results of treatment with intramasseter injections of BTX have been quite overwhelming and satisfying to patients , but the effect has not been well quantified . [44]

THERAPEUTIC USES – In the head and neck region, BTX has been evolved as a tool for the management of focal dystonias , vocal ties and stuttering , cricopharyngeal achalasia , various manifestations of tremor , hemifacial spasm , TMJ dysfunction , bruxism , hyperhidrosis and headcahes .[45,1] Recently , it has been reported for clinical use in dental implantology for the prophylactic reduction of masseter and temporalis muscle strength after implantation in immediate load protocols. [46]

TEMPOROMANDIBULAR JOINT USES –

Many reports of BTX- A on the management of TMJ disorders have dealt with TMJ and masticatory muscle pain .[47,48] limited jaw opening capacity [49,50] , recurrent TMJ dislocations [51,52,53] and masticatory hyperactivity [54] .Temporomandibular joint disorder may be categorized as subgroups of musculoskeletal and rheumatologic disorders and may be considered as the major cause of pain in the orofacial region .[55] Joint noise and pain and limited mandibular movement are the most commonly present symptoms of TMD.[56] BTX-A has been quite effective in providing relief to the patients with TMD with a noticeable high specificity and side effects which are well within the tolerable range.[[57] Injections are usually performed under electromyographic and ultrasonic control.[44]

Most of the patients with restricted mouth opening experienced some degree of improvement in mouth opening and the maximum range of vertical motion after administration of BTX . Reduction in inflammation , muscular relaxation and the guarding response to pain may also contribute to this finding .[58] Earlier studies suggested that the displacement of the articular disc may be caused, precipitated or maintained by lateral pterygoid activity or friction between the articular surfaces of the disc and the condyle and causing clicking.[59] BTX injection into the lateral pterygoid muscle has reduced the clicking associated with Temporomandibular Joint.[60]

The term 'BRUXISM' is derived from the greek word *brychein* which means to grind or gnash the teeth .[61] When severe , this rhythmic grinding is associated with headache , hypertrophy of the masseter , dysarthria , TMJ destruction and dental wear . [62] Some authors have found that BTX-A injection into the flexor

muscles of the mandible produced subjective and objective reductions in the power of voluntary muscular contraction in most of the subjects. [58]

Arthrocentesis is a less invasive surgical intervention than open arthrotomy to relieve the discomfort and dysfunction associated with chronic cases of internal derangement of TMJ.[63] Intra muscular injection of BTX as an adjunct to arthocentesis of the TMJ gave encouraging results regarding duration of improvement , suggesting a possible synergy between the two procedures. [47] Dislocation of the TMJ occurs when the mandibular condyle is displaced anteriorly beyond the articular eminence. It represents 3 % of all reported joint dislocations .[64] There have been several reports of the use of BTX –A for the treatment of TMJ dislocation [51] ,but a controlled clinical trial is needed to prove evidence of its efficacy. BTX-A was first used to treat surgical failures and then used as an initial treatment.[65] Treating the lateral pterygoid muscle appears to be sufficient to prevent temporarily recurrent dislocation of the TMJ , [65] but , in some reports , the superficial part of the masseter at the angle of the mandible was also injected . [66] BTX treatment is also an option in the patients who suffer recurrent dislocation of the TMJ as a result of impaired muscle coordination secondary to oromandibular dystonia , neuroleptically induced early and late dyskinesias , epilepsy and brain –stem syndromes . [66] BTX treatment of protracted TMJ dislocation after medical conditions such as anoxic encephalopathy and stroke or cerebrovascular event has also been reported . [67]

SECRETORY SALIVARY DISORDERS –

Xerostomia is one of the first manifestations of botulism that led to the investigation of its application for sialorrhea and drooling .Topical injection of BTX-A as a minimally invasive option for the treatment of drooling has been used for many years in neurological diseases. [68] The therapeutic effect is based on the inhibitory action of the toxin at the cholinergic receptors of the salivary gland cells as per the various animal experiments conducted . [69,70] Only pilot studies with relatively small group of patients are available with a brief follow up . The outcome of using BTX-A in the treatment of drooling after the treatment of both the parotids or parotid and submandibular glands combined .[71] Treatment is primarily targeted at the parotid gland and to minor degree on the submandibular gland. The sublingual gland is seldom injected .[1]

BTX has found its use in the treatment of sialorrhea in Parkinson's disease.[72] , cerebral palsy [73] . It has also been used for accumulation of saliva and the drooling of saliva caused by swallowing disorders after tumor surgeries of the upper aerodigestive tract[74] and for diseases of the glandular tissue such as post traumatic and iatrogenic salivary mucoceles and cysts .[75]It has also been used successfully to treat auriculotemporal (Frey's Syndrome) [76] as it reduces the skin area affected by gustatory sweating by inhibiting the sweat glands abnormally re-innervated by the cholinergic pathway.[77] BTX- A has been also found to be advantageous in temporary drooling states because its effect is only temporary.[78]

FACIAL PAIN –

Chronic facial pain poses a difficult challenge in the management . It requires interdisciplinary consultations and multiple attempts at management with different therapies. BTX therapy has shown some advantage over existing therapies regarding safety and efficacy.[71] Facial pain relief has been reported after treatment by BTX for other conditions such as Regional dystonias[79,80] facial wrinkles [6] and skull base surgery.[71] Several studies have been conducted on the use of BTX –A in conditions such as myofascial pain , migraine , trigeminal neuralgia , bruxism and hemifacial contracture after facial nerve injury .[71]

BTX has given promising results in post operative wound pain including reconstructive facial and oral surgery , conventional and endoscopic sinus surgery ,TMJ surgery and blowout fracture repair.[81] Chronic facial pain following post dental procedures was , however , associated with poor results .[81] Similar results have been obtained with the use of BTX-B.[82]

FACIAL NERVE PALSY –

BTX injection , through an orbital route or a skin crease , provides a good means of inducing a protective ptosis by temporarily paralyzing the levator palpebrae superioris.[83] This intentionally induced ptosis may be useful in intensive care patients to prevent dessication of the cornea .[84] BTX – A is also used commonly to relieve the symptoms of synkinesis with considerable improvement.[85] Aberrant connection of the salivary secretomotor fibers to the fibers of the lacrimal gland may develop after facial palsy , causing hyperlacrimation whenever the patient salivates (crocodile tears syndrome). Injection of BTX into the lacrimal gland is a successful treatment for hyperlacrimation in such cases. [86]

MUSCLE MOVEMENT DISORDERS –

BTX has been in use since 1977 as a therapeutic agent in the treatment of numerous neuromuscular disorders .[18] BTX- A injections are considered to be safe and efficient local treatment for focal dystonia and muscle spasm .[87] Other serotypes have been used with comparable effects .[88] Dystonia refers to the involuntary contraction of specific muscles .Numerous studies recommend the usefulness of BTX therapy in the

treatment of oromandibular dystonia .[89] , cervical dystonia , torticollis [90] , hemifacial spasm.[91] A specific type in this category is hyperkinesia of the platysma. In the literature , data on successful treatment of platysma with BTX are nearly always related to the use for esthetic indications.[92]

PERIOPERATIVE USE OF BOTULINUM TOXINS –

BTX has a role in weakening the muscle and in doing so , improves the post operative recovery and healing . Wound healing improves if the muscles involved are injected with BTX prior to surgery . [93] In maxillofacial surgery , patients undergoing eyelid reconstructive surgery had considerable improvement in wound healing after adjunct treatment with BTX . BTX was found to be better than placebo in the wound healing of facial lacerations requiring surgery .[94]

BTX has also been found to be useful during the initial osseointegration phase for dental implants.This indication is mostly experimental , but some authors have found it to be safe and effective in the prophylactic reduction of masseter and temporalis muscle strength after implantation in immediate loading protocols .[46]

COMPLICATIONS

Botox has a large margin of safety . [24] The most important side effects reported for cosmetic use of BTX include immunogenicity , allergy and local complications .Neutralizing antibodies to BTX –A toxins can lead to loss of treatment effect estimated as high as 7% [98] and BTX-B is being investigated as an alternative therapeutic agent .[98] Adverse effects such as pain, edema , ecchymosis and short-term hypoesthesia may occur after injection of BTX –A .[99]Others have reported adverse events such as headache and perioral muscular palsy.

In therapeutic applications , complications were mostly local and mild such as pain , erythema , dry eyes , mouth droop , facial muscle weakness , trismus , blurred vision , nasal regurgitation, upset stomach , neck weakness , dysarthria , local injuries to carotid arteries and braches of the facial nerve .[89,71,66]
Some adverse effects such as xerostomia and dysphagia are more frequently seen after treatment with BTX-B than BTX-A [100]

KELOID AND HYPERTROPHIC SCAR –

Clinical observations indicate that BTX –A can improve the appearance of hypertrophic scar and inhibits its growth.[95] Evidence supporting the potential use of BTX –A in hypertrophic scar arises from BTX's ability to prevent excessive muscle contraction of the skin near keloid tissue[96] and its reported influence on cellular apoptosis and cellular proliferation .[97]

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