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BOTOX IN THE DENTAL CLINIC? POSSIBLE THERAPEUTIC APPLICATIONS OF THE BOTULISM TOXIN IN DENTAL CONDITIONS

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ABSTRACT:

Botulinum toxin or Botox is a polypeptide protoxin extracted from the bacteria *clostridium botulinum.* It inhibits the release of acetylcholine at the neuromuscular junction, resulting in localized reduction of the muscle activity and glandular secretion. While Botox is widely known as a cosmetic therapy to treat wrinkles, it is used in medicine since 1987 to treat various pathologies including strabismus and blepharospasm. Nowadays, many dentists are using it to manage many muscle-related dental disorders and as an alternative to surgery for perioral esthetic enhancement such as high lip-line.

This study is a literature review regarding the therapeutic applications of Botox in the dental clinic.

Objectives: The main objective was to determine the effectiveness of the therapeutic applications of Botox in dentistry, understanding its mechanism of action, its benefits and limits.

Materials & methods: Studies were searched in PubMed and Google using the following words: Botox / Botulinum toxin / dentistry / Maxillofacial / therapy / therapeutic applications / non cosmetic / head and neck. Only articles from scientific literature, published in the last 10 years, were selected. Articles were entered into Mendeley which advised similar articles, some of which have been included in the study. The focus of this study has been based on a selection restricted to the diseases treated with Botox with the more scientific evidence in the literature and that are the more relevant for dentistry. This selection includes diseases such as Bruxism, TMJ disorders, neuropathic pains, salivary glands disorders.

Results: Botox has been approved by the FDA as a treatment for chronic migraine and sialorrhea. Significant scientific evidences have been found on the efficiency of Botox to

manage bruxism, TMJ disorders, trigeminal neuralgia and Frey syndrome. However, further research is still required to confirm the effectiveness of Botox in certain conditions and to certify its benefits in interdisciplinary dental treatments.

RESUMEN

La toxina botulínica o Botox es una protoxina polipeptídica extraída de la bacteria *clostridium botulinum*. Inhibe la liberación de acetilcolina en la unión neuromuscular, lo que causa una reducción localizada de la actividad muscular y la secreción glandular. Si bien el Botox es ampliamente conocido como una terapia cosmética para tratar las arrugas, se usa en medicina desde 1987 para tratar diversas patologías como el estrabismo y el blefaroespasmo. Hoy en día, muchos dentistas lo utilizan para tratar muchos trastornos dentales relacionados con los músculos y como una alternativa a la cirugía para mejorar la estética perioral, como la línea de labios alta.

Este estudio es una revisión de la literatura sobre las aplicaciones terapéuticas del Botox en la clínica dental.

Objetivos: El objetivo principal fue determinar la efectividad de las aplicaciones terapéuticas del Botox en odontología, entendiendo su mecanismo de acción, sus beneficios y límites.

Materiales y métodos: Los estudios se buscaron en las bases de datos siguientes: PubMed y Google utilizando las siguientes palabras: Botox / Toxina botulínica / odontología / Maxilofacial / terapia / aplicaciones terapéuticas / no cosmético / cabeza y cuello. Solo se seleccionaron artículos de la literatura científica, publicados en los últimos 10 años. Se ingresaron artículos en Mendeley que aconsejaban artículos similares, algunos de los cuales se han incluido en el estudio. El enfoque de este estudio se ha basado en una selección restringida a las enfermedades tratadas con Botox con mayor evidencia científica en la literatura y que son las más relevantes para la odontología. Esta selección incluye enfermedades como bruxismo, trastornos de la ATM, dolores neuropáticos, trastornos de las glándulas salivales.

Resultados: El Botox ha sido aprobado por la FDA como tratamiento para la migraña crónica y la sialorrea. Se han encontrado evidencias científicas significativas sobre la eficacia del Botox para controlar el bruxismo, los trastornos de la ATM, la neuralgia del trigémino y el síndrome de Frey. Sin embargo, aún se requieren más investigaciones para confirmar la efectividad del Botox en ciertas condiciones y para certificar sus beneficios en tratamientos dentales interdisciplinarios.

1. INTRODUCTION

1.1 What is Botox?

Botulinum toxin or Botox is a polypeptide protoxin extracted from the Gram positive anaerobic bacteriUM *Clostridium botulinum* (*C. botulinum*) and related species (*C. Butyricum*, *C. Baratii* and *C. Argentinense)* (1) (2) (3).

The toxin enters the host nerve endings disuniting and inactivating the proteins called SNARE, essential for neurotransmitter release. The inactivation of this protein inhibits the release of acetylcholine at the neuromuscular junction, resulting in localized reduction of muscle activity and glandular secretion (1) (2) (3).

For this reason, Botox is considered a muscle relaxant and is given as an intermuscular injectable medication. However, its effects are only temporary, lasting for 4-6 months (3)**.**

1.2 History of Botox in dentistry

Botox is considered as one of the most potent naturally occurring biological poisons and was originally responsible for a lot of deaths (1) (4) (5).

The interest in Botox has increased significantly during World War II, and American scientists were the first to produce Botulinum toxin A (BTX-A) for military use (6)(7).

In 1949, It is believed that Burgen brought to light the mechanism of Botox, which works by inhibiting presynaptic acetylcholine, thereby creating the basis of its clinical application (8) (5).

Later, in 1989, US Food and Drug Administration (FDA) approved its use for treatments of strabismus, blepharospasm and hemifacial spasms in patients over 12 years old (6) (9)(10).

In 2002, FDA approval also allowed the application of Botox in cosmetic treatments such as correction of wrinkles and two years later for a variety of treatments including cervical dystonia and hyperhidrosis (1) (7) (4).

Nowadays, a growing number of dentists are using it for both oral and maxillofacial cosmetic and therapeutic treatments (3,10).

1.3 Pharmacology and procedure

Structure and types

Botulinum toxin is a neurotoxic protein synthesized by anerobic bacteria called *Clostridum botulinum* and derivatives *C. butyricum*, *C. baratii* and *C. argentinense*.

These bacterial species have 4 different serotypes from I to V and are also subdivided into 8 immunological serotypes (A, B, C1, C2, D, E, F, G) based on the antigenicity of the toxin produced (1)(3) (6) (7). All are neurotoxins except C2 (1) (5). Botox type A (BTX-A), is the most frequently used type for both cosmetic and therapeutic applications, especially for movement and spasticity disorders followed by Botox type B (BTX-B) (1) (3)(10).

Chemically, the botulinum toxin is produced as a single chain of 150 kDa. Then it is cleaved as a 2-chain metalloprotease composed of heavy (100 kDa) and light (50 kDa) chains. While, the heavy one is responsible for toxin internalization, the light one cleaves the SNARE complex (1) (11) (5).

Mechanism of action

Botox is used to produce only or mostly local long-lasting action when injected into a target muscle or tissue. In a muscle, it results in a temporary dose-dependent localized reduction of

muscle activity, thus allowing a safe and effective therapy to control various head and neck motor diseases with a neurological component (1) (2) (3).

In an exocrine gland, the glandular secretion is stopped as it inhibits the glands innervated (3).

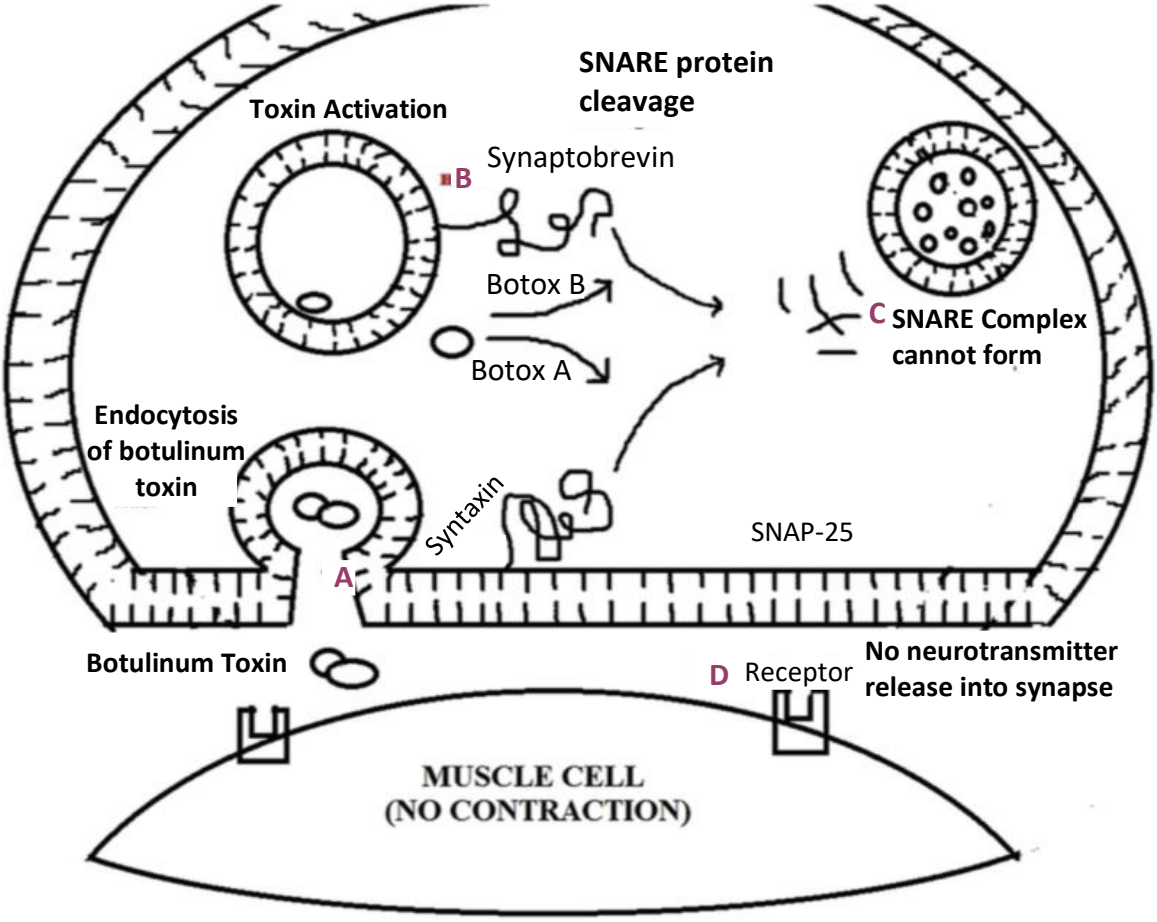
Botox action is based on the inhibition of the exocytosis of the neurotransmitter called acetylcholine (Ach) from presynaptic nerve terminals resulting in neuromuscular inhibition. This means that the targeted tissue will not receive the message from the brain to act (6) (1).

Heavy chains of the Botox favor the endocytosis of the entire molecule into the cytosol, from the neuromuscular junction, by binding to different glycoproteins from presynaptic receptors (1) (3) (7).

Light chains are responsible for the cleavage of SNARE (Soluble N-Ethylmaleimideesensitive factor Attachment protein Receptor) complexes located in the motor neuron. Depending on the type of botulinum toxin used, different SNARE complexes will be cleaved (1) (12).

SNAREs are essential for the fusion of synaptic vesicles with the presynaptic membrane. This mechanism allows the release of the acetylcholine.

Therefore, through the cleavage of SNARE by Botox, acetylcholine cannot be liberated from the motor neuron (Annex 1) (1).



Annex 1 : Mechanism of action of Botox

As a consequence, muscle fibers decrease their intensity or undergo paralysis, starting 6 hours after the injection of the toxin. The effects will be observable on the patient 24 to 72 hours after administration (1) (6) (8) (7)(10).

Nevertheless, by rehabilitation of the SNARE protein complex turnover, through sprouting of the nerve ending and formation of new synapsis, neuromuscular transmission is restored as acetylcholine is released again. As a consequence, normal function is reestablished (3) (8).

Botox therefore has a temporary action that will last from 3 to 6 months, depending on the dosage of the preparation (1) (3) (6) (13). With repeated injections of Botox, its action becomes gradually longer (7).

Preparation procedure

Since the botulinum toxin can be easily administered and can be maintained easily in the lab, it can be easily used as a therapy (1)(3). The doses of Botox depends on different parameters: the treatment including the degree of wrinkles, muscle mass, experience of the physician, gender (as females usually require smaller doses than males) and on the brand/preparation used (8) (3) (14).

In theory, higher concentrations of toxin should be used for thicker and smaller muscles and when toxin migration should not occur. Regarding lower concentrations, they should be used for wide areas and when there is a risk of toxin migration that could cause serious complications (8). Adequate dose of Botox is essential as it is a very toxic compound, with a Median Lethal dose (LD50) of about 1ng/kg (2).

However, there is no specific formula regarding the dosage of Botox that allows to easily establish different doses with the different types of products. Therefore dentists must be aware of the different dosages before using any type of preparation (3) (14).

In the head and neck, Botox doses should not exceed 100-125 Unit of *C. botulinum* per session (7).

1.4 Possible therapeutic uses

Botox is considered as a good alternative to surgery due to a lower cost and its non-invasive conservative procedure (3)**.** Since its discovery, its used has been widespread, especially in dentistry, having both aesthetic and therapeutic purposes.

On one hand, regarding its aesthetic purposes, Botox can be used for gummy smile, masseteric hypertrophy (square jaw), asymmetric smile, and others (3)**.**

On the other hand, regarding its therapeutic applications, studies have shown many conditions that could be improved using Botox. Those with the most evidences and the most relevant in dentistry, in the articles selected, have been classified as followed:

MUSCLE AND JOINT DISORDERS	BRUXISM	(1–5,12–19)
	TEMPORO MANDIBULAR JOINT DISORDERS	(1,2,4–7,12–17,19,20)
	FIRST BITE SYNDROME	(1,4,7)
	OROMANDIBULAR DYSTONIA	(1,12,13,15–17)
	TRISMUS	(3,6,9,12,17)
NEUROPATHY AND NEURALGIA (15)	HEADACHES ➢ Migraines ➢ Tension headaches ➢ Cluster headaches	(3,9,15–17,21) (1,5,6,11,17,22) (1,3,6,7,20) (6)
	TRIGEMINAL NEURALGIA	(1,2,5,11–14,16,17,22)
	FACIAL NERVE PASLY	(2,13,14,16,17)
SALIVARY GLAND SECRETORY DISORDERS (17)	SIALORHEA	(1–3,5–7,11–17)
	FREY SYNDROME	(1,3–5,7,11,13–17)

ADJUNCTIVE TREATMENT (5,14)	MAXILLOFACIAL TRAUMA AND FRACTURE	(5,6,12,14,15,17)
	IN IMPLANTOLOGY	(5,6,8,12,14,15,17)
	IN ORTHODONTICS	(5,8,12,14)
	IN PROSTHODONTICS	(5,12,14)

Therefore, in this project we are going to analyze the different applications of Botox in dentistry, for the diseases previously mentioned in the table, along with its advantages and disadvantages.

2. OBJECTIVES

The main objective of this project is to determine the effectiveness of the therapeutic applications of Botox in dentistry. That includes its use to treat bruxism, temporomandibular joint disorders, first bite syndrome, oromandibular dystonia, trismus, different types of headache including migraines, tension headaches and cluster headaches, trigeminal neuralgia, facial nerve palsy, sialorrhea and Frey syndrome. Botox effectiveness will also be determined when use as an adjunctive treatment in maxillofacial trauma and fractures, implantology, orthodontics, prosthodontics.

The secondary objectives are to analyze:

a. the advantages of using Botox over traditional treatment methods
b. disadvantages of using the toxin to treat different diseases
c. Side effects of the Botulism toxin.

3. MATERIALS & METHODS

Studies were searched in PubMed and Google using the following words: Botox / Botulinum toxin / Dentistry / Orofacial / maxillofacial / therapy / therapeutic applications / non cosmetic / head and neck.

The articles have been selected based on several criteria:

- Articles that are not fully available were excluded of the research,
- Only articles from scientific literature, relevant for the subject and published within the last 10 years have been included in this study.

Articles were all entered into Mendeley which proposed similar articles, some of which have been added in the study. Evaluating the articles researched and chosen, the focus of this study

has been based on a selection restricted to the diseases treated with Botox that have more scientific evidence in the literature and that are the more relevant for the dentistry field. Another selective criterion used is their severity. This selection includes diseases such as Bruxism, TMJ disorders, different neuropathic pain, salivary glands disorders.

4. RESULTS

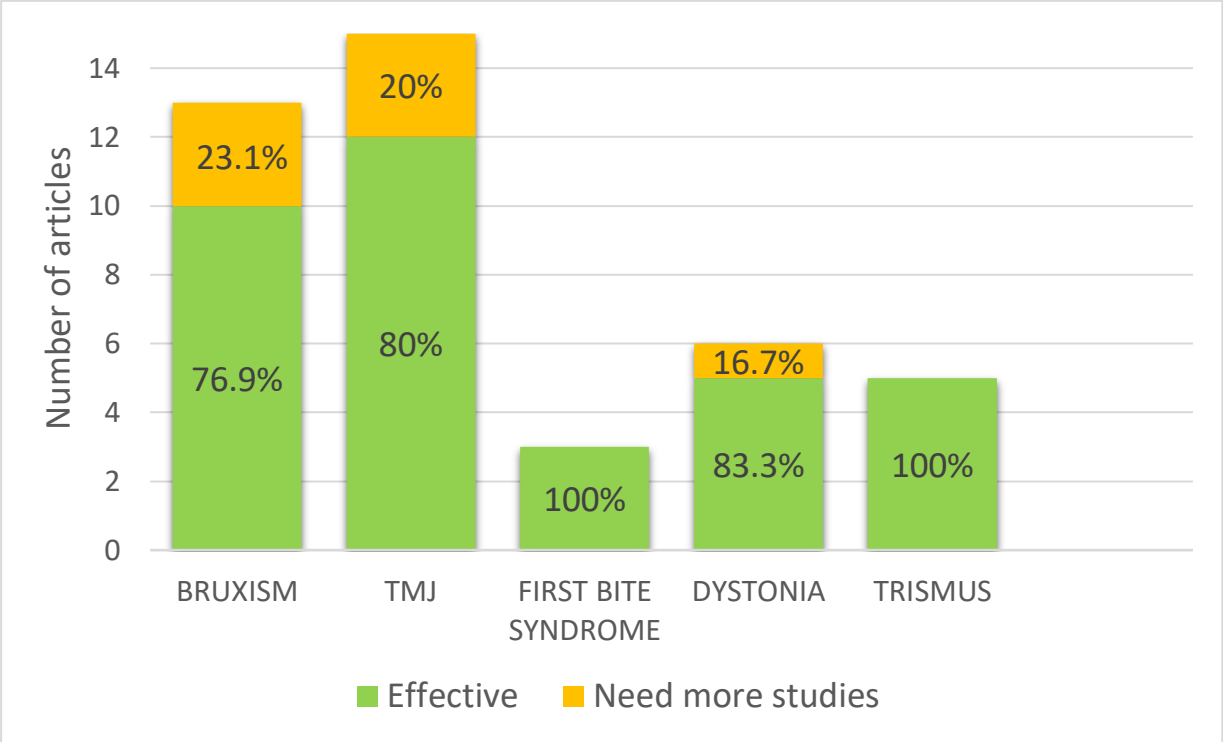
4.1 MUSCLE AND JOINT DISORDERS

Bruxism

Bruxism is defined as a repetitive excessive involuntary masticatory muscle activity involving the masseter and the temporalis muscle. It is characterized by grinding, clenching, bracing or thrusting of the mandibular teeth without functional purpose (1,2,4,13,16). It can lead to several symptoms involving the stomatognathic system such as tooth wear, attrition, headaches, muscle and joint associated symptoms (stiffness, hypertrophy, clicking, pain…), periodontal lesions and others (1–3,13–15). It can be classified as sleep bruxism and awake bruxism (2).

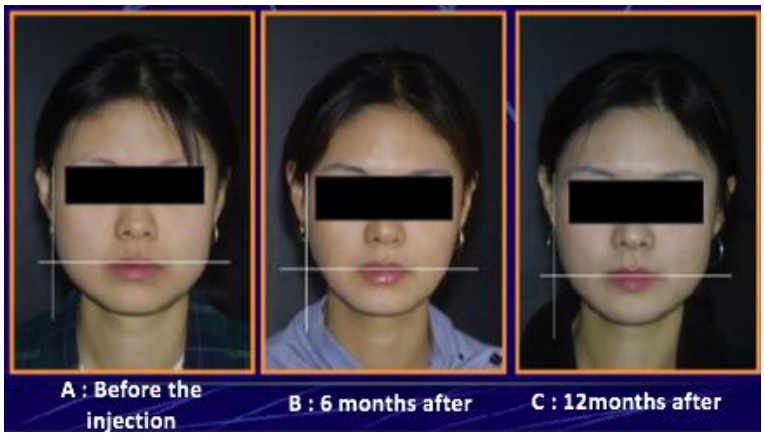
Common treatments such as pharmacotherapy, occlusal interventions and intraoral appliances, focus on reducing the symptoms and muscle activity as well as protecting the affected structures (1,2). Recently, Botulinum neurotoxin has been used as a new method to relieve symptoms caused by bruxism and parafunctional habits (1–3).

In our study, 13 articles studied the efficiency of Botox in bruxism. On one hand, 76.9% of them confirmed its effectiveness in reducing the symptoms of bruxism including pain, the number of events and the intensity of bruxism for both types of bruxism: sleep or awake or both. (1,3,4,12–15,17,19) (Annex 2). Within those in favor of Botox therapy, 30% have mentioned its specific successful use in the management of severe cases (1,12,15) (Annex 2). On the other hand, 23.1% were still questioning the efficiency and reliability of Botox injections in the treatment of bruxism and stated that more research will be required to use it as a treatment option (2,16,18) (Annex 2).



Annex 2: Botox effectiveness in its application in muscle & joints disorders

11 articles have reported the sites were Botox was injected to treat bruxism in their study. Most of them only used the same injection sites, and therefore no comparisons were made about efficiency of Botox regarding the sites of injection. Only one article have evaluated the best injection sites (22).



Annex 3 : Results of Botox injection in masseter muscles in patient with bruxism

Reports about Botox injection state the efficient use of injection in masseter muscles (one injection per side) (3,14,17)(Annex 3), the successful use when injected as a combination in both masseter and temporalis muscle injections (in both sides) (1,5,15,22) along with Botox administration in the lateral pterygoid muscles (2,13). While some articles raise some concerns regarding its effectiveness (2, 16,18), therapeutic outcome was shown to last for a period of 19 weeks ranging from 6 to 78 weeks in the best cases (14,15,17) (Annex 2).

Temporomandibular joint disorder

Temporomandibular joint disorders (TMDs) broadly-define a group of various craniofacial changes often associated with facial pain, having multiple causes affecting the temporomandibular joint (TMJ), masticatory muscles, or associated musculoskeletal structures (1,2,6,14). They are accompanied by pain in the pre auricular region, decreased jaw excursion with difficulty in opening and chewing, TMJ clicking and jaw locking, tension-types headaches, and oromandibular dystonia and malocclusion and others (1–3,5,12,15,20).

In most of the cases, there are classified into 2 subgroups: the myofascial TMD and arthrogenic TMD, both responsible for pain at the TMJ level. Myofascial TMD is produced by excessive activity of the masticatory muscle and arthrogenic TMD is caused by intracapsular pathology (3,14).

Myofascial pain is the most common type of TMD disorder being characterized by myofascial trigger points responsible for persistent and diffuse pain, dysfunction and tenderness mostly of the masseter, temporalis and lateral pterygoid masticatory muscles (1,4,6,7,13,17). It affects women more often and people between 20-40 years old (7).

TMJ disorders requires therapy to restore TMJ function which can be or cannot be combined: occlusal adjustments, orthodontic appliances, psychotherapies, neuromuscular therapies, physiotherapies, laser, surgeries, and pharmacotherapies including muscle relaxants, antidepressants, anti-inflammatories and analgesics (1–3,6,12,14,15).

15 articles studied the efficacy of Botox in the management of TMDs. 80% found multiple evidence to consider Botox effective in reducing TMDs-related symptoms by minimizing the duration, frequency and intensity of muscle contraction as well as relieving pain (Annex 2) (1–5,7,12,14–17,20) for a period of 5 to 12 months (15). Almost half of those articles specified that Botox should be used as a first option only in complex TMD's (1,3,12,15,20).

Many articles stated the injected muscles, 3 were used: Temporalis, masseter, and lateral pterygoid (1-5,7,11,13,14,19). The majority reported results for Botox when injected in all 3 muscles (3–5,7,14,17). When given, the doses were similar and always the minimal possible (1,3), being the highest for the masseter and the smallest for the lateral pterygoid muscle (1–3,7,14,15,20).

Nevertheless; 20% of the studies still consider Botox as a controversial therapy and requested more studies (6,13,19), while reporting Botox useful as an additional treatment (6,13,19) (Annex 2).

First bite syndrome

First bite syndrome is defined by acute and severe pain that starts in the parotid region of salivary glands and produced after the first bite of each meal. After less than a minute, pain improves with more mastication, however it will be recurrent at the beginning of each meal. Therefore, it leads to apprehension of oral intake. Its etiology remains unidentified, but it

often occurs after parapharyngeal surgery or deep parotid lobe removal that seems to impair the myoepithelial cells sensitivity resulting in their maximal contraction at the initiation of mastication, which would be the hypothetical cause of the condition given by some authors (1,4,7).

Only a few articles reported Botox application for this condition (1,4,7). All of them consider its use effective in relieving the symptoms by paralyzing the myoepithelial cells, and one reported a large amount of evidence regarding Botox efficiency (4) (Annex 2). The dose of Botox administered in the involved region was at 40-60U through mandatory ultrasound guidance to deliver the product (1,7). A 24-48h time period was required for the Botox to be effective (7).

Oromandibular Dystonia

Oromandibular dystonia (OMD) is a head and neck movement disorder of focal description meaning that it affects a localized muscle (1,15). It is described as involuntary forceful spasms and contractions of the face, mouth, jaw and/or tongue affecting their corresponding muscles (masticatory, lingual and pharyngeal) (1,12,13,15,17). Indeed, it leads to speech, deglutition, mastication and facial expression alterations and in some cases provokes oral trauma (1,12,15,16).

Oromandibular dystonia has been classified as idiopathic, late or secondary to other neurological disorders, the late type being the most common. Also it has been sub-grouped into jaw-opening dystonia, jaw closing dystonia, jaw-deviation dystonia and pursing of the lips dystonia (1,13). Current therapy for dystonia includes physiotherapy associated with supportive therapy, pharmacotherapy, neurosurgery and Botox (1).

Many articles reported the effect of Botox over oromandibular dystonia.

83% established the effectiveness of Botox for the treatment of the different types of oromandibular dystonia with clear improvements of the symptoms (1,12,13,15,17). 60% of those considered it as a first choice for therapy compared to other available treatments (1,13,15). 16% of the articles concluded in the need for more quality studies to assess the effectiveness of Botox in oromandibular dystonia, even though results were considered encouraging (16) (Annex 2).

All articles reported the injection sites and those selected are closely related to the type of oromandibular dystonia, varying from masticatory, floor of the mouth to extrinsic tongue muscles with submental complex (1,12,13,15–17). Regarding jaw closure dystonia, one study used bilateral injections in the masseter muscles with 30U of Botox (17) while the other confirmed the need for injections in masseter, temporalis and medial pterygoid muscles in each side, giving respective initial dose ranging from 40-50U, 40-50 U and 20U (1). Other articles reporting injection sites for jaw opening dystonia have established the lateral pterygoid as the most important site with an initial dose of 20U of Botox. Moreover all articles suggest an additional injection of 20U of Botox in the submental complex (1,13,17).

The few studies concerning lingual dystonia reported the need for Botox administration of 30U into the tongue muscles (13,17).

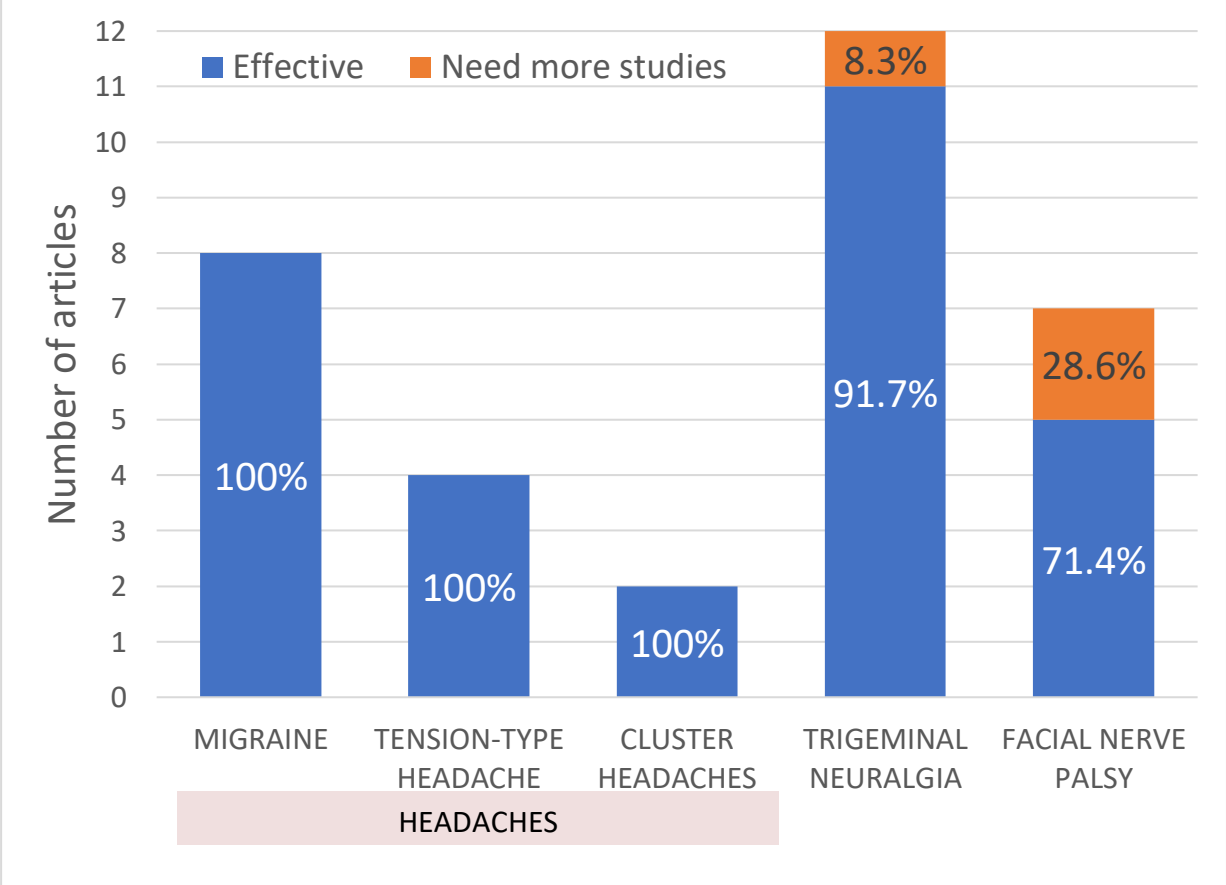
Trismus

Trismus also called mandibular spasm and is a motor alteration of the trigeminal nerve. It produces lasting intermittent contractions of mandibular muscles that manifests as limited

mouth aperture (6,12,17). Therefore it makes oral hygiene, dental treatments, mastication, drinking and others, more difficult (3,9,12).

The use of Botox in the treatment of trismus has been effective in 100% of the articles analyzed. All have considered Botox successful in reducing pain, muscle tenderness and spasms episodes resulting in improved mouth opening (3,6,9,12,17) (Annex 2). Only one study have given the recommended dose and injection site : 25U and 10U of Botox injected into each masseter and temporalis muscles respectively (17).

4.2 NEUROPATHY AND NEURALGIA



Annex 4 : Botox effectiveness in its application in neuropathy and neuralgia

Headaches

There is no given cause for headaches but hypothetically it is believed that they are caused by an unusual excitation of the peripheral sensory fibers that result in central stimulation as well as augmentation of the hardness and tenderness of peri-cranial muscles. Another probable cause is the increased response of the trigeminal nerve resulting in reduced pain modulation implying neurotransmitters (17).

Headaches can be divided in 2 groups: the primary and the secondary. Primary headaches' response to Botox was the one studied in the literature, in all of the articles selected. They include migraine, tension-types headaches and cluster headaches (6).

Archana M.S. *et al.* have evaluated the efficiency of Botox therapy in primary headaches with no distinction between the different types. A significant decrease of duration, frequency, and number of episodes of those from moderate to severe character were observed (16,17). They have offered 4 different action mechanisms of Botox over headaches, most of them leading to decrease muscle activity and one leading to analgesia and reported Botox efficiency over a period of 3 months (17).

Even though Filho *et al.* have found Botox effective in the treatment of migraines, they stipulated the need for more investigation regarding Botox ideal dose, injection site and other secondary parameters for headache treatment (6).

<u>Migraines</u>

It is the most frequent neurological condition (1,3). A list of features have been established to diagnose migraines : at least 5 recurrent headaches within 4-72h that were either successfully treated or not, with a lifetime history of occurrences, and were 2 or more of the following

attributes are present: Unilateral, pulsatile, moderate to severe magnitude, worsen with physical activity ; and with the existence of either photophobia, phonophobia or nausea (3,7). Migraines are classified in 2 types : chronic with more than 15 episodes per months and episodic, less than 14 (7). Management of migraines of mild to moderate intensity have included non-steroidal-inflammatory drugs (NSAIDs) and analgesics, while severe migraines are relieved with Triptans (3).

Success of Botox therapy in the treatment of migraines was related by all articles that analyzed this type of headache (1,3,6,7,11,15–17,21) (Annex 4). However, Nagi *et al*., Alshadwi *et al.,* and Awan K.H, in their articles referred to the effectiveness of Botox in the treatment of chronic forms of migraines. This treatment was approved in 2010 by the Food and Drug Administration and is the only available preventive therapy for chronic migraines (1,7,16).

Depending on the area of occurrence of the migraine, different injection sites and respective doses were used for Botox, and in general was more effective when administered in an active trigger point or areas of compressed nerve. Concerning the most frequent location of migraines, studies showed that for frontal migraines, 35U-40U of Botox was necessary in frontal, corrugator and procerus muscles ; for temporal migraines, 20U-25U of Botox injection were required in both temporal muscles ; the occipital migraines were treated by injection of 10U-30U of Botox in both occipital muscles (1,3,7,21).

Tension headaches

It is another form of common headache related to an increase of skull muscles activity in the temporal and occipital zones but without a known cause (1,20). it is believed that genetic factors, lack of sleep, dehydration, emotions, parafunctional habits and some drugs are

triggering factors (20). It is characterized by bilateral and dull pain, lasting at least for 30 min or being constant, ranging from mild to moderate severity (1,20).

Few articles have considered this type of headache. All were in favor of Botox use in treatment of Tension-type headache due to significant improvements in the intensity and frequency of the episodes (1,6,17,20) (Annex 4). The sites of injections were temporal, pericranial and cervical muscles (1,6,17,20). Furthermore, no product dose was established.

Cluster headaches

No exact definition of cluster headaches was found in the articles. However it is a type of headache produced by the production of a pain output along the ophthalmic part of the trigeminal nerve (6,17). The few articles that refer to it confirmed the effectiveness of Botox for this condition (Annex 4) (6,17). Moreover, Archana M.S., specified the required dose of 24 to 150U of Botox per site. However the exact site of injection was, in no case, pointed out (17).

Trigeminal neuralgia

Trigeminal neuralgia is a rare, incapacitating, facial illness that is described as unilateral, painful, abrupt and short (second to minutes) with stabbing and severe recurring pain attacks, along, at least, one section of the trigeminal nerve. It is often associated with the facial expression and is also called “Tic-douloureux” (1,7,13). It has been classified into classical types which are characterized by vascular compression of the nerve, and Secondary Trigeminal neuralgia due to other irregularities (2).

Trigeminal neuralgia therapy is either pharmacological using mainly antiepileptic drugs such as carbamazepine and local anesthetics or/ and surgical intervention. However, surgical therapy should be used when patient are resistant to other treatment because surgical intervention is undesirable due to its invasiveness, risks and possible complications (1,2,7,13). Botox use for the treatment of trigeminal neuralgia has been widely confirmed. Many articles approved the use of Botox to reduce pain significantly or make it completely disappear in patients suffering from trigeminal neuralgia (Annex 4) (1–3,6,11–17). Among those Muñoz Lora *et al*. affirmed its great success in cases with patients refractory to regular therapies, while Mostafa D. confirmed their great interest in avoiding invasive surgeries, with a great outcome when combined with pharmacotherapy according to Awan K.H. (2,3,16). Nevertheless, one research. have concluded the need for more randomized, controlled trials as results in literature were not conclusive (7).

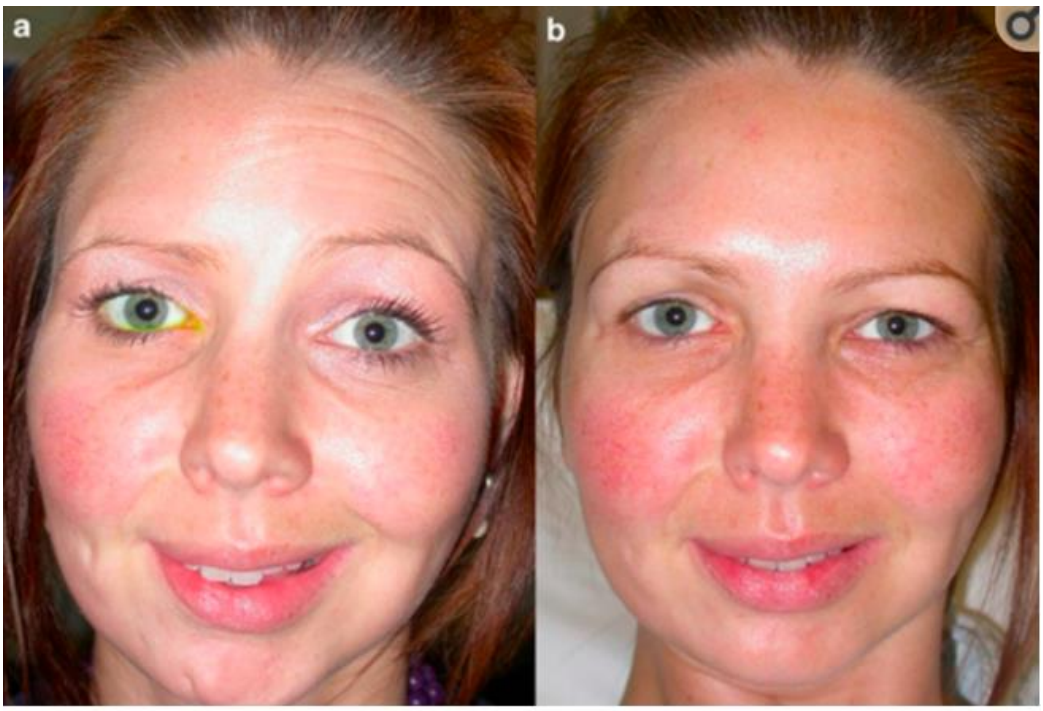
Articles referring to the dose and site of injection suggested the need to administer Botox in the area where the pain is triggered but none of them gave the same doses or precise injection sites (1,2,12,13,17).

Facial nerve palsy

Facial nerve palsy or paralysis is the complete or partial (paresis) loss of facial nerve activity leading to the unilateral facial muscle paresis and synkinesis and is characterized by a sagging half of the face due to loss of muscle tone and a normal side with usual muscle tone. Therefore, facial asymmetry is produced (3,13,17) (Annex 5). It affects significantly the quality of life due to the speech related, eating and drinking alterations and an unpleasant expression in the face (3,13).

Available therapies include nerve grafts, muscle transplantation, myofunctional therapy and microsurgical patches. Despite them, persistence of facial nerve palsy continues (3).

Annex 5 : Case of facial nerve Palsy - Before and after 1 month of Botox injection



a. Before Botox injection with moderate right-sided facial palsy.

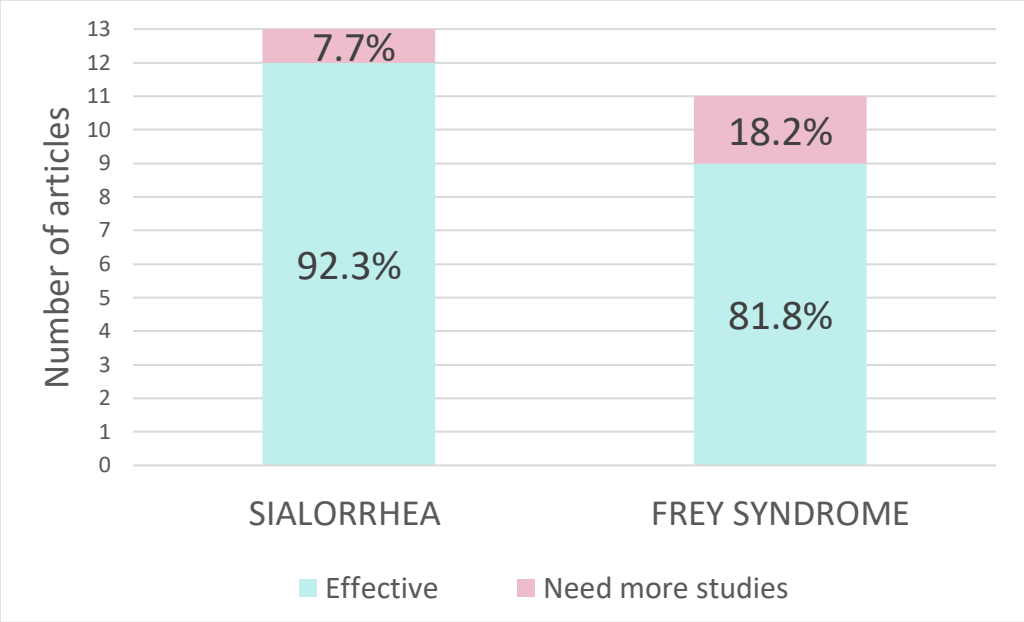
b. After Botox injections to the left face and forehead, as well as for right synkinesis.

On one hand, research has shown success of Botox in correcting facial nerve palsy in 71.4% of the related articles (3,13,14,17,23). It compensates the muscle inactivity of one part of the face by producing the same effect in the contralateral side (3,13,14,17,23). On the other hand, some articles did not confirm the effective use of Botox (5,16). Park *et al*. raised some doubts, and their hypothesis regarding effective use of Botox for facial nerve palsy remains unanswered (5). Although research showed promising results regarding Botox, some confirmed that there was still incomplete information requiring further researches (16,23) (Annex 5).

Some studies have explained the area of administration of the product an important factor for this condition : they said that contralateral unaffected muscle would be the choice as a

site of injection in order to provoke relaxation of that muscle restoring the symmetry of the patient's face, and correcting the facial nerve palsy (17,23). Moreover one author specified the necessity of a dose between 10-80U of Botox for the effect to last an average duration of 3 months (17).

4.3 SALIVARY GLAND SECRETORY DISORDERS



Annex 6: Botox effectiveness in its application in salivary glands disorders

Saliva secretion is regulated by the parasympathetic autonomous system which works through the release of acetylcholine which functions as the main neurotransmitter. When this system is impaired, saliva secretion alteration occurs. There are many disorders related to impaired salivary secretion, including both sialorrhea and Frey syndrome (1,3,7). Treatment of such disorders include varying range of approaches from minimally invasive to more aggressive ones such as surgeries (3).Through its action on acetylcholine Botox may be useful in the treatment of those pathologies (1–3,5–7,11–17) .

Sialorrhea

Sialorrhea is caused by the loss of control over the facial muscles which is often observed in patients with neurological disorders such as Parkinson's disease, cerebral Palsy or as an adverse reaction to some drugs (1,2,6,15,16). It is defined as a persistent excessive salivation in patients over 4 years old therefore referred to also as Hypersalivation or drooling (1,2,6,14,16). This disease affects the quality of life of the patient who, therefore, requires treatment (2,15,16). Treatments include pharmacotherapy with the use of anti-cholinergic and anti-histaminic drugs used for minor sialorrhea, and surgical approaches used in more severe cases (2,6,14,15).

Since its first use as a potential therapy of this condition in 1977, Botox efficiency in sialorrhea has been studied (6). 92.3% of related articles report its efficiency (1–3,5,6,11–17) in seriously reducing salivary secretion through blockage of acetylcholine liberation, without noticeable adverse effects (2,11,12,14,15,17) (Annex 6). In fact, FDA has officially authorized its use in the treatment of this condition since 2018 (2). However, one study. consider that these studies had a very short follow up time that was insufficient to validate the efficient use of Botox and advocated the need for further research with longer time windows (7).

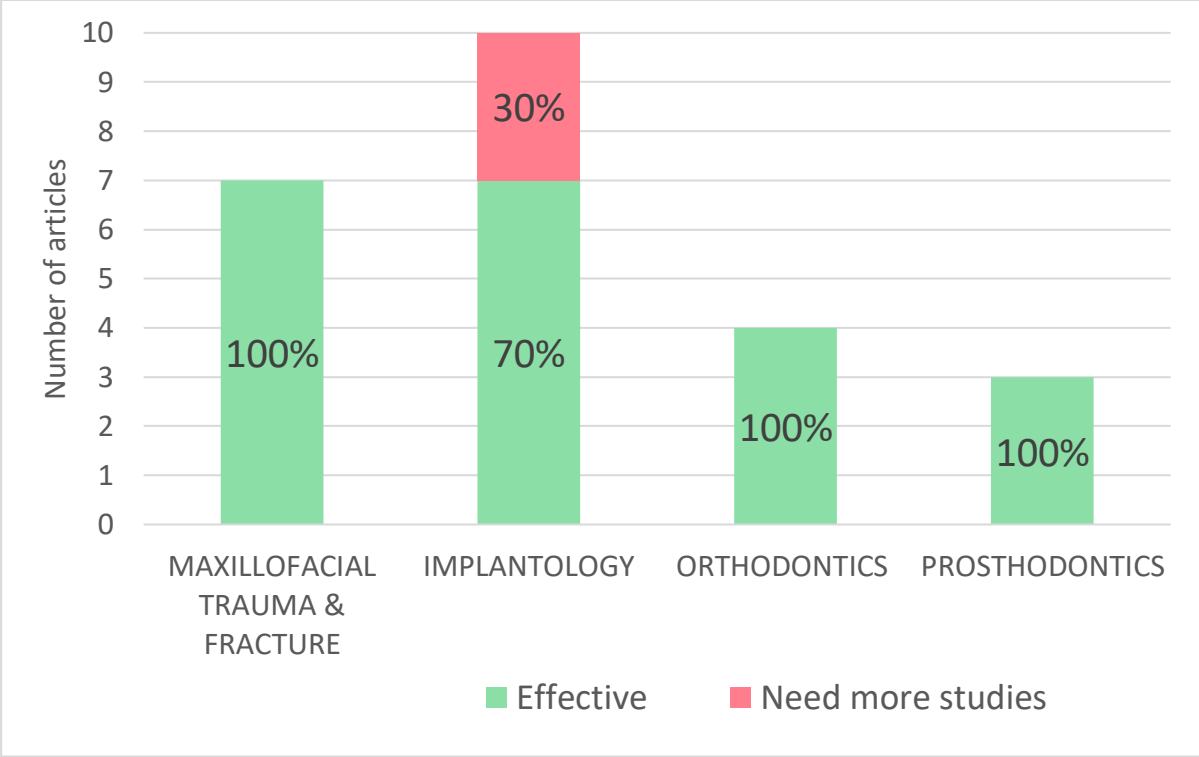
Intraglandular injections in parotid glands and submandibular glands were the ones performed to treat sialorrhea effectively (1,3,7,14,15,17). Botox dosage ranged between 10-100U, with 25 to 70U in the parotid glands (divided in the 4 regions of that gland), and no more than 20U for the submandibular glands in each of the 2 regions (1,3,7,14,15,17). Different methods were used for Botox injection, but the most used strategy was the one with ultrasound guidance (1,6,7). Results were observed in 4 weeks and duration ranged from 1.5 to 6 months (7,14–16).

Frey syndrome

Frey syndrome is a neurological condition caused by damage of the parotid gland region, and auriculotemporal nerve often associated with the surgery of the parotid gland (1,4,7,15). It is characterized by excessive sweating and flushing of the face generated by gustatory stimuli (1,4,7,15,16). Many treatments exist involving radiotherapy, anticholinergic medication and surgeries (7,15).

In 1995, Botox was the first symptomatic therapy suggested for Frey syndrome (1,7). Since that time, many articles have studied its results, and many have confirmed the effective use of Botox (1,3,5,7,11,14–17). Its duration of action varies from 4 months to 2 years (1,7,15,17) (Annex 6). It has minimal adverse effects and is minimally invasive (1,2,15), but complete atrophy is an important adverse effect when Botox is used for a long time (15). Its effectiveness has been reported when injected into the 4 regions of parotid glands (1,7) with the need for ultrasound guidance for its administration (1). The higher the dose the better the effectiveness according to Shilpa *et al.* (15), however many studies suggested that the concentration should range from 25-60U (1,3,7,17). Nonetheless, some articles said that this field required further research (4,13) (Annex 6).

4.4 ADJUNCTIVE TREATMENT



Annex 7: Botox effectiveness in its application as adjunctive treatment

Maxillofacial trauma and fracture

The healing of maxillofacial trauma and fracture must withstand the muscle forces that can impede correct regeneration of the bone (15,17). Botox is used as to reduce those forces facilitating bone repair. Research referred to the use of Botox as an adjunctive treatment to help with maxillofacial repair, during trauma or fracture of the maxillofacial region, such as zygomatic or jaw fractures, and in addition to reparative surgeries. All reported strong benefits of Botox (3,5,6,12,14,15,17) (Annex 7).

Mostafa D. and Nayyar *et al.* explained that Botox avoids the unwanted muscle activity during the healing period and could also be utilized as a temporary splint (3,12). Indeed, when injected into the muscles of the mastication such as masseter, temporalis and anterior belly

of the digastric muscles, it prevents bone displacement, facilitating repair but it requires multiple injection sites (3,5,12). The muscle to be injected will depend on the location where we want to achieve repair (3,12,14,15,17).

In implantology

For an implant to be successful, we must achieve osteointegration. However, due to many factors including surgery, individual characteristics of the patient, the implant itself, occlusal load and parafunctional habits, implants may fail. Indeed, when occlusal load is too strong, implant osseointegration failure may occur. Therefore, measures to adjust the load and prevent an excessive one should be taken (6,8,15,17).

70% of the articles about the combination of Botox with implant placement, found Botox to be an effective help in implantology, increasing the success rate of implant osseointegration and providing better environment for healing (5,6,8,12,14,15,17) (Annex 7). Indeed, Botox injected into the masticatory muscles reduces the forces of occlusion resulting in lower occlusal load over the implant resulting in successful osseointegration. The muscles to be injected to reduce the occlusal load were the same in all the articles reporting them: the temporalis and masseter muscles. Different doses of Botox were specified in the studies (8,12,17).

However, 30% of the articles regarding implants have considered that the studies supporting the application of Botox as adjunctive treatment in implant placement were rare and no conclusions were made (3,13,14).

In orthodontics

Orthodontic therapies are methods whose purpose is the restoration of normal tooth alignment and occlusion. Relapses after an orthodontic therapy are frequent. Indeed, both the teeth and the facial muscles are risk factors (3,8).

Botox effectiveness to help in orthodontics has been confirmed in 100% of the articles of this study (3,8,12,14) (Annex 7). In fact, by reducing muscle activity and resultant occlusal forces, relapses are avoided, and the duration of the orthodontic therapy might also be shortened (8). Some articles reported that injections are usually made in the mentalis muscle (3,12,14). Srivastava *et al*. and Nayyar *et al*. indicated that after the combination of Botox and orthodontics, posterior treatments training the muscles to have a more physiological function are recommended to increase the long-term success rate (12,14).

In prosthodontics

It is common for a patient with a removable denture to face difficulties regarding its retention. This can be caused by an over activity or hypertrophy of their masticatory muscles and/or decrease of the vertical dimension (3,12).

Botox has been considered effective in helping patients with the adaptation of a new denture in all articles referring to this benefit (3,12,14) (Annex 7). Mostafa D. specified that usually Botox was injected into the masseter muscle, the lateral pterygoid muscle and the medial pterygoid muscles (3).

5. DISCUSSION

Botox therapy has been proven to be easy to use, non-invasive, reversible and a comfortable therapy for the patient, with no major adverse effect (1–3,7,13–16,19). Also, It appears to have analgesic properties that are useful when treating pain (1–3,7,13)(7).

By reducing or relieving the pain, Botox significantly improves the patient's quality of life helping with depression, anxiety and sleep disturbances related to this condition (13). However, the dose of Botox should be carefully chosen, as an excess could lead to many unwanted effects including immunization, and a lack would not produce any effect (1,3,12,15,18,19).

5.1 MUSCLE AND JOINT DISORDERS

In many muscle and joint disorders it acts by reducing the intensity, frequency of the symptoms and associated pain (1–3,12,14,15,17,18).

Concerning Bruxism and TMDs, Botox has been proven equally effective as conservative therapy, particularly in mild to moderate cases, therefore it should be used as an alternative or additional method especially when traditional treatments have failed, shows complications or to replace invasive and irreversible therapy such as surgeries

(1,3,8,12–15,18,19). But due to its high cost along with its frequent injection needs, and possible immunization that may occur, Botox might not be the therapy of choice (1,3,8,12–14).

Muscle and joint disorders often present a psychological dimension that could require psychological therapy and associated with Botox this could particularly improve the outcome of the treatment (1,19,22).

Bruxism

Articles have generally offered a positive feedback for its use although results are different in each study, since each article addresses a different objective.

In fact, while 77% of the articles confirm the effectiveness of Botox in reducing the symptoms-related to bruxism (1,3,4,12–15,17,19), for the remaining 23%, the problem was that Botox has not be proven to treat bruxism itself, but to treat the symptoms (2,16,18). Therefore, Botox could be used in an effective way to reduce the severity of bruxism symptoms using a dose between 25-100 U, but we would need further research to accept Botox as a viable method to treat the source of bruxism and cure it. (1–3,12,14,15,17,18)

The injection of Botox into the masseter muscle and the temporalis muscles are the ones that proved to be the most effective but further studies regarding the best injection sites to treat or reduce bruxism are required (1,5,15,22).

Temporomandibular joint disorder

It is not sure which pathologies were included as TMDs in the different studies, as TMDs constitute a diverse group of disorders. We need an exact definition of TMDs and a specific division of the different disorders into subgroups so they can be individually studied for Botox efficiency (19). Therefore this will require further investigations and larger sample sizes for FDA approval (1). Moreover, pain is subjective : this could lead to the wrong inclusion of patients in the different studies (19). The aforementioned facts could explain the differences in the results among the different articles: with 80% confirming the effectiveness of Botox and 20% that ask for more studies (6,13,19). Therefore, in the majority of the cases, Botox has been effective in the control and treatment of symptoms related to TMDs (1,3,12–14).

There is no clear evidence regarding the best sites of injections, as it has not been studied, and all the injection sites have been successfully used in the articles. However it seems that injection in the lateral pterygoid muscle can lead to a fixed smile and must therefore be avoided until further demonstrated to be safe (4,17).

The dose should be the minimal possible as some studies have shown risk of mandibular bone loss and uncontrolled structural changes in the muscles due to its injection (1,20). It should be administered in several sites to prevent incomplete results (3). However, the exact duration of the therapeutic effects remains unclear (15).

Finally, the desired effects of the Botox should be clearly specified: treat the symptoms or the disorder itself.

First bite syndrome

The lack of studies about Botox injection to treat first bite syndrome do not allow to validate its effectiveness to treat this condition (1,4,7) . However, treating first bite syndrome is important as it can significantly improve the quality of life of the patients hence the need for more investigations (1,4,7).

Oromandibular Dystonia

The use of Botox in the management of oromandibular dystonia appears to be effective thanks to the large number of studies reporting positive feedbacks, and almost all studies have shown encouraging results with a decrease in the symptoms (13,15).

Closure dystonia appears to be the one with the best response to Botox therapy but more complex dystonia tends to have a lower response rate and might require additional therapy.

(13). Moreover, this condition shows better results when treated with Botox than with other alternatives. Botox improves patient's quality of life, therefore it appears to be the best treatment for OMD (1,13) . However, the symptoms related to OMD such as dysphagia can complicate the injection and the risk/benefit ratio must then be evaluated to be able to choose the best treatment option for each case. As OMD is constantly changing in intensity and location, the dose and sites of injection must be reassessed for every session (13).

Trismus

Botox effectiveness have been proven in 100% of the articles analyzed (3,6,9,12,18). However, more information regarding the injection site and dose should be examined to confirm its method of application in trismus cases (17).

No alternative treatments were given and compared with Botox; thus, other options should be explored to be able to justify the use of Botox as the therapy of choice for this condition.

5.2 NEUROPATHY AND NEURALGIA

Botox seems to be the option of choice for headaches and trigeminal neuralgia when pharmacological treatment fails, when there is resistance to the standard treatment after long-term use, when secondary reactions to the drug occur or when patients have contraindications (1,3,6,16).

Headaches

Even though, the type of headache researched was not always clear or differentiated in all the articles, Botox use to treat headaches has been recognized in 100% the articles regardless of

the type. Strong evidences have been found regarding migraines and especially chronic migraines for which Botox was approved officially by the FDA and can be considered as the first choice therapy (1,3,6,7,11,15–17,20,21). Moreover, even though Botox appeared efficient for both tension types headaches and cluster headaches, there was a lack of information as only respectively 40% and 20% of headaches-related articles had analyzed those types (1,6,17,20). Therefore, more studies about Botox applied to those types should be examined for better information regarding its effectiveness (3,6). The combination of surgery and Botox shows promising results in elimination of migraines (15).

Botox injection site and dose appears clear for migraines as confirmed by many articles (1,3,7,21) , but more research are still needed regarding tension types headaches and cluster headaches due to the lack of details (1,6,17,20). Moreover, contraindications regarding injection into specified trigger points exist, therefore precautions must be taken, especially when injected into the frontal muscle due to possible complications such as vision problems (3,16,21).

Trigeminal neuralgia

Botox is a great option to treat Trigeminal neuralgia (1–3,6,11–17). It avoids the need for more invasive treatments such as surgeries that have higher risks, but a few surgeons stated that delaying operations can worsen trigeminal neuralgia (3,14,16).

The information regarding sites of injection and doses are scarce and further investigation for a unified protocol is required (13). Although, the need for frequent injections is known, they must be performed every 3 months (1,2).

Botox use in the treatment of trigeminal neuralgia is still on waiting for approval by FDA but as a high level of evidence regarding its effectiveness (2).

Facial nerve palsy

Botox effectiveness in the treatment of cerebral palsy seems to be proven in the literature as confirmed in 71 % of the related articles (3,13,14,17,23). Only a few articles raised doubts (5,16).

Botox effects for facial nerve palsy last for 3 months which is quite acceptable for the patients. It should be used as the first choice of treatment for patients suffering from this condition, even though resistance to it can be developed by the subject. Indeed, current therapy methods are quite aggressive (3,17,23).

Regarding the dose and sites of injections, information provided is scarce, therefore more research will be required to understand this better. However, it is understood that it will be used in the contralateral muscle of patients (23).

Botox could really help improve the quality of life of those patients, but as facial nerve palsy has different etiologies, the research about the use of Botox for this condition should involve this parameter to have more precise results (23).

5.3 SALIVARY GLAND SECRETORY DISORDERS

Botox is a first line therapy for disorders of the salivary glands such as sialorrhea and Frey syndrome. Indeed, the limited effectiveness and the existence of many adverse reactions found in other pharmacotherapies, along with the aggressiveness and adverse effects of surgical therapy shows that Botox maybe the most desirable treatment (1,3,7,13,15,17).

Sialorrhea

The use of Botox in the treatment of sialorrhea seems to be widely accepted in the scientific literature analyzed (13,15,16). However, in severe cases Botox injection might not be enough to treat sialorrhea, frequency and dose of injections will need to be increased and combination with surgical treatment might be required (13).

Parotid and submandibular glands are the ones where Botox should be injected by Botox in doses of 25U to 70U and no more than 40U. It is usually injected with ultrasound guidance to ease the application but effectiveness is equal while not using such guidance (1,3,6,7,14,15,17).

Frey syndrome

Botox effectiveness in Frey syndrome therapy has been proven in many articles (1,4,7,15). Indeed, in the most favorable case, its action is very long, up to 2 years, reducing the possibility of body immunization regarding Botox, and making it a very comfortable treatment option for the patients with increase intervals between injections (1,7,15,17).

However, protocols for the injection procedure must be more searched as it was reported in only 44 % of the articles that confirmed Botox efficiency for this syndrome (1,3,7,17).

5.4 ADJUNCTIVE TREATMENT

Botox can be combined with other treatment of the maxillofacial field to improve their final outcome (5,6,12,14,15,17). However, more clinical trials should be done for its use to be recognized in maxillofacial trauma and fracture, implantology, orthodontics, and

prosthodontics, and should provide additional information regarding site and dose of injection (3,12,14,15,17) .

Maxillofacial trauma and fracture

Botox is a good product to be used with surgery when maxillofacial fracture or trauma is present since it achieves great outcome without significant complications. The protocol of injection is unclear, although it seems that the site of injection will depend on the area of the fracture and in general includes the temporalis and masseter muscles (3,5,6,12,14,15,17).

In implantology

The success of implant procedures may be increased with the use of Botox that favors osseointegration. Again, no complications were reported, which makes it an ideal product to be used as an adjunctive therapy when performing implant placement, but further studies are required to prove its advantage in implantology (5,6,8,12,14,15,17).

It was mainly injected in the temporalis muscle and masseter muscle to reduce the occlusal load (8,12,17).

In orthodontics

Botox is an ideal drug to be used in orthodontic therapies both during and after the procedure (3,8,12,14). Indeed, while used simultaneously with orthodontic therapy, it shortens the time of treatment and while used after the procedure, it prevents relapses (3,8). However, for its use to be really effective, therapies that help the muscle movement to be normal, must be performed after Botox use (3,12,14).

In prosthodontics

Information regarding Botox use in prosthodontics was scarce and do not allow to make a clear conclusion, even though its benefits when used in patients with poor adaptation to removable prosthesis was demonstrated (3,12,14).

6. CONCLUSION

Botulinum toxin is safe and easy to handle. It shows promising results in the treatment of many orofacial disorders of the dentistry field and has been approved by the FDA for some of them. Also, it has been reported to be a great additional therapy in dentistry in situation where we use prosthesis, implant surgery, orthodontics and others. Its use must be regulated and performed by aware and well-prepared professionals.

However, further trials must be performed to get the final approval of Botox for most of the previously mentioned diseases by the FDA and to be clear about what injection protocol should be followed especially with respect to the correct site and dose of injection for each of the disorders. It seems that Botox has many other yet unknown benefits and should be well worth discovering by extensive research in the field in the future.

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ANNEXES

ANNEXES 2 – FIRST PAGE OF ARTICLES

1. Nagi R, Jain S, Naidu G, Patil D, Sahu S. Botulinum toxin in the management of head and neck disorders. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology [Internet]. 2017;123(4). Available from: https://pubmed.ncbi.nlm.nih.gov/28159584/

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Botulinum toxin in the management of head and neck disorders

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Botulinum toxin is a polypeptide protoxin synthesized by *Clostridium botulinum* that results in localized reduction of muscle activity by inhibiting acetylcholine release at the neuromuscular junction. In 2004, the US Food and Drug Administration approved its application in the treatment of various medical conditions, such as facial wrinkles, strabismus, cervical dystonia, blepharospasm, and hyperhidrosis. Later, its application extended to improving dental esthetics and gummy smile. It was found to be a safe and effective alternative to medical therapy to treat various head and neck disorders that have a neurologic component. In this review, we will highlight the mechanism of action and therapeutic benefits of botulinum toxin in the management of head and neck disorders. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;123:419-428)

Van Ermengem first discovered botulinum toxin (BTX) in 19th century.[1] Scott et al. in 1973 performed animal experiments by injecting BTX into extraocular muscles and reported its ability to paralyze a given muscle.[2] BTX is one of the most potent naturally occurring biological poisons. Before its discovery in medicine, it was responsible for many accidental deaths. Its first medical use was in 1980, to treat strabismus. Nine years later, the cosmetic effects of the toxin on wrinkles were noted, but it was only in 2002, after Food and Drug Administration (FDA) approval, that BTX gained widespread popularity as an alternative to cosmetic surgery.[3]

Currently, the clinical indications for BTX are rapidly growing from treatment of overactive skeletal and smooth muscles to management of hypersecretory diseases (e.g., hyperhidrosis), blepharospasm, and painful disorders such as chronic migraine and cervicofacial dystonia. Studies have also shown its application in several dental conditions such as temporomandibular disorders, trigeminal neuralgia, muscular spasm, bruxism, oromandibular dystonia, gummy smile, masseteric hypertrophy, and sialorrhea.[4-6] This review discusses the therapeutic use of BTX in head and neck disorders.

BIOCHEMISTRY OF BTX

Botulinum toxin is isolated from an anaerobic spore-forming bacterium, *Clostridium botulinum*. Chemically, it is a 2-chain metalloprotease composed of heavy and light chains with 8 immunologically distinct serotypes (A, B, C1, C2, D, F, G). All but one (C2) are neurotoxins. Serotype A (BTX type A or onabotulinum toxin A, Botox [Allergan, Parsiippany, NJ]) has been the most widely used for a variety of movement and spasticity disorders as well as in cosmetic procedures.[6]

MECHANISM OF ACTION

Neuromuscular blockade

BTX has a neuromuscular blocking effect that results from inhibiting the exocytosis of acetylcholine from presynaptic nerve terminals.[7] BTX is internalized into the cytosol from the neuromuscular junction by binding to different gangliosides, namely synaptic vesicle −2, synaptotagmin I, or synaptotagmin II. Heavy chains of BTX facilitate uptake of the whole molecule into the cytosol, where light chains cleave soluble N-ethylmaleimide−sensitive factor attachment protein receptor (SNARE) complexes in the motor neuron. SNARE proteins play an important role in the fusion of synaptic vesicles with the presynaptic plasma membrane, resulting in release of the neurotransmitter acetylcholine (Ach). Light chains of BTX types A and E mainly cleave synaptosome-associated protein 25 kDa (SNAP 25), and BTX types B, D, F, and G cleave synaptobrevin, a vesicle-associated membrane protein. BTX type C serotype cleaves SNAP 25, syntoxin, and SNARE proteins. The cleavage effect of light chains of BTX prevents the release of Ach from motor neurons, leading to flaccid

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Statement of Clinical Relevance

Use of botulinum toxin results in localized reduction of muscle activity by inhibiting acetylcholine release at the neuromuscular junction. It was found to be a safe and effective alternative to medical therapy to treat various head and neck disorders that have a neurologic component.

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Botulinum Toxin Type A in Dental Medicine

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Abstract

Botulinum toxins (BoNTs) are a product of the bacteria *Clostridium botulinum*. By entering nerve endings, they cleave and inactivate SNARE proteins, which are essential for neurotransmitter release. Prevention of acetylcholine release at the neuromuscular junction causes long-lasting and potentially fatal flaccid paralysis—a major feature of botulism. However, an intramuscular injection of minute amounts of BoNTs, primarily type A (BoNT-A), has useful long-lasting muscle relaxation effects on spastic motor disorders. This characteristic of BoNT-A is widely used in neurology and cosmetics. Over the last few decades, it has been demonstrated that the functions of BoNT-A are not limited to muscle-relaxing or autonomic cholinergic effects but that it can act as an analgesic agent as well. More recently, it was revealed that this antinociceptive effect starts after entering the sensory nerve endings, where these agents are axonally transported to the central nervous system, suggesting that at least part of their analgesic effect might be of central origin. Because of its antinociceptive effect, BoNT-A is currently approved for treatment of chronic migraine; nonetheless, case reports and preclinical and clinical experiments indicating its benefit in numerous potential painful conditions have increased. In the field of dentistry, the US Food and Drug Administration approved BoNT-A for the treatment of sialorrhea only. Legal status of the use of BoNT-A in other countries is less known. However, there are controlled clinical trials suggesting its efficacy in other conditions, such as bruxism, temporomandibular disorders, and trigeminal neuropathic pain. Thereby, using criteria of the American Academy of Neurology, we critically reviewed the uses of BoNTs in oral medicine and found it effective for trigeminal neuralgia (category A) and probably effective in temporomandibular disorders and bruxism.

Keywords: temporomandibular disorder, bruxism, trigeminal neuralgia, sialorrhea, neuropathic pain, chronic pain

Introduction

Botulinum toxins (BoNTs) are a product of the anaerobic bacteria *Clostridium botulinum* and related species. BoNTs enter nerve endings, cleaving and inactivating SNARE proteins (soluble N-ethylmaleimide-sensitive factor attachment protein receptor), which are essential for neurotransmitter release. The core of the BoNT protein contains heavy (100 kDa) and light (50 kDa) chains. Heavy chain mediates toxin internalization, while light chain, an endopeptidase, cleaves the SNARE complex. All BoNTs share a months-lasting action, which makes them unique pharmacotherapeutic agents. Different BoNTs cleave different proteins inside SNARE. Clinically, the most important BoNT is type A (BoNT-A), which cleaves SNAP25 (synaptosomal nerve-associated protein 25), whereas BoNT-B cleaves the VAMP/synaptobrevin protein. Currently, BoNT-A is made by >20 manufacturers in the United States, Europe, and other parts of the world (Walker and Dayan 2014). Depending on the manufacturers, the content of auxiliary proteins may vary, which could influence its pharmacokinetics and immunogenicity. Therefore, the US Food and Drug Administration (FDA) has designed new names for BoNTs approved in the United States (Walker and Dayan 2014):

Botox (BoNT-A; Allergan, Inc.): onabotulinumtoxinA
Botox Cosmetic (BoNT-A; Allergan, Inc.): onabotulinumtoxinA
Dysport (BoNT-A; Ipsen Group): abobotulinumtoxinA
Xeomin (BoNT-A; Merz Pharma GmbH & Co. KGaA): incobotulinumtoxinA
Myobloc (BoNT-B; Solstice Neurosciences, LLC): rimabotulinumtoxinB

Interest in research and clinical usage of BoNTs increased exponentially during the past 2 decades. This increase also applies to dental medicine, and BoNT-A and BoNT-B are widely used off-label for various chronic conditions. The FDA approved different brands of BoNTs for treatment of muscle hyperactivity (e.g., dystonia), limb spasticity resulting from neurologic conditions, blepharospasm, strabismus, and similar

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Chapter 6

Botulinum Toxin in Dentistry

Diana Mostafa

Additional information is available at the end of the chapter

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Abstract

Botulinum toxin (BT) is an injectable intermuscular medication that is used as a muscle relaxant. In this chapter, we explore the applications of botulinum toxin in dentistry for either cosmetic or therapeutic purpose, such as gummy smile (high lip line), parafunctional habits, temporomandibular disorders and facial pain. It is considered as a non-invasive, conservative and affordable alternative treatment in comparison to surgical procedures. Although, the effect of BT is temporary that lasts for 4–6 months, it is preferred by most of the patients as it gives positive significant results that meet their desires with minimal side effects.

Keywords: Botox, botulinum toxin, gummy smile, temporomandibular joint disorder, asymmetric smile, reverse smile, drooping mouth corners, facial nerve palsy, migraine, excessive salivation, trigeminal neuralgia, parafunctional habits, maxillofacial fracture

1. Introduction

Botulism toxins are exotoxins produced by anaerobic, Gram-positive, rod-shaped, motile bacteria of the genus *Clostridium*, which is called *Clostridium botulinum*, *C. butyricum*, *C. baratii* and *C. argentinense* [1], which are widely distributed in the surrounding environment, including the soil and dust. Also, some food products such as honey, canned and not well cooked food may contain amounts of these bacteria [2]. These bacteria are divided into four distinct phenotypic groups (I–IV) and is also classified into seven serotypes (A–G) based on the antigenicity of the botulinum toxin produced [3]. The most common ones are Botulinum toxin type A and B. However, Onabotulinumtoxin A is marketed under brand names Botox®, Vistabel® and Vistabex®, while Abobotulinumtoxin A is marketed under the brand names Dysport® and Azzalure®. In addition, incobotulinumtoxin A is marketed under the brand names Xeomin®, Xeomeen®, and Bocouture®. Whereas, botulinum toxin

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CLINICAL REVIEW

An evidence-based review of botulinum toxin (Botox) applications in non-cosmetic head and neck conditions

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Contributorship
RP and GG conceived the idea and wrote the initial draft of the paper after reviewing most of the relevant literature. SS, CS and PC also reviewed some of the relevant literature and contributed to the manuscript as well as editing various drafts. KP had access to the data, reviewed and corrected the

Summary

Botulinum toxin (Botox) is an exotoxin produced from *Clostridium botulinum*. It works by blocking the release of acetylcholine from the cholinergic nerve end plates leading to inactivity of the muscles or glands innervated. Botox is best known for its beneficial role in facial aesthetics but recent literature has highlighted its usage in multiple non-cosmetic medical and surgical conditions. This article reviews the current evidence pertaining to Botox use in the head and neck. A literature review was conducted using The Cochrane Controlled Trials Register, Medline and EMBASE databases limited to English Language articles published from 1980 to 2012. The findings suggest that there is level 1 evidence supporting the efficacy of Botox in the treatment of spasmodic dysphonia, essential voice tremor, headache, cervical dystonia, masticatory myalgia, sialorrhoea, temporomandibular joint disorders, bruxism, blepharospasm, hemifacial spasm and rhinitis. For chronic neck pain there is level 1 evidence to show that Botox is ineffective. Level 2 evidence exists for vocal tics, trigeminal neuralgia, dysphagia and post-laryngectomy oesophageal speech. For stuttering, 'first bite syndrome', facial nerve paresis, Frey's syndrome, oromandibular dystonia and palatal/stapedial myoclonus the evidence is level 4. Thus, the literature highlights a therapeutic role for Botox in a wide range of non-cosmetic conditions pertaining to the head and neck (mainly level 1 evidence). With ongoing research, the spectrum of clinical applications and number of people receiving Botox will no doubt increase. Botox appears to justify its title as 'the poison that heals'.

Introduction

Botulinum toxin (Botox) is a protease exotoxin produced from *Clostridium botulinum*. It works by blocking the release of acetylcholine from cholinergic nerve endings causing inactivity of muscles or glands. Its effects are transient and may be graded by varying the dose and frequency of administration. Botox is one of the most potent naturally occurring biological poisons and in the

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Use of a botulinum toxin A in dentistry and oral and maxillofacial surgery

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Botulinum toxin (BT) was the first toxin to be used in the history of human medicine. Among the eight known serotypes of this toxin, those currently used in medicine are types A and B. This review article mainly discusses BT type A (BTA) because it is usually used in dentistry including dental anesthesiology and oral and maxillofacial surgery. BTA has been used mainly in the treatment of temporomandibular joint disorder (TMD) and hypertrophy and hyperactivity of the masticatory muscles, along with being a therapeutic option to relieve pain and help in functional recovery from dental and oral and maxillofacial surgery. However, it is currently used broadly for cosmetic purposes such as reducing facial wrinkles and asymmetry. Although the therapeutic effect of BTA is temporary and relatively safe, it is essential to have knowledge about related anatomy, as well as the systemic and local adverse effects of medications that are applied to the face.

Keywords: Botulinum toxin; Botulinum toxin, type A; Dentistry; Oral and Maxillofacial Surgeons.

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History of medical use of botulinum toxin (BT)

Botulism is derived from the Latin word botulus, which means black sausage, and has been known as food poisoning caused by the ingestion of rotten meat. Botulinum toxin (BT), initially found in rotten sausage, induces food poisoning, which leads to mydriasis and skeletal muscle paralysis. This toxin was initially reported by Justinus Kerner in 1817, and the possibility of using it to relax the hyperactivated motor system was subsequently reported [1,2]. Van Ermengem, a Belgian microbiologist, succeeded in isolating a pathogen from the feces of a patient who ingested rotten sausage in 1897, and named it Bacillus botulinus, which was renamed Clostridium botulinum in 1922. Further, the study was translated and published in English in 1979 [3]. Schantz succeeded in producing massive amounts of BT, and the discovery by Burgen that BT played a role in presynaptic acetylcholine inhibition in 1949 laid the foundation for the clinical application of this toxin [4]. BT type A (BTA) was initially used by Scott [5-7] in 1973 and became the first toxin to be adopted in medicine, with the approval by the US Food and Drug Administration (FDA) in the treatment of adult strabismus and blepharospasm in 1989. Subsequently, while treating a patient with blepharospasm using BTA, Carruthers and Carruthers [8] serendipitously discovered that it reduced the appearance of wrinkles in the glabellar region. They reported that this resulted from the relaxation of the muscles that control facial expressions. Then, they found that it was also effective on wrinkles around the eyes and the nasolabial

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Applications of Botulinum Toxin in Dentistry - Literature Review

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Abstract

The Botulinum Neurotoxins are produced by the anaerobic bacterium *Clostridium botulinum* and are considered the most potent toxins known and its application has become useful and significant in the treatment of oral and maxillofacial injuries. The aim of this study was to review the literature showing the possible therapeutic uses of botulinum toxin in dentistry. There were used articles, that describe the injection of botulinum toxin type A (BTX-A) in areas related to the oral cavity and face, excluding cosmetic purposes. The results show that a toxin is a viable treatment alternative, with beneficial effects in dentistry, but in some cases should be associated with other types of treatment. Although the literature confirm the effectiveness of the BTX-A, these studies should be interpreted cautiously, and more research is needed to confirm the safety and effectiveness of this treatment in larger, well-controlled clinical studies.

Keywords: Botulinum toxin type A; Dentistry

Introduction

The application of botulinum toxin (BTX) has become a useful and significant tool in the control of oral and maxillofacial injuries. Its application began the aesthetic use but has been very effective in various other clinical or surgical medical specialties [1].

Botulinum neurotoxin is synthesized by the Gram-positive, anaerobic, bacterium *Clostridium botulinum* and is considered the most potent toxin known [2]. The neurotoxins produced are proteins, and seven different serological types have been identified (A, B, C1, D, E, F and G), but the most widely used is the Botulinum Type A Toxin (BTX-A) [3,4]. The United States was the first to produce BTX-A during World War II, but the development of Botulinum neurotoxin as drug began in 1981 with the description of the use of BTX-A for the treatment strabismus. In 1989, after thorough clinical and laboratory tests, the Food and Drug Administration (FDA) approved the therapeutic use of BTX-A, for treatment of strabismus, blepharospasm, and hemifacial spasm in patients over 12 years of age. In 2000 the FDA approved BTX for dystonia and in 2002 it was approved for the temporal management of glabellar lines [5,6].

Normally, the brain sends messages to the muscles to contract and to promote the movement. The message is transmitted through a substance called acetylcholine. Botulinum toxin blocks the presynaptic release of acetylcholine (Ach) into the end-plate of the neural junction by interfering with the activity of SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) proteins [7] and as a result, the muscle does not receive the message to contract, but without any systemic effects [8,9]. BTX produces partial muscle chemical denervation, resulting in localized reduction of muscular activity and can be used as a single therapy or as an adjunct to another treatment [10].

It has been proposed that BTX reduces pain directly by producing molecular changes in nociceptive fibres function, blocking the release of neurotransmitters [11,12], and indirectly by reducing excess dysfunctional muscle activity has been reported to have analgesic effects independent of its action on muscle tone [7].

Clinical effects of BTX-A occur within approximately 24-48 h after administration, peaking at 2-3 weeks. Effects generally last about 4 months, then level off to a moderate plateau until eventually full nerve recovery occurs within 3 to 6 months [13,14].

In dentistry, the toxin is used as a form of control for temporomandibular disorders (TMD), headaches, trigeminal neuralgia, migrane, myofacial pain, gummy smile, asymmetrical smile,

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REVIEW ARTICLE

Therapeutic applications of botulinum neurotoxins in head and neck disorders

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KEYWORDS

Botulinum toxin;
Botox;
Temporomandibular disorder;
Dystonia;
Facial pain

Abstract *Objective:* The aim of this article is to review the mechanism of action, physiological effects, and therapeutic applications of botulinum neurotoxins in the head and neck area.

Study design: An extensive literature search was performed using keywords. The resulting articles were analyzed for relevance in four areas: overview on botulinum neurotoxins, the role of botulinum neurotoxins in the management of salivary secretory disorders, the role of botulinum neurotoxins in the management of facial pain, and the role of botulinum neurotoxins in head and neck movement disorders. Institutional review board approval was not needed due the nature of the study.

Results: Botulinum neurotoxin therapy was demonstrated to be a valuable alternative to conventional medical therapy for many conditions affecting the head and neck area in terms of morbidly, mortality, and patient satisfaction with treatment outcomes.

Conclusion: Botulinum neurotoxin therapy provides viable alternatives to traditional treatment modalities for some conditions affecting the head and neck region that have neurological components. This therapy can overcome some of the morbidities associated with conventional therapy.

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Maxillofacial Plastic and Reconstructive Surgery

REVIEW Open Access

Application of botulinum toxin in maxillofacial field: Part III. Ancillary treatment for maxillofacial surgery and summary

Kyung-Hwan Kwon*, Kyung Su Shin, Sung Hee Yeon and Dae Gun Kwon

Abstract

Botulinum toxin (BTX) has various therapeutic indications: bruxism, square jaw, facial wrinkle, oral ulcer and maxillofacial pain, etc. In this paper, we will discuss the effectiveness of using BTX in dental implant surgery and orthognathic and orthodontic treatment. We summarized the clinical application of botulinum toxin in the maxillofacial field at the finale.

Keywords: Botulinum toxin, Clinical application, Maxillofacial field, Dental implant, Orthognathics, Orthodontics, Maxillofacial pain

Background

Botulinum toxin (BTX) weakens the muscle and the temporary muscle paralysis may improve post-operative recovery and healing [1]. In the case of multiple implants or immediate loaded implants, osseointegration can be delayed by excessive functional forces in patients with a parafunctional habit [2]. The muscular relaxation by using BTX can be beneficial by allowing implant structures better osseointegrated [3]. In maxillofacial surgery, BTX was useful in the wound healing process of facial lacerations requiring surgery. And also, BTX has been used to reduce the displacing forces on the fracture site [4]. By reducing the force of masseteric muscle, orthognathic and orthodontic treatment may be improved. However, the research about the clinical use of botulinum toxin for implant and maxillofacial surgery is yet insufficient. It may be necessary to discuss about application of botulinum toxin in these fields.

Main text

Clinical application of botulinum toxin in immediate loading and immediate postextraction implant surgery

Implant occlusion and osseointegration

Basically, an implant is connected by a screw structure, and when lateral pressure is applied, it will exert a torque causing loosening of the prosthesis fixing screw of the upper structure or loosening of the abutment screw, which ultimately leads to the disintegration of the implant fixture. Additionally, according to the study of Richter, even though the effect of excessive occlusal pressure acting on natural teeth and implants do not differ each other much, the grinding and clenching of natural teeth, such as bruxism, cause excessive attrition of teeth, and for the case of implants, it results in damage to the implant fixture or the upper structure of implants [5]. Isidor noted that most of the implants that received excessive occlusal pressure are having osseointegration failure and would require measures against non-functional or parafunction mostly caused during the sleep [6].

Countermeasure for bruxism

A study by Duyck et al. have also shown that if the number of implants decreases, the amount of bite pressure exerting on implants increases [7]. Therefore, increasing the number of implants withstanding the bite pressure is considered one of the measures against parafunction. However, due to financial issues and the location of implants, there is a case where only a small number of implants are used for prosthetic restoration. According to the report by Maan et al., the muscle activities of the masseter muscles undergone occlusion therapy such as bite plane treatment have reduced [8]. The study of al-

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Review Article

Botox Therapy in Dentistry: A Review

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Abstract:

There are many medical and dental conditions which do not have complete treatment modalities in conventional ways. The botulinum toxin can be used as an alternative treatment modality working through chemo denervation method in many medical and dental conditions. An internet research was done for botulinum toxin used in dentistry and all articles and studies were selected, articles related to dentistry were extracted and summarized. This article explains the basic of botulinum toxin and some of its uses in dentistry. In next parts, the extensive details of its use in dentistry will be dealt with.

Key Words: Botox, botulinum toxin, bruxism, chemodenervation, cosmetics, dentistry, facial wrinkles, temporomandibular disorders

Introduction

Botulinum toxin used in dentistry for the treatment conditions, such as parafunctional clenching, extracapsular myogenic temporomandibular disorder, trismus, and the associated headaches, is a new option for symptom relief in patients in whom conventional treatments are not effective.[1]

Botulinum toxin which is available in the market is purified exotoxin of the anaerobic bacteria, clostridium botulinum. This neurotoxin is the cause of serious paralytic illness, botulism. Seven types of botulinum toxins have been isolated but only two, Types A and B, have been made commercially available. Initially, only botulinum toxin A was available commercially on prescription but more recently, Type B also available in the market.[2]

Botulinum Toxin Overview[3]

Botulinum toxin is a deadly poison produced by a Gram-positive bacterium called c botulinum. The bacteria produce 7 antigenically distinct toxins that are lettered A through G. Toxin A, however, has been the most extensively studied. The clinical syndrome of botulism occurs after ingestion of contaminated food, from colonization of the infant gastrointestinal tract, or from wound infection. When foods containing the toxin are ingested, the toxin spreads to peripheral cholinergic nerve endings and blocks acetylcholine release. This results in a bilaterally symmetric descending neuroparalytic illness. The incubation period after ingestion is 18-36 h. In human beings, botulism is mainly caused by Types A, B, E, and rarely F, whereas in animals, it is caused by Types C and D. The toxin is heat labile and denatured by cooking.

History[3]

The idea for a possible therapeutic use for botulinum toxin was first developed by the German physician Justinus Kerner (1786-1862). He deduced that the toxin acted by interrupting signal transmission within the peripheral sympathetic nervous system, leaving sensory transmission intact. He called the toxin a "sausage poison," because it was observed that illness followed ingestion of spoiled sausage. In 1870, John Muller, another German physician, coined the name "botulism" (from the Latin root botulus, which means "sausage"). In 1949, Burgen was the first to discover that the toxin was able to block neuromuscular transmission. Scott *et al.* proved this fact by experimentally administering the Type A strain in monkeys. This strain was approved by the US Food and Drug Administration (FDA) in 1989 under the trade name Botox (Allergan, Inc, Irvine, Calif) for treating strabismus, blepharospasm, and hemifacial spasm in patients younger than 12-year-old. In the year 2000, Botox was approved for use in treating cervical dystonia (wry neck) and 2 years later for the temporary improvement of moderate to severe frown lines between the eyebrows (glabellar lines). Serotype B has been FDA approved for treating cervical dystonia, and serotype F is under investigation in patients who are resistant to serotypes A and B.

Mechanism of Action[3,4]

The botulinum toxin causes muscle paralysis by inhibiting acetylcholine release at the neuromuscular junction via 3 steps as shown in the Flow chart 1.

Preparation[3]

Botox is prepared by laboratory fermentation of C botulinum, which lyses and liberates the toxin into the culture. The toxin is then harvested, purified, crystallized with ammonium sulfate, diluted with human serum albumin, lyophilized, bottled in

10. Satriyasa BK. Botulinum toxin (Botox) a for reducing the appearance of facial wrinkles: A literature review of clinical use and pharmacological aspect. Clinical, Cosmetic and Investigational Dermatology [Internet]. 2019 Apr [cited 2020 Oct 9] ; 12 : 223-228. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6489637/

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REVIEW

Botulinum toxin (Botox) A for reducing the appearance of facial wrinkles: a literature review of clinical use and pharmacological aspect

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Clinical, Cosmetic and Investigational Dermatology

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Background: Botulinum toxin (Botox) consists of 7 types of neurotoxins; however, only toxins A and B are used clinically. Botox A is used for several disorders in the field of medicine, particularly in dermatology, for cosmetic purposes. It is produced by the bacterium *Clostridium botulinum* and can be used as a treatment to reduce the appearance of wrinkles in the upper areas of the face, elevate the eyebrows and treat problems such as hyperhidrosis, lichen simplex, pompholyx (dyshidrotic eczema) and acne vulgaris.

Objectives: This article provides a literature review regarding the general issue of Botox as a treatment for reducing facial wrinkle.

Discussion: Botox works by blocking the release of acetylcholine, resulting in paralysis of the local muscles, which usually occurs 24 hrs to two weeks following Botox injection. This effect will last three to six months. The optimal dose of cosmetic Botox in dermatology is 20 units. Botox is relatively safe and does not result in any adverse side effects. However, in certain circumstances, the effect of Botox will gradually resolve, resulting in reduced muscle paralysis over time.

Conclusion: Botox is good and safe medicine to reduce the appearance of facial wrinkles.

Keywords: Botox, botulinum toxin, drug, facial wrinkles

Introduction

Botulinum toxin (Botox) is a drug made from a toxin produced by the bacterium *Clostridium botulinum*. In large amounts, this toxin can cause botulism, an illness that affects the nerves. Botox has been used since the 1970s in the field of ophthalmology, and in the last 20 years, its use has expanded to various health scopes, especially dermatology.[1,2]

Botox consists of 7 types of neurotoxins; however, only toxins A and B are used clinically. Botox A is used for several disorders in the field of medicine, particularly in dermatology, for cosmetic purposes.[3] The first type of Botox introduced to the market was onabotulinum toxin A. In 2002, it was recommended to be used as a cosmetic treatment for glabellar frown lines by the Food and Drug Administration (FDA).[2,4,5] The second formulation of onabotulinum toxin A, which was produced in France, obtained its license to be used for esthetic purposes from the European Union in 2006 and was approved by the FDA in 2009.[5,6] Botox type A has become a term used by the society to describe all ingredients used in cosmetic treatments.[7]

A study in 1994 reported the effectiveness of Botox A for reducing the appearance of facial wrinkles; since then, it has been used as a cosmetic treatment.[8] Botox injections can be used to treat glabellar frown lines, wrinkles

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Review Article

Botulinum toxin the poison that heals: A brief review

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ABSTRACT

Botulinum neurotoxins, causative agents of botulism in humans, are produced by *Clostridium botulinum*, an anaerobic spore-former Gram-positive bacillus. Botulinum neurotoxin poses a major bioweapon threat because of its extreme potency and lethality; its ease of production, transport, and misuse; and the need for prolonged intensive care among affected persons. This paper aims at discussing botulinum neurotoxin, its structure, mechanism of action, pharmacology, its serotypes and the reasons for wide use of type A, the various indications and contraindications of the use of botulinum neurotoxin and finally the precautions taken when botulinum neurotoxin is used as a treatment approach. We have searched relevant articles on this subject in various medical databases including Google Scholar, PubMed Central, ScienceDirect, Wiley Online Library, Scopus, and Copernicus. The search resulted in more than 2669 articles, out of which a total of 187 were reviewed. However, the review has been further constricted into only 54 articles as has been presented in this manuscript keeping in mind the page limitation and the limitation to the number of references. A single gram of crystalline toxin, evenly dispersed and inhaled, can kill more than one million people. The basis of the phenomenal potency of botulinum toxin (BT) is enzymatic; the toxin is a zinc proteinase that cleaves neuronal vesicle-associated proteins responsible for acetylcholine release into the neuromuscular junction. A fascinating aspect of BT research in recent years has been the development of the most potent toxin into a molecule of significant therapeutic utility. It is the first biological toxin which is licensed for the treatment of human diseases. The present review focuses on both warfare potential as well as medical uses of botulinum neurotoxin.

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Key words: Botulinum toxin, botulism poisoning, facelift, Frey's syndrome, neuromuscular junction

Introduction

The neurotoxin called botulinum toxin (BT) is produced by the bacterium *Clostridium botulinum*. This toxin is capable of causing muscle paralysis by blocking the release of Ach at the neuromuscular (NM) junction of striated muscle. Among the several types of BT, subtype A (Botox, Allergan, Inc., Irvine, CA, USA) is the most potent toxin produced by the bacterium.[1] The basis of botulinum neurotoxin therapy is the localized inhibition of exocytosis from selected neurons after the toxin has been injected into specific target areas such as muscles. The local route of administration along with the specific features of the neurotoxin formulation results in such properties.[2] The BT Type A (BT-A) is a purified

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Review Article

Dentistry Section

BOTOX: Broadening the Horizon of Dentistry

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ABSTRACT

Botox has been primarily used in cosmetic treatment for lines and wrinkles on the face, but the botulinum toxin that Botox is derived from has a long history of medically therapeutic uses. For nearly 13 years, until the introduction of Botox Cosmetic in 2002, the only FDA-approved uses of Botox were for crossed eyes (strabismus) and abnormal muscle spasms of the eyelids (blepharospasm). Since then botulinum A, and the seven other forms of the botulinum toxin, have been continuously researched and tested. Botox is a neurotoxin derived from *bacterium clostridium botulinm*. The toxin inhibits the release of acetylcholine (ACH), a neurotransmitter responsible for the activation of muscle contraction and glandular secretion, and its administration results in reduction of tone in the injected muscle. The use of Botox is a minimally invasive procedure and is showing quite promising results in management of muscle-generated dental diseases like Temporomandibular disorders, bruxism, clenching, masseter hypertrophy and used to treat functional or esthetic dental conditions like deep nasolabial folds, radial lip lines, high lip line and black triangles between teeth.

Keywords: Black triangles, Botulinum toxin A, Bruxism, Gummy smile, Hyperfunction

INTRODUCTION

Many of us think of Botox primarily as a cosmetic treatment for lines and wrinkles on the face, but the botulinum toxin that Botox is derived from has a long history of medically therapeutic uses such as in cervical dystonia, hyperhidrosis, strabismus and blepharospasm. Botox has now been increasingly used in dentistry as well due to its therapeutic uses in treatment of certain oral conditions. The Dental Quality Assurance Commission (DQAC) of Washington has released an interpretive statement effective July 26, 2013, which now affirms the ability of general dentists to use Botox and dermal fillers when "used to treat functional or aesthetic dental conditions and their direct aesthetic consequences and the treating dentist has appropriate, verifiable training and experience."Similarly, Michigan board of dentistry and New Jersey state board also approves the use of Botox and dermal fillers by general dentists. Botulinum toxin is a protein and neurotoxin produced by the *bacterium Clostridium botulinum* [1] [Table/Fig-1] [2]. Currently, seven botulinum neurotoxin serotypes (A, B, C1, D, E, F, and G) produced by *Clostridium botulinum*, are recognized. Although botulinum toxin is a lethal, naturally occurring substance, it can be used as an effective and powerful medication [3].

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.

Each vial of BOTOX contains-

1. 100 Units (U) of *Clostridium botulinum* type A neurotoxin complex,
2. 0.5 milligrams of Albumin Human,
3. And 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative.

Botulinum toxin type A can be used in following dental conditions:-

1. Temporomandibular joint disorders
2. Bruxism
3. Oromandibular dystonia
4. Mandibular spasm
5. Pathologic clenching
6. Dental implant and surgery
7. Gummy smile
8. Masseteric hypertrophy

MECHANISM OF ACTION

Injecting overactive muscles with minute quantities of botulinum toxin type-A results in decreased muscle activity. Botulinum toxin type-A inhibits the exocytosis of acetylcholine on cholinergic nerve endings of motor nerves [4], as it prevents the vesicle where the acetylcholine is stored from binding to the membrane where the neurotransmitter can be released. Botulinum toxin achieves this effect by its endopeptidase activity against SNARE proteins, which are 25-kd synaptosomal associated proteins that are required for the docking of the ACH vesicle to the presynaptic membrane [5]. Botulinum toxin type-A thus blocks the release of acetylcholine by the neuron. This effectively weakens the muscle for a period of three to four months [6].

TEMPOROMANDIBULAR JOINT DISORDERS

Temporomandibular disorder (TMD) is a term used to describe a number of diseases affecting masticatory function, which may include true pathology of the temporomandibular joint as well as masticatory muscle dysfunction [7,8]. TMD manifests with facial pain, joint sounds, headache, peri-auricular pain, neck pain, and/or decreased jaw excursion. The majority of TMD cases include a myogenic component [9,10] and muscular spasticity secondary to bruxism, external stressors, oromandibular dystonia, and psychomotor behaviours are common aetiologic factors of TMD [11].

TMD caused by excessive biting forces has conventionally been treated with intraoral appliances, occlusal adjustments, dental restoration, and/or surgery. These techniques are invasive, irreversible, and expensive for the majority of patients.

Techniques currently employed for aesthetic, conservative restorations may not withstand the parafunctional forces continually applied by some patients. Thus, many of these treatment options are not ideal for all patients, and muscular relaxation with botulinum toxin A is a viable alternative. When a muscle relaxant is used with the muscles of mastication, this clenching reflex can be reduced or eliminated [12]. Because a very small percentage of available force is required to masticate food, a slight relaxation of muscle function reduces bruxing and is usually insufficient to affect chewing and swallowing [13].

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Review

Use of Botulinum Toxin in Orofacial Clinical Practice

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Abstract: Introduction: Botulinum neurotoxin (BoNT) is a potent biological toxin and powerful therapeutic tool for a growing number of clinical orofacial applications. BoNT relaxes striated muscle by inhibiting acetylcholine's release from presynaptic nerve terminals, blocking the neuromuscular junction. It also has an antinociceptive effect on sensory nerve endings, where BoNT and acetylcholine are transported axonally to the central nervous system. In dentistry, controlled clinical trials have demonstrated BoNT's efficiency in pathologies such as bruxism, facial paralysis, temporomandibular joint (TMJ) disorders, neuropathic pain, sialorrhea, dystonia and more. Aim: This study's aim was to conduct a systematic literature review to assess the most recent high-level clinical evidence for BoNT's efficacy and for various protocols (the toxin used, dilution, dosage and infiltration sites) used in several orofacial pathologies. Materials and methods: We systematically searched the MedLine database for research papers published from 2014 to 2019 with randomly allocated studies on humans. The search included the following pathologies: bruxism, dislocation of the TMJ, orofacial dystonia, myofascial pain, salivary gland disease, orofacial spasm, facial paralysis, sialorrhea, Frey syndrome and trigeminal neuralgia. Results: We found 228 articles, of which only 20 met the inclusion criteria: bruxism (four articles), orofacial dystonia (two articles), myofascial pain (one article), salivary gland disease (one article), orofacial spasm (two articles), facial paralysis (three articles), sialorrhea (four articles) or trigeminal neuralgia (three articles). Discussion: The clinical trials assessed showed variations in the dosage, application sites and musculature treated. Thus, applying BoNT can reduce symptoms related to motor muscular activity in the studied pathologies efficiently enough to satisfy patients. We did not identify the onset of any important side effects in the literature reviewed. We conclude that treatment with BoNT seems a safe and effective treatment for the reviewed pathologies.

Keywords: botulinum toxin; bruxism; salivary fistula; facial spasm; sialorrhea; orofacial dystonia; myofascial pain; facial paralysis; Frey syndrome; lockjaw; trigeminal neuralgia

Key Contribution: Treatments with BoNT in the oral area have aroused interest, as expressed in the studies and clinical indications reviewed in the present work.

1. Introduction

1.1. History

Botulinum toxin (Botox, BoNT) emerged in the 19th century when the Belgian bacteriologist van Ermengem discovered it in 1895. This bacterium produces a protein that can produce the most powerful neurotoxic substance known. In the 1920s, Sommer isolated BoNT type A (BoNT-A) in

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Review Article

Applications of botulinum toxin in dentistry: A comprehensive review

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ABSTRACT

The horizons of treatment options in dentistry are broadening rapidly. In this scenario, applications of unconventional treatment options like use of botulinum toxin (BT) are gaining momentum. The use of BT has been popularly accepted in esthetic procedures like management of facial wrinkles; however, it has been documented to be successful in a variety of conditions. Of particular interest to this paper are applications of BT in the maxillofacial region, concerned to dentistry. BT offers a transient, reversible, relatively safe treatment option to many conditions of interest to a dental practitioner. Dental surgeons by their virtue of being extensively aware of the anatomy of faciomaxillary region are a potential pool of operators who can use BT in their armamentarium with minor skill enhancement and thus widen the perspective of alternative, minimally invasive options to refractory conditions or invasive protocols.

Key words: Botulinum toxin A, bruxism, gummy smile, temporomandibular joint disorders

Introduction

"Botulism" is a life-threatening disease first described by Kerner.[1] It is caused by botulinum toxin (BT) also known as botulinum neurotoxin produced under anaerobic conditions by *Clostridium Botulinum*. Botulinum is one of the most lethal toxins known and has found applications in bioterrorism as well.[2] However, botulinum toxin is a double-edged sword. Botulinum is the first toxin to be accepted for therapeutic uses. Since the first therapeutic use by Scott for strabismus[3] till today, the spectrum of therapeutic applications of BTs has widened. BTs can be differentiated into seven types from A to G. However, commercially available variants are purified exotoxin and only BT type A (BTA) and BT type B (BTB) are marketed by various brand names.

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BTA is marketed as follows:
- Botox® (Allergan, Irvine, CA) in the USA
- Dysport® (Speywood Pharmaceuticals, Maidenhead, UK) in Europe
- Xeomin® (Merz Pharmaceuticals, Germany) in Germany
- Prosigne® (Lanzhou Biological Products Institute, China) in China.

BTB is marketed as follows:
- Myobloc® (Elan Pharmaceuticals, San Diego, CA) and
- Neurobloc® (Elan Pharmaceuticals, Shannon, County Clare, Ireland).

Mechanism of Action

BT produces a transient dose-dependent weakening of muscle activity.[4] It is a neurotoxin and produces

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Review Article

Botulinum toxin: The Midas touch

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Abstract

Botulinum Toxin (BT) is a natural molecule produced during growth and autolysis of bacterium called *Clostridium botulinum*. Use of BT for cosmetic purposes has gained popularity over past two decades, and recently, other therapeutic uses of BT has been extensively studied. BT is considered as a minimally invasive agent that can be used in the treatment of various orofacial disorders and improving the quality of life in such patients. The objective of this article is to review the nature, mechanism of action of BT, and its application in various head and neck diseases.

Key words: Botulinum toxin, head and neck disease, temperomandibular diseases

INTRODUCTION

Botulism is a rare but serious illness caused by botulinum toxin (BT), which is metabolic waste produced under anaerobic conditions by the bacterium *Clostridium botulinum*, a condition first described by Justinus Kerner.[1,2] This is a life-threatening disease characterized by paralysis of muscles of face, limbs and in severe cases, paralysis of respiratory muscles leading to respiratory failure and death.[3] Although BT is a lethal toxin, it can be used as an effective and powerful medication by injecting in minute quantities of toxin into the overactive muscles. A.B Scott was first to use BT therapeutically to correct strabismus injecting the standardized toxin into external eye muscles.[4] Use of BT for cosmetic purposes has gained popularity over past two decades since it has been approved by the Food and Drug Administration (FDA) for therapeutic treatments of eye muscle problems (in 1989), neck problems (in 2000), and excessive sweating (in 2004). Recently, other therapeutic uses of BT have been extensively studied, and BT is considered as an agent that can be used in the treatment of various orofacial disorders.[5] The objective of this article is to review the nature, mechanism of action of BT, and its application in various head and neck diseases.

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NATURE OF TOXIN

BT is a natural molecule produced during growth and autolysis of anaerobic gram-positive bacterium called *Clostridium botulinum*. BT can be differentiated serologically into eight kinds of toxins named from A to G (A, B, Cb C2, D, E, F, and G).[6,7] These toxins occur both naturally and in *in vitro* culture.[8] Commercially available BT are botulinum toxin type A (BTA) and botulinum toxin type B (BTB), both of these have 150-Kd dichain polypeptides. BTA and BTB have light and a heavy chain connected with disulfide bond. Light chain of BTA bond with 5-Kd synaptosome-associated protein (SNAP-25), a protein which plays a major role in acetylcholine secretion from vesicle in the nerve ending. Light chain of BTB bond with synaptiobevin or vesicle-associated membrane protein (VAMP), which is less specific. For this reason, BTA is more effective as compared to BTB.[9]

MECHANISM OF ACTION

The BT primarily acts on cholinergic receptors and prevents the release of neurotransmitter Acetyl choline, thus causing widespread paralysis of muscles, characteristic feature of botulism infection.[8] When therapeutic dose of BT is administered to isolated muscle, localized paralysis

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REVIEW

The therapeutic usage of botulinum toxin (Botox) in non-cosmetic head and neck conditions – An evidence based review

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Review;
Toxin

Abstract Botulinum toxin (Botox) is an exotoxin produced from Clostridium botulinum. It blocks the release of acetylcholine from the cholinergic nerve end plates resulting in inactivity of the muscles or glands innervated. The efficacy of Botox in facial aesthetics is well established; however, recent literature has highlighted its utilization in multiple non-cosmetic medical and surgical conditions. The present article reviews the current evidence pertaining to Botox use in the non-cosmetic head and neck conditions. A literature search was conducted using MEDLINE, EMBASE, ISI Web of Science and the Cochrane databases limited to English Language articles published from January 1980 to December 2014. The findings showed that there is level 1 evidence supporting the efficacy of Botox in the treatment of laryngeal dystonia, headache, cervical dystonia, masticatory myalgia, sialorrhoea, temporomandibular joint disorders, bruxism, blepharospasm, hemifacial spasm and rhinitis. For chronic neck pain there is level 1 evidence to show that Botox is ineffective. Level 2 evidence exists for vocal tics and trigeminal. For stuttering, facial nerve paresis, Frey's syndrome and oromandibular dystonia the evidence is level 4. Thus, there is compelling evidence in the published literature to demonstrate the beneficial role of Botox in a wide range of non-cosmetic conditions pertaining to the head and neck (mainly level 1 evidence). With more and more research, the range of clinical applications and number of individuals getting Botox will doubtlessly increase. Botox appears to justify its title as 'the poison that heals'.
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REVIEW ARTICLE

Toxin yet not toxic: Botulinum toxin in dentistry

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KEYWORDS

Acetylcholine;
Neurotoxin;
Neurotransmitters;
Oro-facial disorders

Abstract Paracelsus contrasted poisons from nonpoisons, stating that "All things are poisons, and there is nothing that is harmless; the dose alone decides that something is a poison". Living organisms, such as plants, animals, and microorganisms, constitute a huge source of pharmaceutically useful medicines and toxins. Depending on their source, toxins can be categorized as phytotoxins, mycotoxins, or zootoxins, which include venoms and bacterial toxins. Any toxin can be harmful or beneficial. Within the last 100 years, the perception of botulinum neurotoxin (BTX) has evolved from that of a poison to a versatile clinical agent with various uses. BTX plays a key role in the management of many orofacial and dental disorders. Its indications are rapidly expanding, with ongoing trials for further applications. However, despite its clinical use, what BTX specifically does in each condition is still not clear. The main aim of this review is to describe some of the unclear aspects of this potentially useful agent, with a focus on the current research in dentistry.
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Contents

Abbreviations: BTX, botulinum neurotoxin; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; SNAP-25, synaptosomal-associated protein; MPDS, myofacial pain dysfunction syndrome; EMG, electromyography; TGF-β1, transforming growth factor β-1

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REVIEW

Is there enough evidence to use botulinum toxin injections for bruxism management? A systematic literature review

Giancarlo De la Torre Canales[1] & Mariana Barbosa Câmara-Souza[1] & Camilla Fraga do Amaral[1] & Renata Cunha Matheus Rodrigues Garcia[1] & Daniele Manfredini[2]

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Abstract

Objective The objective of the study was to conduct a systematic review of the literature assessing the effects of botulinum toxin (BoNT-A) injections in the management of bruxism.

Materials and methods Search for articles involved the PubMed, Scopus, Web of Science, Embase, Cochrane, Scielo and Lilacs databases. Specific terms were used and the search carried out from 1980 to March 2016 by three independent researchers. Randomized controlled studies (RCTs), prospective and before–after studies that applied BoNT-A at the masseter and/or temporalis muscles were included.

Results Three RCTs and two uncontrolled before–after studies out of 904 identified citations were included in this review. All five articles dealt with sleep bruxism and featured a small sample size. None of them was about awake bruxism. Two randomized clinical trials were double-blinded, with a control group using saline solution. Two studies used polysomnography/electromyography for sleep bruxism diagnosis, whilst others were based on history taking and clinical examination. All studies using subjective evaluations for pain and jaw stiffness showed positive results for the BoNT-A treatment. In contrast, the two studies using objective evaluations did not demonstrate any reduction in bruxism episodes, but a decrease in the intensity of muscles contractions.

Conclusion Despite the paucity of works on the topic, BoNT-A seems to be a possible management option for sleep bruxism, minimizing symptoms and reducing the intensity of muscle contractions, although further studies are necessary especially as far as the treatment indications for bruxism itself is concerned.

Clinical relevance BoNT-A has been increasingly diffused in dentistry over recent years, being also used for pain management in patients with bruxism. Nonetheless, there is no consensus about its effects in this disorder.

Keywords Bruxism · Sleep bruxism · Botulinum toxin type A · Treatment · Facial pain

Introduction

Bruxism is an oral condition of relevance for researchers and clinicians involved in many medical fields, such as sleep medicine, neurology and psychology [1]. It is also a source of concern for dentists due its potential clinical impact on the stomatognathic system [2]. The clinical approach to this phenomenon should actually take into account for its multifaceted nature, viz. bruxism is a term grouping different entities that may have different etiology and clinical consequences, if any [3].

Recently, an international consensus panel defined bruxism as a repetitive masticatory muscle activity (RMMA) characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible [1], also distinguishing among the two circadian manifestations: it can occur during wakefulness

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Clinical Paper
TMJ Disorders

Clinical outcomes of Botox injections for chronic temporomandibular disorders: do we understand how Botox works on muscle, pain, and the brain?

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S. T. Connelly, J. Myung, R. Gupta, G. M. Tartaglia, A. Gizdulich, J. Yang, R. Silva: Clinical outcomes of Botox injections for chronic temporomandibular disorders: do we understand how Botox works on muscle, pain, and the brain?. Int. J. Oral Maxillofac. Surg. 2017; 46: 322–327. Published by Elsevier Ltd on behalf of International Association of Oral and Maxillofacial Surgeons.

Abstract. The main objective of this retrospective review was to analyze the clinical outcomes following the use of botulinum toxin (onabotulinumtoxinA, Botox) injections to relieve the symptoms of chronic temporomandibular disorders (TMD). Seventy-one patients with a diagnosis of TMD (according to the RDC/TMD international consortium) associated with or without bruxism and refractory to conventional treatment (e.g. oral appliances, physiotherapy, etc.) received Botox injections into the temporalis and masseter muscles. Subjective responses to Botox were categorized as 'beneficial' or 'not beneficial', as patient-reported outcomes based on the subjective reduction in pain and/or improvement in function. Fifty-five of the 71 subjects (77%) reported beneficial effects with Botox. Subjects with a concomitant bruxism diagnosis reported significant improvement over subjects without bruxism (87% vs. 67%; P = 0.042). Subjects with stress-related psychiatric comorbidities and bruxism had a significantly higher benefit than those with stress-related psychiatric comorbidities alone (P = 0.027). Patients reported less improvement if the time between the initial Botox injection and follow-up was less than an average of 5 weeks, compared to an average follow-up of 5–10 weeks (P = 0.009). The subgroup TMD diagnosis and time interval post-injection are important predictors of patient-reported beneficial outcomes.

Key words: temporomandibular joint; Botox; chronic pain; bruxism; post-traumatic stress disorder; anxiety.

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The Journal of Headache and Pain

RESEARCH ARTICLE Open Access

The efficiency of botulinum toxin type A for the treatment of masseter muscle pain in patients with temporomandibular joint dysfunction and tension-type headache

Malgorzata Pihut[1], Ewa Ferendiuk[1], Michal Szewczyk[1], Katarzyna Kasprzyk[2] and Mieszko Wieckiewicz[3*]

Abstract

Background: Temporomandibular joint dysfunction are often accompanied by symptoms of headache such as tension-type headache which is the most frequent spontaneous primary headache. Masseter muscle pain is commonly reported in this group. The purpose of the study was to assess the efficiency of intramuscular botulinum toxin type A injections for treating masseter muscle pain in patients with temporomandibular joint dysfunction and tension-type headache.

Methods: This prospective outcome study consisted of 42 subjects of both genders aged 19–48 years diagnosed with masseter muscle pain related to temporomandibular joint dysfunction and tension-type headache. The subjects were treated by the intramuscular injection of 21 U (mice units) of botulinum toxin type A (Botox, Allergan) in the area of the greatest cross-section surface of both masseter bellies. Pain intensity was evaluated using visual analogue scale (VAS) and verbal numerical rating scale (VNRS) 1 week before the treatment and 24 weeks after the treatment. The obtained data were analyzed using the Wilcoxon matched pairs test ($p \leq 0{,}005$).

Results: The results of this study showed a decrease in the number of referred pain episodes including a decrease in pain in the temporal region bilaterally, a reduction of analgesic drugs intake as well as a decrease in reported values of VAS and VNRS after injections ($p = 0{,}000$).

Conclusions: The intramuscular botulinum toxin type A injections have been an efficient method of treatment for masseter muscle pain in patients with temporomandibular joint dysfunction and tension-type headache.

Keywords: Botulinum toxin, Masseter muscle pain, Temporomandibular joint dysfunction, Tension-type headache

Background

Symptoms characteristic for temporomandibular joint dysfunction (TMJD) such as masticatory muscles pain, temporomandibular joint pain, derangements of the condyle-disc complex and deviations of mandible movements are often accompanied by symptoms that are not directly related to the functioning of the temporomandibular joint [1–8]. Such signs include otologic symptoms (ear pain, tinnitus, vertigo), neurovascular headaches and tension-type headaches (TTH) [9–13]. TTH are the most frequent spontaneous primary headaches. They are observed more frequently in women, and occurred in all age groups. It should be emphasized that in most cases the TTH affect middle-aged patients. This kind of headache was also observed in approximately 5–7 % of students aged 5–15 years. The American Dental Association stated that more than 15 % of American adults suffer from chronic headache pain [11–16].

Diagnostics of TTHs is based on the data collected in a screening history consisted short questions which let to analyze the background of the pain and the factors responsible for pain origin. Specialized neuroimaging modalities (magnetic resonance, angiography, positron emission tomography) are used less frequently. The

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Maxillofacial Plastic and Reconstructive Surgery

REVIEW Open Access

Application of botulinum toxin in maxillofacial field: Part II. Wrinkle, intraoral ulcer, and cranio-maxillofacial pain

Kyung-Hwan Kwon*, Kyung Su Shin, Sung Hee Yeon and Dae Gun Kwon

Abstract

Botulinum toxin (BTX) is used in various ways such as temporarily resolving muscular problems in musculoskeletal temporomandibular disorders, inducing a decrease in bruxism through a change in muscular patterns in a patient's bruxism, and solving problems in patients with tension headache. And also, BTX is widely used in cosmetic applications for the treatment of facial wrinkles after local injection, but conditions such as temporomandibular joint disorders, headache, and neuropathic facial pain could be treated with this drug. In this report, we will discuss the clinical use of BTX for facial wrinkle, intraoral ulcer, and cranio-maxillofacial pain with previous studies and share our case.

Keywords: Botulinum toxin, Clinical application, Maxillofacial field, Wrinkle, Oral ulcer, Maxillofacial pain

Background

In oral maxillofacial surgery, the frequency of use of botulinum toxin is increasing rapidly. Particularly, it is used not only for symptomatic treatment for a disease but also used as a method of causative treatment approach. Botulinum toxin is used in various ways such as temporarily resolving muscular problems in musculoskeletal temporomandibular disorders, inducing a decrease in bruxism through a change in muscular patterns in a patient's bruxism, and solving problems in patients with tension headache. It is used not only for treating these diseases but also for the cosmetic purpose to smoothen wrinkles caused by the muscle of expression of the face [1].

Clinical use for wrinkle treatment

When using botulinum toxin in various treatments, the clinician should be thorough with the concepts and knowledge of anatomical structures. It is true that the importance of knowledge on anatomical structures to reduce side effects and increase efficacy and ability to cope with each event keeps increasing. As botulinum toxin can be used for various treatments, accordingly, it is also important to acquire knowledge on anatomical structures for various purposes [1–5].

Anatomy of facial expression muscles

The superficial musculoaponeurotic system (SMAS) layer is an important anatomical structure when acquiring anatomical knowledge for muscles of expression. When we observe the skin of the face and muscle layers beneath the skin, the head, and the neck, SMAS is connected to the dermis at one end, and the other end is connected to fascia of facial muscles. Superiorly, it is connected to temporalis muscles and frontalis muscles, anteriorly connected to orbicularis oculi, inferiorly connected to platysma, and posteriorly connected to trapezius muscles. Description of the SMAS layer is shown schematically in Fig. 1.

The SMAS layer is also used in facelift surgery, which is a procedure to lift the SMAS layer posteroinferiorly and flatten the facial wrinkles [6, 7].

The frontalis muscle has no bony attachments since it originates from galea aponeurotica and inserts into the skin of the eyebrows (Fig. 2). Its function is to lift the skin around the nasal root, making wrinkles on the forehead. It is supplied by a temporal branch of the facial nerve and supraorbital and supratrochlear artery. It is responsible for forehead crease, and botulinum toxin

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Maxillofacial Plastic and Reconstructive Surgery

REVIEW Open Access

Application of botulinum toxin in maxillofacial field: part I. Bruxism and square jaw

Kyung-Hwan Kwon*, Kyung Su Shin, Sung Hee Yeon and Dae Gun Kwon

Abstract

The application of botulinum in oral and maxillofacial surgery begins in 1982, where Jan Carruthers started using it for reducing the muscle mass and smoothing the skin, and since then it has been used for cosmetic purposes. In Korea, it is already being used by various specialties including dentistry (oral and maxillofacial surgery, oral medicine), plastic surgery, dermatology, ophthalmology, general surgery, and orthopedic surgery, etc. Each specialty approaches to Botox with its own medical indications. In this article, we will discuss the maxillofacial application of botulinum toxin, which includes theoretical and practical aspects of such as bruxism and square jaw.

Keywords: Botulinum toxin, Clinical application, Maxillofacial field, Bruxism, Square jaw

Background

Nowadays, an agent used to smooth the facial wrinkles and fine lines, Botox (botulinum toxin A), is of great attention in the dentistry field. Botox is the commercial name for botulinum toxin. It is like we simply call acetaminophen as Tylenol. Botulinum toxin is known to be four times more toxic than common tetanus toxin, and more than ten times toxic than curare. Since its introduction in the plastic surgery for cosmetic use in the 1980s, it is being widely used in various fields including dentistry, dermatology, ophthalmology, plastic surgery, general medicine, etc. [1]. At present, botox under the brand names BTXA (Hanall pharmaceuticals, China), Dysport (Beaufour Ipsen Korea (Ltd), France), and Botox (Daewoong Pharma Importer, Allergan, USA) are marketed in Korea. Commercially available forms that we commonly use are of serotype A; serotype B was released in the USA under brand name Myoblock but it is not available in Korea [2].

The therapeutic effect of botulinum toxin is due to its action on neuromuscular junction. It induces flaccid paralysis by inhibiting acetylcholine release [3]. Mechanism of action consists of three stages: binding, internalization (energy-dependent receptor-mediated endocytosis), and flaccid paralysis through inhibition of releasing neurotransmitter [2]. This therapeutic effect continues for 3–6 months; within that period, botulinum toxin corrects the patterns of muscle exercises, decreases facial wrinkles or square jaw, and alleviates pain by changing the patient's lifestyle [4].

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Background

History of botulinum toxin

Justinus Kerner had discovered toxin from rotten sausages and reported in 1829. In 1897, Professor Emile Pierre van Ermengen from Belgium discovered anaerobic bacteria capable of forming spores from salted pork meat and from a cadaver infected with botulinum toxin (botulism) [5]. Since then, this bacteria is named as *Clostridium botulinum*, and exotoxin protein BTX-A, which this bacteria expresses was named after the bacteria [6]. With the outbreak of World War I and World War II, people refined botulinum for weaponization, and scientists started to research using refined BTX-A to study its mechanism of action, and its action on the contracting mechanism of muscle. In 1973, Alan B. Scott was the first to use BTX-A for treating strabismus. Since 1979, as the FDA (American Food and Drug Administration) approved BTX-A for treating strabismus; it is being widely used for various treatment purposes [1]. After then, clinical studies were performed on blepharospasm or hemifacial spasm, and in

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CLINICAL STUDY

Botulinum toxin to improve lower facial symmetry in facial nerve palsy

SA Sadiq[1,2], S Khwaja[3] and SR Saeed[4]

Abstract

Introduction **In long-standing facial palsy, muscles on the normal side overcontract causing difficulty in articulation, eating, drinking, cosmetic embarrassment, and psychological effects as patients lack confidence in public.**

Methods **We injected botulinum toxin A (BTXA) into the normal contralateral smile muscles to weaken them and restore symmetry to both active and passive movements by neutralising these overacting muscles.**

Results **A total of 14 patients received BTXA (79% women, median age 47 years, average length of palsy 8 years). They were all difficult cases graded between 2 and 6 (average grade 3 House–Brackmann). All 14 patients reported improved facial symmetry with BTXA (dose altered in some to achieve maximum benefit). Average dose was 30 units, but varied from 10 to 80 units. Average time to peak effect was 6 days; average duration of effect was 11 weeks. Three patients had increased drooling (resolved within a few days).**

Conclusion **The improvement in symmetry was observed by both patient and examining doctor. Patients commented on increased confidence, being more likely to allow photographs taken of themselves, and families reported improved legibility of speech. Younger patients have more muscle tone than older patients; the effect is more noticeable and the benefit greater for them. BTXA improves symmetry in patients with facial palsy, is simple and acceptable, and provides approximately 4 months of benefit. The site of injection depends on the dynamics of the muscles in each individual patient.**

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Keywords: facial palsy; botulinum toxin; symmetry

Introduction

In facial palsy, paralysis of muscles on the affected side of the face results in loss of forehead creases, loss of the nasolabial fold, lagophthalmos, brow droop, and drooping of the corner of the mouth. In contrast, muscles on the unaffected side of the face no longer have opposing forces.[1] This may cause difficulty in articulation, eating, drinking, and is often cosmetically unacceptable to patients because of asymmetry, especially when speaking, smiling, and laughing. There are significant psychological effects as patients lack the confidence to carry out many daily activities in public, such as appearing in photographs.

Although management is difficult, there are a range of reanimation options available. These include nerve grafts, muscle transfers, myofunctional approaches, and microsurgical patches usually for the more severe facial palsies (House–Brackmann grades 4 to 6).[1] However, despite these procedures, facial symmetry may not improve.

Botulinum toxin A (BTXA) has been used since the 1970s to treat a variety of conditions resulting in abnormal muscle contraction or spasm. It works by preventing the release of acetylcholine into the neuromuscular junction thereby inhibiting muscle contraction.[2] Its benefits in synkinesis in facial palsy (aberrant neural regeneration of the paralysed muscles) are well recognised.[1,3]

Our aim was to document the use of BTXA injections to the unaffected side to improve symmetry in patients with facial nerve palsy. BTXA was administered to the normal lower side, which exaggerates the asymmetry (especially on movement such as smiling) in order to reduce this asymmetry.

BTXA was injected into the contralateral lower facial muscles complex to weaken the unopposed normal muscles to improve

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