



**FACULDADE DE
MEDICINA DENTÁRIA
UNIVERSIDADE DO PORTO**

Monografia de Revisão Bibliográfica do Mestrado Integrado em Medicina Dentária
Faculdade de Medicina Dentária da Universidade do Porto

Toxina Botulínica e as suas diferentes aplicações em Medicina Dentária

Marta Silva Teles Parente da Costa

Porto, 2018



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Autor

Marta Silva Teles Parente da Costa¹

¹ Estudante do 5ºano do Mestrado Integrado em Medicina Dentária da Faculdade de Medicina Dentária da Universidade do Porto

Orientadora: Professora Doutora Ana Isabel Pereira Portela

Professor Auxiliar da Faculdade de Medicina Dentária da Universidade do Porto

aportela@fmd.up.pt

Porto, 2018

ACKNOWLEDGMENT

Toxina Botulínica e as suas diferentes aplicações em Medicina Dentária

To my dear parents, source of my values and principles.

Thank you for helping me to conquer this stage of my life, for all the love, affection, and unconditional support you have had throughout my life. Thank you for teaching me how to work and for believing in me.

To my dear Aunt Lenita, an essential part of my education, my most thankful for all the love, patience, availability and unconditional dedication.

To my beloved grandmother Juca, who, although she is no longer here, has never ceased to be the other fundamental part of my life. Thank you for the trust, love, affection and respect you have always had for me.

To my counselor, Professor Ana Portela, thank you for all the dedication and sympathy from the beginning. Thank you for all the help and advice, but, especially, for all the patience, encouragement and help in the accomplishment of this work.

To all my teachers, who from the first day contributed to my training.

To my friends of course, I will never forget the fun times and the endless hours of study. My door will always be open to you.

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LIST OF ABBREVIATIONS AND ACRONYMS

BT - Botulinum Toxin

BTX - Botulinum neurotoxin

FDA - US Food and Drug Administration

TMD - Temporomandibular disorders

BTA - Botulinum Toxin type A

BTB - Botulinum Toxin type B

MPS - Myofascial pain syndrome

AO - Atypical odontalgia

Ach - Acetylcholine

ALS - Amyotrophic lateral sclerosis

ABSTRACT

Botulinum toxin (BT), obtained from the bacterium *Clostridium botulinum*, has wide applicability not only in the area of Plastic Surgery to avoid aging, but also in the area of reconstruction.

It has undergone tremendous evolution in the last decade, starting as a poison and evolving into a versatile clinical agent with various uses / indications for minimally invasive therapeutic purposes.

It became famous because of its ability to produce deadly neurotoxins. Its versatility has made this bacterium one of the best-known bacterial pathogens in the history of medicine. Botulinum neurotoxin (BTX) was first used for therapeutic purposes, then as a biological weapon, and finally for cosmetic use.

Although the effect of BT is minimally safe and temporary and its indications are evolving from day to day, greater knowledge about the related anatomy is needed as well as local and systemic adverse effects.

Therefore, it was intended with the present study to describe the state of the art of the use of botulinum toxin in dental medicine.

A bibliographic search was performed in PubMed, Scielo and Google Academic databases. In turn, the keywords used were the following “Botulinum Toxin”, “Toxina Botulínica”, “Odontologia”, “Dental Medicine”, “Dentistry”, “*Clostridium botulinum*” and “botox”.

It is increasingly used in several areas of medicine, such as Dermatology, Ophthalmology, Neurology and, fundamental for this article, Dental Medicine. In this last area, there are several functions, both at the level of aesthetics (facial wrinkles, gingival smile and asymmetries), such as hypertrophy and hyperactivity of the masticatory muscles, pain relief, temporomandibular dysfunction (TMD), parafunctional habits, sialorrhoea and functional recovery of surgery dental, oral and maxillofacial.

KEYWORS

“Botulinum Toxin”, “Toxina Botulínica”, “Odontologia”, “Dental Medicine”, “Dentistry”, “*Clostridium botulinum*”, “botox”.

INTRODUCTION

Botulinum neurotoxin (BTX) was first considered as a poison. It was found, initially, in the rotten sausage, leading, in this way, to food poisoning. The very word botulism derived from the Latin *botulus*, which means black sausage, and has been known to cause food poisoning when eating rotten meat.⁽¹⁻⁶⁾

Botulism is produced by botulinum toxin (BT) or botulinum neurotoxin (BTX), under anaerobic conditions, by *Clostridium Botulinum* (Gram-positive anaerobic rod-shaped bacteria present in contaminated food, causing several deaths in Europe to poor hygienic conditions in the preparation of food during the Napoleonic War.⁽¹⁻¹³⁾

It was Justinus Kerner, in 1817, who described "botulism" for the first time as a fatal disease and calling it "sausage poisoning," for these were the cause of intoxication. In 1822 with the study and publication of the first monograph on this subject Kerner came to crucial points and to some conclusions. Among them was that the toxin developed in the sausages, growing in anaerobic environment; interrupted the neurotransmitter in the Peripheral and Autonomic Nervous System and was lethal in small doses.⁽¹³⁻¹⁵⁾

In addition, this German physicist was able to report some of the neurological symptoms of this toxin: vomiting, intestinal spasms, ptosis, dysphagia, respiratory failure and mydriasis (pupil dilation).⁽¹⁴⁾

However, Kerner also realized the possibility of using it for therapeutic purposes, such as in the reduction of the activity of the Sympathetic Nervous System when it is associated with movement disorders, hypersecretion of body fluids, ulcers caused by malignant diseases, delusions and anger. After several attempts to artificially produce this toxin, he concluded that it had biological and animal origin.⁽¹³⁻¹⁵⁾

Over time it has been described as a very useful tool for minimally invasive therapeutic purposes and was the first toxin to be accepted and adopted in medicine in 1973 with the approval of the US Food and Drug Administration (FDA) in the treatment of adult strabismus and blepharospasm in 1989.^(1, 11, 16, 17)

It was Burgen's discovery in 1949, about the role of this toxin in the inhibition of presynaptic acetylcholine, that laid the foundation for the clinical application of BT.^(12, 15)

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It was used for the first time in 1968 in ophthalmology, in the treatment of strabismus (blocking the neurotransmitter involved in muscle activity causing this problem) by Alan Scott and Edward Schantz.^(2, 4, 13, 14, 17, 18)

The introduction of botulinum toxin in the field of Ophthalmology led to a series of investigations in Neurology that allowed the use of this toxin to treat spasmodic torticollis, dystonia, spasticity, tremor, vocal disorders, cerebral palsy in children, gastrointestinal disorders, tension, headache and pain syndromes.⁽¹⁴⁾

Subsequently, in 1987, ophthalmologist Jean Carruthers observed that type A botulinum toxin reduced the appearance of wrinkles in the glabellar region when treating a patient with blepharospasm and were the first to discover that this toxin was effective in relaxing muscles which control the facial expressions, such as the horizontal wrinkles around the eyes and nasolabial folds.⁽¹²⁾

After this discovery, Carruthers shared her observations with her husband dermatologist, leading to the promotion of this new substance as a cosmetic product, starting in 1990.⁽¹⁴⁾

Since then, BT's application has extended its range to several areas of Medicine, such as Dermatology, Ophthalmology, Neurology and, fundamental for this review, Dental Medicine. In this last area has several functions in terms of aesthetics (facial wrinkles, gingival smile and asymmetries), as well as hypertrophy and hyperactivity of masticatory muscles, pain relief, temporomandibular joint disorder (TMD), parafunctional habits, sialorrhoea and functional recovery of dental, oral and maxillofacial surgery.^(7, 12)

Botulinum toxin can be differentiated into seven types from A to G, however commercially, BT has two presentations, types A (BTA) and type B (BTB).^(1, 2, 4-6, 10)

The objective of the present study was to investigate, through the literature review, the use of this toxin in Dental Medicine, as well as to study its composition and to know its use throughout history.

MATERIAL AND METHODS

A search was performed through Pubmed, Scielo and Google Scholar databases. In the PubMed database, using the keywords "botulinum toxin AND dental medicine", using the filters "Full text", "5 years" and "humans", 25 articles were found, being used 7.

In the database Scielo, using the keyword "botulinum toxin" found 268 articles, of which 10 were used. With the keyword "clostridium botulinum", in the same database, 52 articles were found and used 5. With the keyword "botox" 21 articles were found and used 6. No filters were used in this database.

In the Google Academic database, using the keyword "clostridium botulinum" 14400 results were found but only 3 were used. With the keywords "toxina botulínica e odontologia" 776 results were found, using only 4 articles. With the words "botulinum toxin AND gummy smile" was found 673 results, using 4. With the keyword "masseteric hypertrophy AND botox" 1100 results were found, being used 7. No filters were found matching any of these keywords. With the keywords "gummy smile AND botox", 18 results were found, being used 4. The "2014 year" was used as a filter. With the keywords "myofascial pain AND botox", 73 results were found, being used 4. As a filter was used "since 2018". With the keywords "atypical odontalgia AND botulinum toxin", 144 results were found, being used 2. No filters were used. With the keywords "parafunctional Habits AND Implants AND botulinum toxin" were found 220 results, being used 8. No filters were used.

Only those articles were used, since after reading the abstract, it did not fit the theme, and most of them did not have access to the article.

Review articles, case reports, clinical trials and studies were selected.

RESULTS

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Table I. Method used in the selection of articles through electronic research in the PubMed database.

Keywords	Nº of Articles	Nº of Selected Articles	Year	Type of Study	Selected Articles	Included	Excluded
“botulinum toxin AND dental medicine”	25	7	2016	Review	“Clinical Aspects of the Use of Botulinum Toxin Type A in the Treatment of Dysfunction of the Masticatory System”	X	
			2017	Review	“Effectiveness, Safety, and Predictors of Response to Botulinum Toxin Type A in Refractory Masticatory Myalgia: A Retrospective Study”	X	
			2016	Case Report	“Botulinum Toxin Type A as Preoperative Treatment for Immediately Loaded Dental Implants Placed in Fresh Extraction Sockets for Full-Arch Restoration of Patients With Bruxism”	X	
			2015	Review	“Applications of botulinum toxin in dentistry: A comprehensive review”	X	
			2016	Review	“Toxin yet not toxic: Botulinum toxin in dentistry”	X	
			2020	Review	“Use of a botulinum toxin A in dentistry and oral and maxillofacial surgery”	X	

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			1 6				
			2 0 1 6	Case Report	“Botulinum Neurotoxin Type-A for the Treatment of Atypical Odontalgia”	X	

Table II. Method used in the selection of articles through electronic research in the Scielo database.

Keywords	Nº of Articles	Nº of Selected Articles	Year	Type of Study	Selected Articles	Included	Excluded
“botulinum toxin”	268	10	2 0 1 7	Case Report	“Botulinum toxin as an adjuvant in the treatment of gummy smile”	X	
			2 0 1 7	Case Report	“Use of botulinum toxin type a in temporomandibular disorder”	X	
			2 0 1 4	Review	“Botulinum toxin-how a poison turned to a fascinating ally against an old adversary”	X	
			1 9	Review	“Treatment of dystonias with botulinum toxin Type A”	X	

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			9 5				
			2 0 0 5	Clinical Trial	"Application of botulinum toxin to reduce the saliva in patients with amyotrophic lateral sclerosis"	X	
			1 9 9 5	Clinical Trial	"Botulinum toxin in blepharospasm, hemifacial spasm and cervical dystonia: results in 33 patients"	X	
			1 9 9 6	Review	"Dystonias: therapeutic aspects"	X	
			2 0 0 3	Case Report	"Bilateral hemifacial spasm: Case report"	X	
			2 0 1 1	Review	"Presentation: Botulinum toxin in the low third of the face"	X	
"clostridium botulinum"	52	5	2 0 0 9	Review	"Botulinum Toxin in Pain Treatment"	X	

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			2007	Case Report	"Botulism and dysphagia"	X	
			2003	Review	"The History of Clostridium botulinum"	X	
			2006	Study	"Botulinum toxin type A in the management of Myofascial pain syndrome"	X	
			2004	Review	"Botulinum toxin and its use in oral and maxillofacial pathology"	X	
"botox"	21	6	2003	Study	"Treatment of essential blepharospasm and related facial dystonia with botulinum toxin injection - study of 16 cases"	X	
			2004	Review	"Botox. It is not about wrinkles"	X	
			200	Study	"Botulinum toxin type A for the management of pain in patients with chronic myofascial pain"	X	

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			1 0				
			2 0 1 5	Case Report	“Smile enhancement with botulinum toxin in a patient with facial palsy”	X	
			2 0 0 7	Review	“Salivary gland application of botulinum toxin for the treatment of sialorrhea”	X	
			1 9 9 7	Clinical Trial	“Botulinum toxin A: experience in the treatment of 115 patients”	X	

Table III: Method used in the selection of articles through electronic research in the Google Académico database.

Keywords	Nº of Articles	Nº of Selected Articles	Year	Type of Study	Selected Articles	Included	Excluded
“clostridium botulinum”	14400	3	2005	Review	“Clostridium botulinum: A Bug with Beauty and Weapon”	X	
			1982	Review	“Clostridium botulinum Toxins”	X	

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			1980	Review	"Clostridium botulinum Neurotoxin"	X	
"toxina botulínica e odontologia"	776	4	2015	Review	"Applications of botulinum toxin in dentistry"	X	
			2018	Review	"Uso Da Toxina Botulínica Como Meio Terapêutico Para Tratamento De Assimetria Facial Causada Por Hipertrofia Do Músculo Masseter"	X	
			2013	Review	"Uso da toxina botulínica tipo A em pacientes com bruxismo reabilitados com prótese do tipo protocolo em carga imediata"	X	
			2014	Case Report	"Application of botulinum toxin associated to the integrated clinic in the management of gummy smile"	X	
"botulinum toxin AND gummy smile"	673	4	2009	Study	"Surface Anatomy of the Lip Elevator Muscles for the Treatment of Gummy Smile Using Botulinum Toxin"	X	
			2012	Clinical Trial	"A Simplified Method for Smile Enhancement: Botulinum Toxin Injection for Gummy Smile"	X	
			2011	Review	"The use of botulinum toxin type A in cosmetic facial procedures"	X	

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			2012	Review	"Current Strategies in the Treatment of Gummy Smile Using Botulinum Toxin Type A"	X	
"masseteric hypertrophy AND botox"	1100	7	2018	Study	"Effect of the masseter muscle injection of botulinum toxin A on the mandibular bone growth of developmental rats"	X	
			2015	Study	"Growth effects of botulinum toxin type A injected unilaterally into the masséter muscle of developing rats"	X	
			2015	Study	"Early effect of Botox-A injection into the masséter muscle of rats: functional and histological evaluation"	X	
			2012	Study	"Botulinum toxin in masticatory muscles: short- and long-term effects on muscle, bone, and craniofacial function in adult rabbits"	X	
			2018	Review	"Botulinum Toxin in Aesthetic Medicine: Myths and Realities"	X	
			2018	Case Report	"A successful management of sever gummy smile using gingivectomy and botulinum toxin injection: A case report"	X	
			2018	Case Report	"Tratamento De Assimetria Facial Causada Por Hipertrofia Do Músculo Masseter Com o Uso De Toxina Botulínica Tipo A Relato De Caso Clínico"	X	
"gummy smile AND botox"	18	4	2018	Review	"O Uso De Toxina Botulínica Como Alternativa Para O Tratamento Do Sorriso Gengival Causado Pela Hiperatividade Do Lábio Superior"	X	
			2018	Case Report	"Adult gummy smile correction with temporary skeletal anchorage devices"	X	

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			2018	Case Report	"Myomodulation with Injectable Fillers: An Innovative Approach to Addressing Facial Muscle Movement"	X	
			2018	Case Report	"Treatment of gingival smile with botulinum toxin type A: A case report"	X	
"sialorrhea AND botox"	313	3	2018	Review	"Surgical Management of the Drooling Child"	X	
			2018	Review	"Botulinum Toxin A for Sialorrhoea Associated with Neurological Disorders: Evaluation of the Relationship between Effect of Treatment and the Number of Glands Treated"	X	
			2015	Study	"A Double-Blind Randomized Controlled Trial Investigating the Most Efficacious Dose of Botulinum Toxin-A for Sialorrhea Treatment in Asian Adults with Neurological Diseases"	X	
"myofascial pain AND botox"	73	4	2018	Review	"Botulinum Toxin Injections for Chronic Pain"	X	
			2018	Review	"A critical overview of the current myofascial pain literature"	X	
			2018	Study	"The effectiveness of Clostridium botulinum toxin A (Dysport®, AbobotulinumtoxinA) in the management of temporomandibular dysfunction (TMD) and a small number of other maxillofacial conditions; an open cohort study"	X	

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			2018	Review	"Mandibular bone loss: a hidden side effect of botulinum toxin type A injection in masticatory muscles"	X	
"atypical odontalgia AND botulinum toxin"	144	2	2007	Review	"Temporomandibular Disorders and Other Causes of Facial Pain"	X	
			2017	Review	"Atypical Facial Pain: a Comprehensive, Evidence-Based Review"	X	
"parafunctional Habits AND Implants AND botulinum toxin"	220	8	2001	Review	"A bibliographical survey of bruxism with special emphasis on non-traditional treatment modalities"	X	
			2003	Review	"Current knowledge on awake and sleep bruxism: overview"	X	
			2013	Review	"Role of Botox in Efficient Muscle Relaxation and Treatment Outcome: An Overview"	X	
			2016	Review	"Toxina Botulínica Tipo A para bruxismo: análise sistemática"	X	
			2006	Review	"Bruxism: its multiple causes and its effects on dental implants – an updated review"	X	
			2006	Review	"Dental implants in patients with bruxing habits"	X	
			2011	Review	"Bruxism: Overview of Current Knowledge and Suggestions for Dental Implants Planning"	X	
			2014	Review	"Botulinum toxin: The Midas touch"	X	

DISCUSSION

Botulinum toxin as a material

Botulinum toxin (BT) is produced by fermentation of *Clostridium botulinum*, a Gram-positive, anaerobic bacterium. There are seven variants of this neurotoxin, from type A to G, type A (BTA) being most often used for therapeutic purposes.^(5, 6, 8-10, 13, 19, 20)

Commercially, BTX comes in two presentations, types A and B. BTA is the most potent variant and the only one clinically used because it is a biological agent obtained in the laboratory. It is a stable crystalline substance, lyophilized in human albumin and stored in a vacuum, to be diluted in saline. It's better known by its trade name "Botox" (Allergan, Inc, USA), than by its very name. BTA was initially approved for cosmetic and therapeutic use.^(2, 19)

BTX is a protease that causes temporary desensitization of the skeletal muscles; it's a neurotoxin with high affinity for cholinergic synapses, blocks the release of acetylcholine by nerve endings without interfering with neuronal conduction of electrical signals or synthesis and storage of acetylcholine. It has been proven that BTX can selectively weaken painful muscles, interrupting the spasm-pain cycle. Several studies have demonstrated the efficacy and safety of BTA in the treatment of migraines, myofascial pain, masseteric hypertrophy and facial asymmetry of muscular origin, parafunctional habits, sialorrhea, temporomandibular disorders (TMDs), gingival smile, among others.^(7, 9, 13, 15, 19-24)

Masseteric hypertrophy and facial asymmetry of muscular origin

The massometric hypertrophy is the excessive development of the masseter muscle, uni or bilateral, being of idiopathic character. It leads to aesthetic facial compromise interfering with the patient's self-esteem and affects, usually, young people. In some cases, besides the aesthetic, there is functional incapacity of this muscle due to occlusal disharmony and orofacial pains that are difficult to solve.^(3, 25-27)

Clinically it is observed the increase of volume of the masseter muscle, uni or bilaterally, of easy delimitation, smooth consistency to palpation and generally asymptomatic. Although most often the main complaint is aesthetic, it may be present tenderness to palpation, functional disability due to pain and complaint of occlusal disharmony.^(3, 26-28)

Surgical treatment involves interventions that are performed, only in the compromised muscles, only in the bone structure of the mandibular angle or the association of both procedures. The main treatments currently known are occlusal adjustments, use of spasmolytic medications, tranquilizers and antidepressants.^(3, 27, 28)

When injected into a muscle, BT causes interference with the neurotransmitter mechanism producing selective paralysis and successive atrophy of the muscle which is a common treatment for cosmetic reduction of the masseters as well as for conditions involving muscle spasm and pain.⁽²⁷⁻²⁹⁾

Currently, facial growth has been influenced by the use of botulinum toxin type A that has been used to induce muscular hypofunction. Because it is noninvasive and reversible, it represents, for the clinician, a safe and effective alternative for the treatment of masseter muscle hypertrophy, when conservative treatments have been unsuccessful.^(3, 18, 25, 28, 30)

According to several authors, there was satisfactory regression of muscular hypertrophy and a significant improvement of facial asymmetry. The results appeared acceptable aesthetic and short-term effect, which indicates that BTA is effective in the treatment of facial asymmetries.^(3, 26, 28, 30)

However, to several authors, using TB in a long term the mechanical properties of the temporomandibular joint may be compromised and even may occur bone loss.^(18, 23, 28, 29)

Chronic Pain: Myofascial Pain, Migraine

Orofacial pain may be caused by a massive assortment of diseases. There are a set of conditions that belong to the group of chronic pain such as myofascial pain, migraine and atypical odontalgia.^(31, 32)

Myofascial pain syndrome (MPS) is defined as a musculoskeletal disorder caused mainly by the active point of the trigger (trigger point) exhibiting sensory, motor and autonomic symptoms. Sensory disorder that apparent dysesthesia, hyperalgesia, and referred pain. It's usually a result and sometimes a product of, both emotional influences and physical factors. Fatigue, depression, anger, sleep disturbance, and altered mental function are commonly experience by patients with MPS, and an interdisciplinary approach to address the many dimensions of the pain experience is needed.^(15, 30, 33-35)

Migraine is a chronic neurological/neurovascular disturb associated with sterile inflammation and vasodilatation, which activate the trigeminal afferents on the vessel wall causing pain .^(15, 30)

Atypical odontalgia (AO) is one of the few sources of facial pain. It is a subform of persistent idiopathic facial pain, and is defined as a continuous toothache in which a thorough examination reveals no dental pathology. AO is believed to be a neuropathic condition, given that some cases are preceded by dental procedures. Different topical and systemic medications have been used for the treatment of AO, but their effect is often deficient.^(31, 32, 36)

BTX may reduce muscle contractility by preventing ACh release from the presynaptic terminal and decrease parasympathetic outflow, leading to analgesia. Because of that it may be a therapeutic option.^(30, 33, 37)

Parafunctional Habits and Implants

The parafunctional habit of controversial origin, ranging from psychological disturbances, central nervous system disorders, malocclusion to genetic factors is called bruxism. It is characterized by the grinding of teeth, being nocturnal or diurnal. The tooth wear, muscle or temporomandibular pain and, in more advanced cases, postural and / or skeletal dysfunction and degenerative temporomandibular joint arthritis are the complications of this habit.^(4, 19, 38-43)

In the planning of dental implants, bruxism becomes a highly relevant factor and should be minimized so that there is no occlusal overload and, consequently, no loss of the implant. The failure of most implants is because to occlusal overload and not due to osseointegration problems or peri-implant diseases. It is due to the absence of the periodontal ligament the low resistance of the implant to this overload, which greatly limits the proprioception and hampers the distribution of tension in the peri-implant. Thus, it is necessary and relevant to verify signs of bruxism during the planning of clinical cases, and in these situations, it is necessary to resort to methods that can minimize it. Sleep bruxism leads to an increase in occlusal and lateral forces, both in magnitude and duration, and is therefore related as a considerable risk factor for dental implants, and the prognosis for prosthetic treatment with implants in patients who this condition is always doubtful.^(4, 37, 41-45)

About the use of botulinum toxin for the treatment of bruxism much has been said about. Botox reduces the muscle activity by blocking overactive nerve impulses that trigger excessive muscular contractions by selectively preventing the release of the neurotransmitter acetylcholine(ACh) at the neuromuscular junction. Also in the planning of dental implants, is very effective the prophylactic use of botox injections in achieving true bone to implant connection.^(4, 27, 37, 45)

BT may be used as a treatment option in patients with bruxism, since the treatments available for this parafunctional habit are not completely effective. It works by reducing peripheral muscle activity because it is a potent and specific muscle relaxant. Botox reduces pain by promoting relaxation of masticatory muscles and allowing proper mandibular function. Side effects are rare and, even if they exist, are transient, causing no major problems for patients.^(2, 4, 7, 30, 37-39, 42, 43, 46)

Sialorrhea

The spillage of saliva due to either the excessive production of saliva (primary sialorrhea) or decreased frequency of swallowing (secondary sialorrhea) in which there is accumulation of saliva in the oral cavity with continuous need of elimination, causing difficulties in speech, social embarrassment, oral infections, halitosis and dehydration and associated with several neurological disorders what can be considered as the definition of sialorrhea.⁽⁴⁶⁻⁴⁹⁾

In patients with sialorrhea, the application of BTX-A in the salivary glands was advantageous, conceding the reduction of saliva accumulation in the oral cavity and pharyngeal recess and consequent onset of speech-language therapy. During the botulinum toxin effect period one of the main aspects observed was the improvement of swallowing function. One only application of the medicine was enough for patients to present conditions for speech therapy and reintroduction of oral feeding. There are a improvement of mobility and strength of oropharyngeal structures, a reduction of saliva accumulation and improvement of swallowing, a reintroduction of food by mouth and a removal of the tracheostomy cannula and occlusion of the tracheostoma after application of BTA associated with speech therapy. BT acts on the cholinergic nerve endings, causing proteolysis of SNAP-25, chemical denervation, and loss of neuronal activity.^(19, 30, 48)

The use of botulinum toxin in salivary glands in vivo was reported primary in patients with amyotrophic lateral sclerosis (ALS) to block the action on cholinergic autonomic fibers. Saliva remains the same in the oral cavity and oropharynx and/or extraoral leak of saliva indicate neurogenic failure in coordination of tongue, palate and facial muscles that act in the first stage of swallowing, in many neurological diseases.^(19, 47, 50)

Among the treatment option, it is used anti-Parkinson drugs, drugs with anti-cholinergic effects, radiotherapy in salivary glands, surgical treatment of salivary ducts or glands and more, recently, application of botulinum toxin type A in salivary glands. Botox may be a better alternative in the case of patients who are intolerant to the

adverse effects of the medication used or who present very advanced and severe clinical situations of the neurological disease that prevent the surgical treatment. ^(48, 50)

Recently, the percutaneous injection of botulinum neurotoxin type A into salivary glands has been shown to be effective in abolishing excessive sialorrhoea associated with several neurological disorders. Since it is able to improve quality of life, may be a valid treatment option in patients with sialorrhea in a medium-term solution. ^(47, 48, 50)

Gingival smile and lip asymmetry

The gingival smile, also called the doggy or horse smile, is a very common and unsightly condition defined as an individual displaying a smile of more than 3 mm of gingival tissue, with a greater incidence in females. In Even over, a person's smile can express a sense of joy, happiness, pleasure, good mood, success and sensuality, that is, it is a form of communication, socialization and attraction. ^(8, 9, 51-57)

With the increase of aesthetic requirement of the patients, currently, a stereotyped smile is proposed. The harmony of the smile is determined by the gingival tissue and not only by the shape, position and color of the teeth. The so-called gingival smile is characterizes by the excessive exposure of the periodontium. Firstly, a correct diagnosis should be established by properly classifying the gingival level, respecting variables such as gender, age and periodontal health. After the diagnosis has been made, the etiology must be determined. So a gingival smile is not exclusive to a short lip. This is attributable to several factors, including hyperfunction of the perioral muscles (orbicularis oris, zygomaticus major and minor, depressor septi nasi, levator labii superioris alaeque nasi/anguli oris), lip length, clinical crown length, skeletal problems caused by maxillary excess, altered passive eruption of teeth and dentoalveolar extrusion, resulting in gingival problems. Many authors have proposed surgical approaches, but these procedures are associated with morbidity and high cost and are time-consuming. ^(8, 9, 19, 51-58)

Diagnosing the gingival smile, BTX serves as a substitute for surgical treatment, being a modality of minimally invasive correction treatment.^(9, 19, 21, 57)

Despite being a simple and safe procedure, the injection of botulinum toxin may be associated with some adverse effects such as, edema, pain at the site of injection, dysphonia, bruising, smile asymmetry, infection, dysphagia and ptosis or upper lip stretching. The dentist should be aware of the posology, the accuracy of the technique and the location of the puncture.^(8, 55)

The gingival smile has implications on the patient's self-esteem and social life. In fact, this affects the esthetic and the psychological status as it usually decreases the self-confidence leading to hidden or controlling the smile.^(8, 9, 51, 55, 58)

For successful treatment are crucial the correct diagnosis of the cause and the proper selection of the technique for correcting the gummy smile. In addition, extensive surgical procedures can be replaced by botulinum Toxin. BTX acts by cleaving SNAP-25, which blocks ACh release from motor neurons and enables repolarization of the postsynaptic terminal, resulting in partial chemodenervation and blockade of muscular contraction. It is considered as one of the minimally invasive, easy, quick and affordable therapy. However, for Walsh (2012), botox may not be the best form of treatment, although it is the most desired option for the patient because it is better known and due to its immediate effect. The author also reports that dental surgeons could not administer botox for three reasons: for the pharmacological principles of botox are addressed in dentistry at a very basic level; because the dentist does not have enough training on the detailed anatomy of the face for the safe application of botox; and for the use of botox to be more used at the cosmetic level and not so much at the dental level. With a strong understanding of actions and limitations and careful selection of cases, BTX may represent a strong treatment option for patients with a gingival smile. Thus, the application of BT requires a great dominance over the anatomy and an abundant learning about its application.^(8, 9, 30, 51, 52, 55, 56, 58, 59)

It is the duty of all professionals to keep up-to-date on the technical and scientific knowledge required for professional practice.^(9, 56, 59)

Facial Dystonias

A normal facial function is of a colossal significance to the physical, psychological, emotional and social well-being of a person.⁽⁶⁰⁾

In recent years, in the more developed neurological centers, the use of botulinum toxin type A has become a relatively growing practice, especially indicated in the treatment of movement disorders, such as: focal dystonias (blepharospasm), hemifacial spasm (“involuntary tonic or clonic contractions, paroxysmal, limited to the muscles of one side of the face, innervated by the facial nerve. It usually begins with intermittent eyelid tremors in one eyelid. In months or years, there is progression and involves adjacent areas innervated by the facial, compromising all muscles on the side of the affected face”), craniofacial dystonias (“a group of diseases characterized by involuntary movements of the face, tongue, palate, pharynx, vocal chords and neck”), facial paralysis (“the inability to express emotions and perform functional movements. This leads to a decrease in quality of life to cause functional and aesthetic problems that are emphasized to speak and smile, causing psychological effects such as loss of confidence to perform daily activities in public”) among others.^(22, 60, 61)

The diagnosis of these dystonias is basically clinical. The diagnosis is made retrospectively, with the progression of symptoms and the interference of daily activities and the clinical picture is instated insidiously. These symptoms are exacerbated by environmental conditions such as light, brightness, optokinetic stimulus, stress and interpersonal relations.^(61, 62)

BTX acts at the neuromuscular junction by inhibiting the release of ACh and preventing muscle contraction and that is why this toxin has proven to be a safe and highly effective method for the treatment of facial dystonias.^(17, 22, 30, 61, 63, 64)

Cosmetic Usage

The botulinum type A toxin, currently, plays an important role in aesthetic-medical treatments of the face. It has been used, since first described by Carruthers, for the treatment of facial wrinkles. (19, 52, 65, 66)

Its use has extended especially in the treatment of external lines of the can thus (crow's feet), forehead wrinkles, for modifying the position of the eyebrows in the glabella area, as well for horizontal neck lines. In the middle and lower third of the face it is less used. It has been used to create the effect of a fuller top lip, for the treatment of peribuccal lines or to modify the nasolabial angle, among other applications. The dentist need to be aware of their safe action on the various anatomical structures involved. (19, 37, 65-69)

How to use

Partial chemical denervation of the muscle is produced by Botox, resulting in localized reduction in muscle activity. It can be used as an adjunct to oral medication or as a single therapy. It is unknown the lethal dose of Botox in humans although it has been estimated at around 3000 U. The usual maximum recommended dose for dental applications in an injection session is about 80-100 U. It would be necessary injected 30 bottles of Botox before a potentially lethal result. A fatal overdose is almost impossible because the disproportion between the clinical dose and the lethal dose. The skin should be cleaned with chlorhexidine swab / alcohol / betadine before injecting Botox into muscle and / or joint and / or skin. A small electric recorder or EMG machine can be used to determine the site to be injected into the muscle, helping to correctly locate the area of the muscle to be injected. Can also be used for deeper joints or muscles Ultrasound guided injections. Botox is injected using 1 ml of tuberculin syringe and 0.30 gauge half inch needle. Injections of a small amount of this toxin into a muscle produces atrophy and weakness in 1-20 days and recovers within 2-4 months as new terminal axons germinate and restore the transmission. To minimize the risk of antibody formation to

the protein the injections are spaced for a minimum of 3 months, which would prevent Botox from functioning in the subsequent time. The injected muscle is paralyzed or weakens by Botox, but leaves the other muscles the same. Injections block extra muscle contractions but leave enough force for normal use.^(27, 37)

Side effects and contraindications to the use of botulinum toxin

The side effects of botulinum toxin on the body are related to the frequency and amount of the dose. These are dizziness, anxiety, fever, hypotension, nausea, headache, facial pain, pruritus, dry mouth and eyes, speech difficulties, edema of face, dysphagia, allergic reaction like rash, flu-like symptoms, urticaria, sweating, itching, chills, paralysis respiratory infection, loss of strength, among others.^(26, 27, 30, 66)

The use of Botox is contraindicated during an infection or inflammation of the area where the toxin injections are planned, in primary muscular disorders (muscular dystrophy, neuromyopathy, congenital myopathies, myotonic disorders, mitochondrial myopathy and unspecified or other primary muscle disorders), in women during pregnancy and lactation, in patients with musculoskeletal conduction disorders, in patients with known hypersensitivity to any component of the drug, in patients being treated with succinylcholine, pancuronium, aminoglycoside antibiotics, tubocurarine, ciclosporin, galamine, hydroxychloroquine, D-penicillamine or chloroquine. The risk of transmission of a viral infection cannot be eliminated with certainty due to the hemagglutinin content. The availability of anti-allergic medicinal products should be ensured prior to the application of the medicinal product.^(8, 9, 16, 27, 28, 30, 66, 70)

So, summing up, this toxin proved to be a safe, effective, minimally invasive and reversible alternative in the treatment of many conditions.^(3, 26, 28, 30)

However, more studies are needed to reach a definitive conclusion about efficacy and safety in cases of chronic pain, parafunctional habits and implants. With regard to sialorrhoea it is necessary to evaluate the maximum doses, the location of the most effective and safe injection points and the definition of the number of infiltrations required by the TBA. Lastly, in facial dystonias it's needed confirm the hypothesis of the drug tolerance effect, which should only be administered by professionals familiar with

the pharmacological properties of the drug and with full knowledge of the anatomical characteristics of the region in which the drug should be injected).^(2, 4, 15, 30, 31, 35, 37, 38, 47, 48, 50, 61, 63, 64, 66)

Thus, it is require a thorough learning and a greater dominance of the dynamic anatomy with the application of BT. When administered in the appropriate doses by an experienced clinical specialist is a safe therapy option. However, the largest counterpart is that the effect of BT is reversed by motor endplate regeneration and generally leads to the re-establishment of symptoms. The treatment has to be repeated at intervals of two to three months once the symptoms re-appear.^(8, 9, 27, 30, 51, 52, 55, 56, 58)

Legislation

On BTX applications in dentistry, it is important that the Dentist is aware of its possible risks, as well as the correct indications, avoiding possible damages.

There are specific guidelines for each indication, as BTX should only be administered by physicians with appropriate qualifications and experience in the treatment and use of the necessary equipment. For all indications, the ideal dose or the number of generally suitable injection sites for muscle have not yet been established. In these cases, individual treatment regimens should therefore be established by the physician. The optimal dose should be determined by adjusting the individual dose, but the maximum recommended dose should not be exceeded. (INFARMED, 2014)

In individuals with known hypersensitivity to Botulinum Toxin type A or in the presence of infection at the proposed injection site, the application is contraindicated. The recommended doses and dosing frequencies for BTX should not be exceeded because of the potential for overdose, excessive muscle weakness, diffusion of the toxin to distant sites and formation of neutralizing antibodies. The starting dose for patients who have not been previously treated should be the lowest recommended dose for the particular indication. Prescribers and patients should be aware that even if previous injections have been well tolerated adverse effects may occur. Therefore, precautions should be taken in each administration. (INFARMED, 2014)

CONCLUSION

In patients with head and face disorders of different etiologies, BT is a useful and minimally invasive treatment option in the treatment of challenging clinical problems, improving the quality of life. It is clear that the potential use of BT in the dental profession can be of great value, although broader confirmation of its use is required in multiple dental applications.

The fundamental limitations of botulinum toxin are due to the average duration of its therapeutic effect which requires the repetition of the treatment every three months throughout the life of the patient, which is not only uncomfortable, but also favors the emergence of resistances.

In future the effects of these treatments are expected to be longer lasting.

In conclusion, Botox is one of the most promising and exciting new additions to the dentist's arsenal for treating numerous conditions. Although further studies on botulinum toxin are needed in the future, this has proved to be a great ally of the dental surgeon in the therapeutic treatment of several symptomatic alterations.

Finally, there was also an increase in the training of dentists for its use, but legislation in Portugal is still lacking for its correct application.

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ANEXOS

ANEXO 1- DECLARAÇÃO DE AUTORIA

Declaração de Autoria

Declaro que o presente trabalho intitulado “Toxina Botulínica e as suas diferentes aplicações em Medicina Dentária”, no âmbito da monografia de revisão bibliográfica, integrado no MIMD, da FMDUP, é da minha autoria e todas as fontes foram devidamente referenciadas.

Porto, 21 de maio de 2018

Marta Silva Teles Parente da Costa

Marta Silva Teles Parente da Costa

ANEXO 2- PARECER DA ORIENTADORA

PARECER

(Entrega do trabalho final de Monografia)

Informo que o Trabalho de Monografia desenvolvido pelo(a) Estudante Marta Silva Teles Parente do 1º ano com o título: Toxina Botulínica e as suas diferentes aplicações em Medicina Dentária, está de acordo com as regras estipuladas na FMDUP, foi por mim conferido e encontra-se em condições de ser apresentado em provas públicas.

21/05/18

O(A) Orientador(a)

L. S. L. Parente

ANEXO 3- DECLARAÇÃO DE TRANSCRIÇÃO


Declaração

Mestrado Integrado em Medicina Dentária

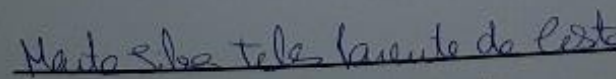
Declaro que o presente trabalho, no âmbito da Monografia de Investigação, integrado no Mestrado Integrado em Medicina Dentária, da Faculdade de Medicina Dentária da Universidade do Porto, com o título "Toxina Botulínica e as suas diferentes aplicações em Medicina Dentária", apresenta-se traduzida na totalidade em inglês.

A transcrição, por mim conferida, encontra-se fidedignamente traduzida, não existindo nenhuma alteração ao conteúdo.

Porto, 17 de Maio de 2018



(Professora Doutora Ana Isabel Pereira Portela)



(A aluna Marta Silva Teles Parente da Costa)