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# MECHANISMS OF ACTION OF BOTULINUM TOXIN IN OROFACIAL HARMONIZATION

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**Abstract:** Since 2019, the Federal Council of Dentistry (CFO) has regulated orofacial harmonization as a dental specialty in resolution 198/2019, given that dental surgeons are professionals capable of competently performing facial aesthetic procedures. Among the procedures that cover facial harmonization, botulinum toxin stands out, a neurotoxin that blocks the transmission of nervous stimulus and reduces the potential for muscle contraction. Botulinum toxin presents itself as a minimally invasive technique with both aesthetic and therapeutic applications in the area of dentistry, presenting a low risk of adverse effects with safe and effective protocols. The mechanism of action of botulinum toxin is to temporarily inhibit the neuromuscular junction by blocking the release of acetylcholine in response to a nerve impulse. Given the above, the central objective of the present study was to describe the mechanisms of action of botulinum toxin in facial aesthetic procedures. To this end, a bibliographical search was carried out in the Google Scholar, Pubmed, and Scielo databases.
**Keywords:** Botulinum Toxin. Harmonization. Orofacial. Dentistry.

## INTRODUCTION

In 1946, the World Health Organization (W.H.O.) defined health as a state of complete physical, mental and social well-being, which goes far beyond the condition of absence of illness. Therefore, an individual's self-esteem directly impacts their health and must be approached from this perspective.

Since 2019, the Federal Council of Dentistry (CFO) has regulated in resolution 198/2019, that orofacial harmonization as a dental specialty, given that dental surgeons are professionals capable of competently performing facial aesthetic procedures (CFO, 2019).

The Federal Council of Dentistry, through resolution CFO-176, authorized the use of botulinum toxin and facial fillers for functional and/or aesthetic purposes by dental surgeons, as long as the anatomical limits of this professional's performance were respected.

In 2011, in Brazil, dental surgeons were recognized and licensed by the Federal Council of Dentistry to use botulinum toxin. Since then, the toxin has been used in dentistry (MARCIANO, et al., 2014).

Among the procedures that cover facial harmonization, botulinum toxin stands out, a neurotoxin that blocks the transmission of nervous stimulus and reduces the potential for muscle contraction. Its use can have broad benefits in the health sector, such as, for example, in chronic pain that is refractory to medication, reducing gummy smile and correcting asymmetries in the muscles associated with smiling. As well as to smooth out aesthetic wrinkles resulting from facial expressions. (SRIVASTAVA et al., 2015; AWAN, 2017; CAVALCANTI, et al., 2017).

Botulinum toxin produced by the bacterium Clostridium botulinum has gained great prominence in the dental sector as it presents a protocol with numerous safety advantages, due to its quick results and very few side effects (OLIVEIRA, 2018).

Botulinum toxin is well known for its application in reducing facial hyperkinetic lines, however, it also has several other applications in the facial region, such as: correction of gummy smile, facial asymmetries, temporomandibular disorders, masseteric hypertrophy, hemifacial spasm, pain myofascial, sialorrhea, bruxism and can even be used to alleviate "cellulite chin" in patients with difficulty closing their lips (MACHADO, 2020, p. 68).

The main muscles that are subjected to the application of botulinum toxin are the

following: orbicularis oculi muscle, frontalis muscle, corrugator supercilii, procerus, elevator muscle of the upper lip and wing of the nose, nasal muscle, the aforementioned toxin is used in aesthetics for improvement of aspects such as asymmetry of the smile, hyperkinetic lines (wrinkles) - which will provide rejuvenation of the face - gingival exposure, increase in interdental volume - thus leading to the reduction of periodontal black spaces - thus culminating in a harmony of the face so general (CHAVES, 2018; PAPAZIAN et al., 2018).

Although the use of this toxin generally presents no risks, it is worth highlighting pregnant or lactating women and people allergic to the product must not use this type of treatment. treatment There are also other cases in which it must not be used, these are: muscular neuropathy, muscular diseases such as amyotrophic lateral sclerosis (ALS), Lambert Eaton Syndrome, muscular dystrophy, multiple sclerosis and those who use calcium channel blockers and aminoglycosides (SENISE, et al., 2015).

The difference between a cure and a poison depends on the dose used. The average lethal dose is 1 nanogram of toxin per kilogram of body weight (10-9 g/kg) and approximately 50% of the population exposure to this dose can be fatal (CAZUMBÁ et al., 2017).

Nowadays, with the development of mass media and the introduction of beauty standards, the cult of the "perfect face" generates insecurity in self-esteem. That's why patients come in addition to health, they also seek harmony and facial rejuvenation (PAPAZIAN et al., 2018).

Given these considerations, the central objective of the present study was to describe the mechanisms of action of botulinum toxin in orofacial aesthetic procedures.

## BOTULINUM TOXIN MECHANISM OF ACTION

The action of botulinum toxin is to temporarily inhibit the neuromuscular junction. Therefore, the mechanism of action is to block the release of acetylcholine in response to a nerve impulse (SANTOS et al., 2015; CARVALHO, 2014). After this inhibition, the impulse can be reestablished by the proliferation of affected neurons, establishing a temporary pathway until the motor endplate is reactivated.

Botulinum toxin acts by inhibiting the release of acetylcholine in the synaptic cleft (JOHNSON and MONTECUCCO, 2008). Among the theories about the mechanism of action by which this occurs, the most well accepted is that this molecule acts on some component of the pre-synaptic protein complex SNARE (soluble N-ethylmaleimide-sensitive factor [NSF] – attachment protein receptor), which is essential in the release of acetylcholine in the synaptic cleft, thus inhibiting the release of this neurotransmitter in the cleft and, consequently, preventing the contraction of the innervated muscle fiber (COOPER, 2009; DRESSLER AND BENECKE, 2007; SPOSITO, 2004).

After selective fragmentation of the chain, botulinum toxin becomes active (Swaminathan, 2011 as cited in Fujita & Hurtado, 2021), forming a polypeptide molecule composed of two portions: a light one (50 KDa) and a heavy one (100 KDa). This function is to transport the toxin to the motor cell, ensuring the binding, internalization and translocation of the light fraction to the cell cytoplasm, which, in turn, is responsible for disintegrating the specific SNAP-25 proteins, inhibiting contraction. muscle (BAGRAMYAN et al., 2013; SOUZA & MENEZES, 2019). Both remain linked by a disulfide bridge, guaranteeing biological activity.

The light chain is the catalytic and proteolytic part. Its active site is a cavity that contains zinc ions and accommodates at least 16 amino acids. The light chain weighs 50 kDa and is responsible for the activity of zinc-dependent metalloprotease, which prevents the release of neurotransmitters by preventing presynaptic fusion vesicles (POLI et al, 2002).

It is divided into two parts, Hn and Hc, which together make up 100 kDa. Hn, the binding domain, is a helical structure associated with membrane fusion activity and involved in the formation of transmembrane voltage-gated selective ion channels. 1Hc is composed mainly of beta protein and has two visual domains: Hc-N and Hc-C.1 This domain is involved in specific binding to neuronal receptors on the outer surface of peripheral cholinergic neurons. Thus, the heavy chain is responsible for the union of extracellular receptors and internalization in the neuron, in addition to the transfer of the light chain to the neuron's cytoplasm (POLI et al, 2002).

Each neurotoxin particle contains one atom of zinc, with the exception of BoNT/C, which has two atoms of this substance. The proportion of the number of molecules with zinc (potentially active) and without zinc (inactive) will depend on the temperature and incubation time of the bacterial culture.

The harmfulness is due to the effect of the catalytic activity inherent in the light portion. However, there is loss of damage if the simple covalent bond between the constituent parts of the polypeptide molecule is broken before internalization of the toxin in the target cell, as the chain with the lowest mass will not penetrate the axon terminal synaptic membrane (COLHADO, et al., 2009 apud FUJITA, 2019).

According to Costa (2016), the mechanism of action of botulinum toxin is due to cholinergic neuromuscular transmission, a process that involves the following steps: synthesis, storage, release, binding, degradation and recycling of acetylcholine. For synthesis, choline is transported from the extracellular environment to the neuronal cytosol through cotransport with sodium, then this molecule interacts with acetyl coenzyme A to form acetylcholine. Subsequently, ACh is transported into synaptic vesicles, where it is stored in the form of granules. Release into the synaptic cleft occurs when the nerve impulse depolarizes the nerve ending and voltage-dependent calcium channels open in the presynaptic membrane, increasing the concentration of intracellular calcium. Thus, high levels of calcium lead to the fusion of presynaptic vesicles with the cell membrane through a mechanism that involves the participation of SNARE proteins, culminating in the release of ACh that will bind to nicotinic receptors in the muscle fiber. This binding of ACh to nicotinic receptors triggers a messenger system that results in muscle contraction. In the sixth step, acetylcholine is degraded by the enzyme acetylcholinesterase into choline and acetate. Finally, choline can be recycled by a high-affinity transport system that takes the molecule back to the neuronal cytoplasm.

Botulinum toxin does not enter the central nervous system (CNS) by diffusion; the blood-brain barrier prevents this. As botulinum neurotoxin requires an acidic environment for translocation of the light chain to the cytoplasm of the neuromuscular junction, and this condition exists, potential retrograde transport is probably avoided (MEUNIER et al, 2002).

In the findings of Nawrocki, (2020), botulinum toxin acts on the autonomic nervous system, inhibiting the release of neurotransmitters responsible for transmitting nerve signals to sweat glands. This results in a reduction in excessive sweating in areas

treated with the toxin, such as armpits, palms and soles. This effect is used in the treatment of hyperhidrosis, a condition characterized by excessive sweat production.

For Ture et al., (2021) the mechanism of action of botulinum toxin is also related to its effect on the salivary glands. When administered in adequate amounts, the toxin can reduce saliva production, making it useful in treating conditions such as sialorrhea (excess salivation) in patients with neurological disorders or who have undergone radiotherapy treatments.

In the results of Menezes (2019) and Pedron (2017) there is regeneration of motor nerve terminals and specific SNAP-25 proteins, while others claim that there is formation of new acetylcholine receptors.

Evidence suggests that the analgesic effect of botulinum toxin is more important than its success in motor control, as pain relief can be reported in syndromes that are not necessarily related to spasm

For Dressler et al., (2005), the toxin acts by preventing the fusion of synaptic vesicles with the presynaptic membrane, which prevents the release of the neurotransmitter. As a result, localized muscle relaxation occurs, since acetylcholine is responsible for transmitting the nerve signal for muscle contraction. In addition to muscle relaxation, botulinum toxin also has an analgesic effect. This effect is believed to be the result of reduced release of inflammatory substances, such as glutamate, which are involved in pain perception. Therefore, in addition to its aesthetic use for reducing wrinkles.

After about two months, the nerve ending begins to expand into sprouts that extend across the surface of the muscle. When the sprouts form a physical synaptic connection with the neuromuscular junction, the neuromotor unit is regenerated (AOKI, 2004).

In the findings of Choi et al., (2019), botulinum toxin is also used in the treatment of painful conditions, such as chronic migraines and muscle spasms.

Therefore, botulinum toxin presents itself as a non-invasive treatment alternative with a maximum effect of up to six months on the human body.

## FINAL CONSIDERATIONS

The dentist specializing in orofacial harmonization must have a detailed understanding of the structure and function of facial muscles, as well as the correct application techniques.

It is suggested that future studies in the area of orofacial harmonization focus on investigating the mechanisms of action of botulinum toxin. Therefore, an in-depth understanding of these mechanisms by the dentist, specialist in orofacial harmonization, is essential to guarantee the correct indication of therapy to their patients, contributing based on scientific evidence of the mechanisms involved.

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