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Review

Treatment of Orofacial Pain with Botulin Toxin Type A (Bont – A) and its Long-Term Effect: A Literature Review

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Abstract

Botulinum toxin type A (BoNT-A) is being increasingly used off-label for the treatment of orofacial pain, although there are reports of pain relief while the effect of the toxin persists, some studies indicate long-term adverse effects such as loss of bone density in the mandibular condyle, weakness of the masticatory muscles, difficulty opening the mouth, among others. Methodology: This study qualifies as a literature review having the database "Pubmed" as a bibliographic survey, using keywords such as "Botulinum toxin type A", "BoNT - A", "Orofacial Pain", "Bony changes", "Masseteric hypertrophy", "TMD". We conclude that because it is a means of treatment without regulated protocols and the scarcity of studies related to adverse effects, it can become a dangerous intervention for the patient, causing more harm than good. Therefore, it requires a closer look at this area and more studies are needed to prove the real effectiveness of botulinum toxin in the treatment of orofacial pain.

Keywords: Bony changes, BoNT – A, Botulinum toxin type A, Masseteric hypertrophy, Orofacial Pain

INTRODUCTION

Orofacial pain is attributed to any painful symptomatology in the head and neck region, the most common are neuropathic disorders associated with the trigeminal nerve such as trigeminal neuralgia, temporomandibular dysfunctions of joint and/or muscular origin, hypertrophy of the masseter, temporalis, and accessory muscles of mastication (Crandall, 2018).

Botulinum toxin serotype A is the most widely used in medical and aesthetic practices, Botulinum Toxin Type A acts in selective muscle paralysis, promoting the inability of the neurotransmitter acetylcholine to bind to muscle receptors preventing the processes of movement and contraction (Fedorowicz et al., 2013).

Currently in the dental field has been growing more and more treatments for orofacial pain with botulinum toxin off-label, as there is no specific and regulated clinical protocol for each type of orofacial pain, the dentist uses the manufacturer's dosage recommendations or optsfor dosages based on their own clinical point of view, besides having this scarcity of studies and clinical protocols, there is a deficiency in the training of the dental surgeon for applications of this toxin, many use one-week courses that do not provide a sufficient amount of practical classes to become qualified, or use dubious teaching sources. Thus, care should be doubled to avoid possible adverse effects in the short and long term (Gerwin, 2012).

METHODOLOGY

The present study is characterized as a literature review with qualitative analysis, using the PubMed database as support for the bibliographic survey of scientific articles. The keywords used in the PubMed database search were "Botulinum toxin type A", "Orofacial pain", "Bony changes", "Masseteric hypertrophy" and "TMD". During the search the key words were used with the Boolean operator "AND" between them and filtering publications from the last 12 years.

Based on the methodology used, an initial sample was obtained, taking as inclusion criteria the evaluation of articles with titles and abstracts that matched the research theme, clarity in methodology, articles in

English, availability of full text, resulting in a total of 17 articles as sources of concepts on the subject.

After reading and interpreting all the articles, some were included and others were excluded for not fitting the theme under discussion. Part of this was used for the theoretical framework, from which fully relevant authors were selected, these authors were included in the references of the primary research articles, and these additional papers were downloaded, read and added as sources for the secondary research.

RESULTS AND DISCUSSION

Etiology BoNT – A

Botulism was first described in 1820 in Germany by Justinus Karner, when he associated the many deaths at the time with the ingestion of smoked sausages. Justinus detailed the symptoms of hundreds of patients, suspecting that the source of the poisoning was a biological rather than environmental poison, symptoms such as dry mouth, weakness, reduced bodily secretions, caused Karner to associate this poisoning with potential to relieve symptoms related to muscular hyperactivity, during his research, he suggested the use of this substance in medicine, especially in hyperactive nervous disorders (Jabbari, 2016).

Tinastepe (2015), reports that during several cases of deaths by ingestion of canned sausages in Belgium in 1895, Professor Emile Van Ermegen in his research, isolated the bacterial agent that was causing the deaths and named it *Bacillus botulinum* (Tinastepe et al., 2015). In the 20th century, this agent was renamed *Clostridium botulinum.* At the end of the Second World War, Schantz, E. et al. isolated and purified the toxin of

C. botulinum, after some decades of research, they obtained eight serotypes of this toxin, being classified as Type A, B, C, D, E, F, G and H (Jabbari, 2016).

According to Matak (2019), Burgen et al, discovered that Botulinum Toxin Type - A (BoNT - A) acted in inhibiting the release of Acetylcholine from neuro-muscular junctions, promoting the paralysis of skeletal muscles. Through this discovery, it was first used as a therapeutic form in the correction of ocular misalignment caused by strabismus (Matak et al., 2019).

Botulinum toxin type A is the most widely used in the medical field today, with serotypes A and B being the most associated with humans (Tinastepe et al., 2015).

Orofacial Pain (OFP)

According to Crandall (2018), orofacial pain (OFP) can be defined by musculoskeletal, neurovascular, neuropathic pain conditions and are often accompanied by a variety of comorbidities. Parafunctional habits such as object biting, nail biting, bruxism, excessive force etc. collaborates with the aggravation and onset of orofacial pain (Crandall, 2018). The pain interferes directly in the personal life of the individual, such as mood alteration, hindering social interaction and work, developing anxiety, stress and even depressive mood(Karamat et al., 2022). Badel (2019) reports that, it is still possible to develop emotional triggers, making the anticipation of the pain mood, thus, the professional must perform the treatment in a multiprofessional way due to the comorbidities such as psychological factors, behavioral, sleep disorders, headache disorders, trauma and systemic disorders that can hinder the treatment of OFP if not perform a multidisciplinary approach (Badel et al., 2019).

According to Van Deun (2020), temporomandibular dysfunctions (TMD) is part of the musculoskeletal and neuromuscular disorders that have a multifactorial origin that affects the temporomandibular joint, and can be unilateral or bilateral, has a high prevalence in the population being women more affected than men (2:1). TMD patients have their condition worsened by movements of the temporomandibular joint (TMJ) and masticatory muscles; the levels of pain can range from mild discomfort to acute pain. Besides TMJ pain, other symptoms may be associated such as limited mouth opening, deviations of the mandibular condyle, clicking and crackling during the process of opening and closing the mouth, sensitivity in the masticatory muscles, headache in the region of the temporal muscles and hypertrophy of the masticatory muscles, the most common being the masseter muscle (Van Deun et al., 2020).

Trigeminal neuralgia (TN) is one of the most common neuropathic orofacial pain syndromes that affects the second branch of the trigeminal nerve and is related by extreme and intense unilateral pain and has a duration of a few seconds. One of the aspects of TN, besides spontaneous pain, pain caused by touch, drinks and food can occur (Ziegeler et al., 2021).

Mechanism of action: BoNT – A

Botulinum Toxin is a neurotoxin, being the fermentation product of the Gram-Positive anaerobic bacterium *Clostridium botulinum,* eight serotypes of *Clostridium botulinum* related toxin have been found, they are type A, B, C1, D, E, F and G and H. Serotype C2 is not classified as a neurotoxin (Kasyanju Carrero et al., 2019). BoNT - A produces an interference in the neuro-transmitter mechanism, producing a selective paralysis in the muscles causing a state of muscle atrophy in the applied region (Matak et al., 2019).

According to Fedorowicz, the mechanism of BoNT - A occurs through four steps, they are, (I) BoNT - A will bind to the SV - 2 receptor on the neural presynaptic membrane; (II) internalization of BoNT - A occurs through

Table 1. Search strategies according to database PubMed. Palmas – TO, Brazil, 2023.

Lead author	Country	Year	Subject
Karen G. Raphael	EUA	2014	Osteopenic consequences of botulinum toxin injectionsin the masticatory muscles
C. S. Chang	EUA	2011	Mandible Changes Evaluated by Computed Tomography Following Botulinum Toxin A Injections in Square-faced Patients
Julián Balanta-Melo	Holland	2018	Early molecular response and microanatomical changes in the masseter muscle and mandibular head after botulinum toxin intervention in adult mice
Alexander M.Tatara	EUA	2014	The Role of Muscle Loading on Bone (Re)modeling atthe Developing Enthesis
Robert Gerwin	EUA	2012	Botulinum Toxin Treatment of Myofascial Pain
Yu-Ting Yeh MD	IND	2018	adverse events associated with botulinum toxin injectionfor the masseter muscle hypertrophy
Zbys Fedorowicz	UK	2013	Botulinum toxin for masseter hypertrophy

an endocytosis done by the SV - 2 receptor; (III) BoNT-A translocates the light chain (L - Chain) from the endocytosed vesicle into the neural cytosol; (IV) Snap-25 protein cleavage is initiated, causing the acetylcholine-containing vesicle to not bind to the degraded receptor, preventing its release, and consequently causing muscle paralysis (Fedorowicz et al., 2013). Table 1

Case Analysis

Botulinum Toxin Type A is increasingly being used in the treatment of orofacial pain, headache and temporo-mandibular dysfunction of muscle origin, BoNT - A is used intramuscularly with therapeutic doses, leading the affected region to a localized paresis (Chang et al., 2011). Although BoNT - A has already demonstrated safety for numerous therapeutic indications, because it is a recent drug in the treatment of orofacial pain, there are no specific protocols proven and scientifically regulated, leading the professional to commit possible iatrogenic as overdose causing a toxicity to the patient, which can lead to various problems, some of them are respiratory impairment, difficulty swallowing and even death (Raphael et al., 2014). Gerwin reiterates that BoNT is approved by the Food and Drug Administration in the United States only to treat chronic migraine, strabismus, cervical dystonia, axial hyperhidrosis, blepharospasm, and some cosmetic procedures. All other treatments with BoNT are done off-label (Gerwin, 2012).

According to Tatara, muscle loading on bone plays a role in (re)shaping bone tissue, and this removal of loads on bone can lead to a demineralization process of the bone region and a delay of remineralization (Tatara et al., 2014).

There are studies that botulinum toxin used in orofacial pain treatments shows effectiveness in relieving facial pain, but this relief persists only during the effect of the toxin on the muscle, requiring recurrent applications of botulinum toxin so that it does not lose its effect (De la TorreCanales et al., 2017). Although some authors report efficacy, there is a controversy in the literature (Balanta-Melo et al., 2018).

A series of randomized, controlled, double-blind studies were performed on patients with facial muscular dystonia separated into two groups, one group receiving applications of BoNT-A on masseter pain trigger points, and the other group receiving Saline applications as a placebo on masseter pain trigger points. After the conclusion of the studies, Gerwin (2012), reports that there was no significant difference between the two groups, as both the group that received BoNT-A and the group that received the placebo obtained improvements in relation to pain. Another study conducted in TMD patients following the same pattern as the previous study of trigger points in the masseter region, but with a dosage of 50 units of BoNT - A, showed that BoNT - A obtained a small advantage over the group that was injected with the placebo, but after 3 months the painful symptomatology reappeared (Gerwin, 2012).

A study conducted in adult rats and growing mice by Balanta-Melo, used Botulinum Toxin Type A to induce masseter muscle paralysis, generating muscle atrophy, with four weeks of performing the procedure was seen a reduction in masseter muscle mass and after fourteen days was observed subchondral bone loss in the mandibular condyle. Julián concludes that, the levels of the cytokine RANK-L which is responsible for the differentiation of osteoclasts, increased in the mandibular head two days after application of BoNT — A (Balanta-Melo et al., 2018).

A study by Raphael K. (2014), separated into two groups women with orofacial pain from TMD, one group was treated with BoNT-A while the other was given Saline as a placebo, both groups were applied to pain trigger points in the masseter muscles. It was found through dual energy x-ray absorptiometry (DXA) imaging performed after 6 - 10 weeks after application, that the group of women treated with BoNT - A had a detectable decrease in trabecular bone density of the mandibular

condyle. With this study it was possible to show a certain fidelity between the studies performed in rodents and other studies in humans (Raphael et al., 2014).

In his research, Yeh (2018), reports several adverse events related to botulinum toxin applications to the masseter muscle to treat hypertrophy, the doses of the toxin ranged from 20 to 140 units, depending on the subtype used. During the post-clinical period, edema at the application site was reported at about 6.3% to 22. During the post-clinical period, post-treatment hematomas had an incidence of 2.5% to 6.3% and other studies reported that 1 in 16 patients developed the hematomas, painful processes were also reported around the application site with an incidence of 12.5% to 59.1% with recovery after 3 weeks, Weakness in the masticatory muscles was the most reported effect during treatment with botulinum toxin along with a reduction in bite force, some patients presented effects related to facial asymmetry in the paralyzed region, there was also interference in the movement related to TMJ, making it difficult to open the mouth, with 220 patients reporting this adverse effect. Most complications appear between 2 to 4 weeks after application of the toxin and disappear within 12 weeks (Yeh et al., 2018).

Through a systematic review conducted by Fedorowicz (2013), on the treatment of bilateral benign hypertrophy of the masseter muscle, expresses the lack of randomized controlled studies and controlled clinical trials and the scarcity of evidence that demonstrates the effectiveness or ineffectiveness of botulinum toxin for hypertrophy of the masseter, as well as the lack of studies relating the long-term effect. Although there is a lot of talk about PFO treatments with botulinum toxin, it is unquestionable that there is a lack of relevant studies proving the long-term efficacy and safety (Fedorowicz et al., 2013).

CONCLUSION

The treatment of orofacial pain using botulinum toxin type A in an off-label way, demonstrates a relief of the painful symptomatology while the action of the toxin persists in the muscle. However, there is low scientific evidence to demonstrate the real efficacy of botulinum toxin in the treatment of orofacial pain, as well as its long-term adverse effects since several studies contradict each other regarding its safety and efficacy. Therefore, more studies are needed on the long-term adverse effects and the establishment of scientifically proven clinical protocols.

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