

**Effect of botulinum toxin treatment in patients with bruxism and orofacial pain -  
randomized double-blind clinical trial**

**Efeito do tratamento com toxina botulínica em pacientes com bruxismo e dor orofacial -  
ensaio clínico duplo-cego randomizado**

**Efecto del tratamiento con toxina botulínica en pacientes con bruxismo y dolor orofacial  
- ensayo clínico aleatorizado doble ciego**

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**Abstract**

Introduction: Bruxism is defined as a parafunctional chewing activity characterized by the clenching and / or grinding of teeth that occurs both during sleep and during the surveillance period. Methods: Thirty female patients between 18 and 40 years old who had bruxism and orofacial pain were selected and randomized into two groups: control group (n = 15), where individuals received 0.05 ml of sterile saline solution that was applied to the bundle anterior temporal muscles and 0.2 ml for each masseter muscle, and an experimental group (n = 15), individuals received 20 units of A-botulinum toxin (Botox®) applied to each masseter muscle and 5 units of A-botulinum toxin applied to the anterior bundle of each temporal muscle. Patients were called back for reevaluation every thirty days. At these moments, they underwent an evaluation of the load force and electromyography. Results: At 30, 60, 90 and 120 days, a decrease in electromyographic activity was observed in the A-botulinum toxin group ( $p < 0.001$ ). In the experimental group, the left masseter muscle showed no significant difference between the variable load cell and time ( $p = 0.968$ ), nor between electromyography versus load ( $p = 0.072$ ), with a statistically significant difference between time and electromyography. (coef = 0.322;  $p < 0.001$ ). Conclusion: The intramuscular application of botulinum toxin type A in patients with bruxism has proved to be an effective method for hyperactivity of the masseter muscle in patients with bruxism, improving and decreasing the levels of muscle contraction.

**Keywords:** Botulinum toxin type A; Facial pain; Dentistry; Bruxism; Ear-jaw articulation; Temporomandibular joint dysfunction.

### Resumo

**Introdução:** O bruxismo é definido como uma atividade parafuncional de mastigação caracterizada pelo aperto e / ou ranger dos dentes que ocorre tanto durante o sono quanto durante o período de vigília. **Métodos:** Trinta pacientes do sexo feminino entre 18 e 40 anos que apresentavam bruxismo e dor orofacial foram selecionadas e randomizadas em dois grupos: grupo controle (n = 15), onde os indivíduos receberam 0,05ml de solução fisiológica estéril que foi aplicada no feixe anterior dos músculos temporais e 0,2ml para cada músculo masseter, e um grupo experimental (n = 15), os indivíduos receberam 20 unidades de toxina A-botulínica (Botox®) aplicadas em cada músculo masseter e 5 unidades de toxina A-botulínica aplicado ao feixe anterior de cada músculo temporal. Os pacientes foram chamados de volta para reavaliação a cada trinta dias. Nesses momentos foram submetidos novamente a avaliação da força de carga e eletromiografia. **Resultados:** Aos 30, 60 90 e 120 dias, uma diminuição na atividade eletromiográfica foi observada no grupo A-toxina botulínica ( $p < 0,001$ ). No grupo experimental, o músculo masseter esquerdo não apresentou diferença significativa entre a variável célula de carga e o tempo ( $p = 0,968$ ), nem entre a eletromiografia versus carga ( $p = 0,072$ ), sendo observada diferença estatisticamente significativa entre o tempo e a eletromiografia (coef = 0,322;  $p < 0,001$ ). **Conclusão:** A aplicação intramuscular de toxina botulínica tipo A em pacientes com bruxismo e mostrou-se um método eficaz para hiperatividade do músculo masseter em pacientes com bruxismo, melhorando a diminuindo os níveis de contração muscular.

**Palavras-chave:** Toxina botulínica tipo A; Dor facial; Odontologia; Bruxismo; Articulação temporomandibular; Disfunção da articulação temporomandibular.

### Resumen

**Introducción:** El bruxismo se define como una actividad masticatoria parafuncional caracterizada por el apretamiento y / o rechinar de dientes que ocurre tanto durante el sueño como durante el período de vigilancia. **Métodos:** Se seleccionaron 30 pacientes de sexo femenino entre 18 y 40 años que presentaban bruxismo y dolor orofacial y se aleatorizaron en dos grupos: grupo control (n = 15), donde los individuos recibieron 0.05 ml de solución salina estéril que se aplicó al paquete. músculos temporales anteriores y 0,2 ml por cada músculo masetero, y un grupo experimental (n = 15), los individuos recibieron 20 unidades de toxina

A-botulínica (Botox®) aplicadas a cada músculo masetero y 5 unidades de toxina A-botulínica aplicado al haz anterior de cada músculo temporal. Se llamó a los pacientes para una reevaluación cada treinta días. En estos momentos, se les realizó una evaluación de la fuerza de carga y electromiografía. Resultados: A los 30, 60, 90 y 120 días, se observó una disminución de la actividad electromiográfica en el grupo de la toxina botulínica A ( $p < 0,001$ ). En el grupo experimental, el músculo masetero izquierdo no mostró diferencia significativa entre la celda de carga variable y el tiempo ( $p = 0,968$ ), ni entre la electromiografía versus la carga ( $p = 0,072$ ), con diferencia estadísticamente significativa entre el tiempo y la electromiografía. (coef = 0.322;  $p < 0.001$ ). Conclusión: La aplicación intramuscular de toxina botulínica tipo A en pacientes con bruxismo ha demostrado ser un método eficaz para la hiperactividad del músculo masetero en pacientes con bruxismo, mejorando y disminuyendo los niveles de contracción muscular.

**Palabras clave:** Toxina botulínica tipo A; Dolor facial; Odontología; Bruxismo; Articulación temporomandibular; Disfunción de la articulación temporomandibular.

## 1. Introduction

Bruxism is defined as a parafunctional chewing activity characterized by clenching and/or grinding of teeth, which occurs during both sleep and vigilance. It is related to emotional factors, occlusal interference and neurological disorders (Lobbezoo et al. 2018). On average 90% of the population is diagnosed with bruxism at some time in their life (Goldstein, 2000).

Bruxism is caused by several factors, which makes it difficult to accurately discover its etiology, making it complex to establish a treatment plan for all patients with this parafunction. Therefore, there is no specific treatment, and each patient should be individually evaluated and controlled (Ferrario, Sforza, Tartaglia, & Dellavia, 2002; Guarda-Nardini et al., 2008). Studies on bruxism show an association of the syndrome with anxiety, stress, depression, personality types, nutritional deficiencies (magnesium, calcium, iodine and vitamin complexes), dental malocclusion, central nervous system dysfunction and/or disorders, neurochemical drugs and genetic factors (Goldstein, 2000; Guarda-Nardini et al., 2008; Majid, 2010).

Central Nervous System (CNS) disorders are directly related to bruxism. According to the neurophysiology, the nuclei of the base are anatomical structures of the brain responsible for the modulation of the movements, and catecholamines are the regulatory substances of

their action (Bader & Lavigne, 2000). Dysfunctions in catecholamine concentration are associated with certain conditions such as Parkinson's disease, Huntington's disease, Shy-Drager syndrome, oral mandibular dystonia, late oral dyskinesia, Gilles de laTourette syndrome, hemifacial spasms, akathisia, late dystonia (all of these conditions are movement-associated disorders) (Bader & Lavigne, 2000; Aloé, 2009).

Pain is a frequent symptom in clinical signs of bruxism. Dentin hypersensitivity, excessive tooth wear, fractures of teeth and restorations, hypertrophy and myalgia of the masticatory muscles (mainly temporal and masseter), headache and TMJ pain are among the most commonly observed clinical manifestations (Spsoito, 2009; Laskin, 2018)

The control plan developed for bruxism should meet the following objectives: reduction of physical and psychological tension, treatment of signs and symptoms, minimization of occlusal interference and disruption of habitual neuromuscular pattern. Occlusal therapy is performed with occlusal adjustment. Occlusal splints may be indicated for controlling the muscle activity and occlusal commitment. The use of medication (such as muscle relaxants) to subside and eliminate patient's pain and consequently bruxism is a temporary treatment (Ferrario, et al. 2002; Kato et al., 2003; Guarda-Nardini, et al., 2008; Laskin, 2018).

Botulinum toxin is produced by gram-positive anaerobic bacteria called *Clostridium botulinum*, which form a protease of neurotoxins that are divided into seven distinct forms ranging from type A to G, where each subtype produces a different neurotoxin (Ferrario, et al. 2002; Aoki, 2004; Sposito, 2009; Majid, 2010). Its protease activity causes temporary chemical desensitization of skeletal muscles by blocking the  $Ca^{+2}$ -mediated release of acetylcholine from nerve endings in alpha and gamma motor neurons that inhibits acetylcholine release in motor nerve terminals, causing a decrease in muscle contraction. This property makes it useful in regions where there is excess contraction (Litham, 2004; Silberstein, 2004; Carruthers & Carruthers, 2007).

Type-A botulinum toxin has been employed to control several chronic pain conditions, including myofascial pain, neuralgia and hyperesthesia, and is related to the pain relief mechanism, not only in neuromuscular junction receptors, but also in the nociceptive receptor system (Aoki, 2004; Silberstein, 2004; Sposito, 2009). Side effects are rare and, even if they exist, are transient, causing no major problems for patients (Yu, Philip & Chen, 2007; Zhang, Liu, Zou, & Yu, 2016; Awan et al., 2019). The use of botulinum toxin to control bruxism is increasing, but there is no consensus regarding the effectiveness of this method (Freund, Schwartz & Symington, 1999). Given the above and realizing the scarcity of specific studies,

the present study aimed to evaluate the effect of botulinum toxin type A in the control of pain, quality of life and masticatory force in female patients with sleep bruxism, by means of a double blind randomized clinical trial.

## **2. Material and Methods**

The present study is a randomized clinical research, carried out in human beings where neither the examined person (object of study) nor the examiner know what is being used as a variable at a given moment. It is commonly used as a criterion for the validation of quantitative experimental practices in science and double blind in order to reduce the maximum possible bias, to evaluate effectiveness; application of botulinum toxin in patients with myocardial pain and temporomandibular disorders. It is a study of a quantitative nature, since this study brings the collection of numerical quantitative data through the use of measurements of quantities for objective analysis of the numerical results presented.

### **2.1 Ethical Criteria**

This study was approved by the Institutional Human Research Ethics Committee (register: CAEE64309416.1.0000.5152). All participants signed an informed consent form.

### **2.2 Patient Selection**

This is a randomized, double-blind controlled clinical study carried out according to the CONSORT (Consolidated Standards of Reporting Trials) standards and registered in the National Clinical Trial Registry under number U1111-1217-7400. The patients were recruited by digital media and appointment of dental surgeons in the city of Uberlândia, Minas Gerais, Brazil, and were accomplished at the School of Dentistry of the Federal University of Uberlândia, Minas Gerais, Brazil from April to November of 2017.

Inclusion criteria were individuals between 18 and 40 years-old, female, with self-reported sleep bruxism and associated orofacial pain reported in the last 3 months. The exclusion criteria were patients with active psychosis, other active psychiatric illness or cognitive impairment; serious comorbid diseases; individuals exposed to botulinum toxin in the last 6 months; participation in another experimental therapeutic protocol; patients with myasthenia gravis, amyotrophic lateral sclerosis and other acute diseases; history of

dysphagia and/or botulism; impairment of intellectual capacity, pregnancy, making use of myorelaxant plaques, and egg allergies.

### **2.3 Experimental Protocol**

Patients were randomized into two groups: (1) Experimental, with 15 individuals received 20 units of A- Botulinum Toxin (Botox®, Allergan Pharmaceuticals LTDA, Dublin, Ireland) applied to each masseter muscle and 5 Units to the most anterior bundle of each temporal muscle, and (2) Control, with 15 individuals received 0.2ml of sterile saline to each masseter muscle and 0.05ml applied to the anterior temporal muscle bundle.

Patients were allocated according to a list created at the website [www.sealedenvelope.com](http://www.sealedenvelope.com) by the operator 1 (A.C.M), which also placed saline or botox syringes inside the envelopes with corresponding patient's identification (4 syringes per envelope, one for each muscle), without group identification, in order to keep the operator 2 blinded. The latter (M.C.P.S.), an experienced professional in charge of all of the interventions, only opened the envelope when was to perform the procedure.

A third researcher (C. E. F.), without knowledge of the group allocation, was responsible to assess the response of the patients to the intervention. In the first session, previous to any procedure (baseline), and in follow-up after 30, 60, 90, 120, 150 and 180 days. Electromyography and chewing force test (Load Cell) at maximum contraction with a dynamometer were also obtained in each of these periods.

### **2.4 Load Cell Test and Electromyography**

For Load Cell Test, a calibrated dynamometer (Model IDDK V4, Kratos Industrial Equipment, Cotia, SP, Brazil) was inserted at the region of the first molar on right side then at the left side. The patient was asked to bite three times with maximum force, and the value was recorded in Newtons (N). The average was considered the final value, for each side.

For electromyography, records were obtained using a computerized electromyograph (830 C model, EMG System of Brazil LTDA, Sao Jose dos Campos, SP, Brazil) designed in accordance with the International Society of Electrophysiology and Kinesiology standards (ISEK). The device had the following characteristics: eight input channels for EMG signals from passive or active electrodes; two input channels for auxiliary signals such as load cells, electrogoniometers and isokinetic equipment. During collection, the skin was prepared with

alcohol friction to remove dead epithelial cells. During the electromyographic record the patient was kept sitting with the Frankfurt horizontal plane parallel to the ground. Electrode positioning in the masseter muscle was performed through muscle palpation, and the patient was instructed to keep the teeth in occlusal contact. In the masseter muscle, an electrode was positioned in the center of the equidistant point of the upper and lower insertions. Patients were instructed to keep the maximum usual intercuspal position with maximum force, for 10 seconds, for analysis of muscle contraction. Each one made the collection 3 times to avoid possible external interference of electrical signals, being the final value the average between the three collections.

## **2.5 Statistical analysis**

Comparative analysis between two groups with a 95% confidence interval. T-test for when the data were considered parametric and Mann-Whitney Rank Sum Test for non-parametric data. \* Mean difference between the control and botulinum toxin groups at the same time of comparison ( $p < 0.05$ ). For the calculation, a test power of 80% was considered, a significance level of 5%, pain reduction rate of 91% for the intervention group and 72% for the control group; and a 30% risk reduction for treatment to consider statistical difference, in a randomized clinical trial design.

## **3. Results**

### **3.1 Load Cell Evaluation (dynamometer)**

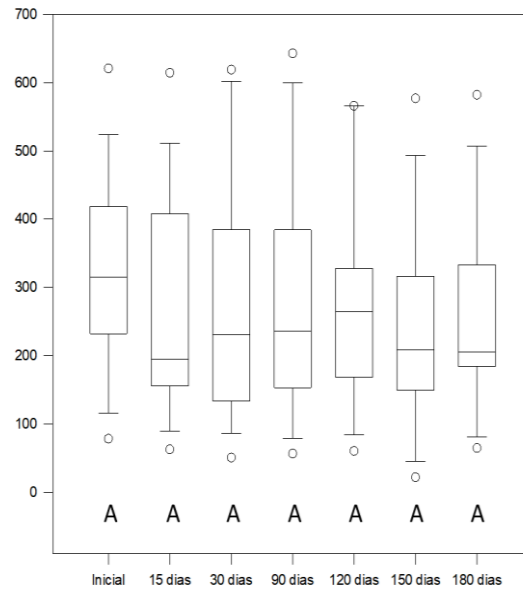
The values of total masticatory force of the masseter muscle were for the Control group were compared between the baseline and the other periods after application of A-Botulinum Toxin. The mean chewing force in the Control group masseter at the baseline was (518N), at 30 days (355N), at 60 days (430N), at 90 days (458N), at 120 days (449N), at 150 days (429N) and at 180 days (408N). There was only a significant difference in the comparison between baseline versus 150 days ( $p < 0.05$ ) (Figure 1A and 1B).

In Figures 1A and 1B, it is possible to note that there was no decrease in masticatory strength over time, as it was the control group, butolinic toxin, the study drug in question, was not applied. We noticed only a slight drop in the force values in both masseters as time went



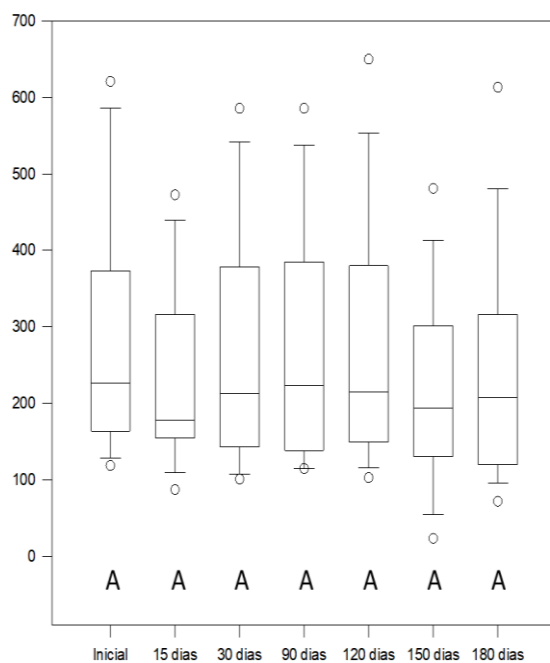
by in the control group, to which the researchers credited this phenomenon to the placebo effect.

**Figure 1A** - Left Masseter- Control. (Home X Follow-up Times).



Graphs generated by the MathWorks statistics program - MATLAB software.

**Figure 1B** - Right Masseter- Control. (Home X Follow-up Times).

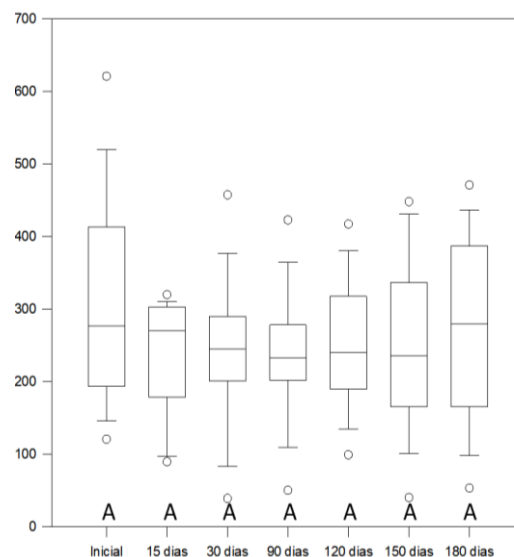


Graphs generated by the MathWorks statistics program - MATLAB software.

The measurement of total masticatory force of the masseter muscle in the Botox group at baseline was (468), at 30 days (479), at 60 days (480), at 90 days (435), at 120 days (481), at 150 days (465) and 180 days (522), with no significant difference between the baseline and the other time intervals ( $p < 0.05$ ) (Figure 1C and D).

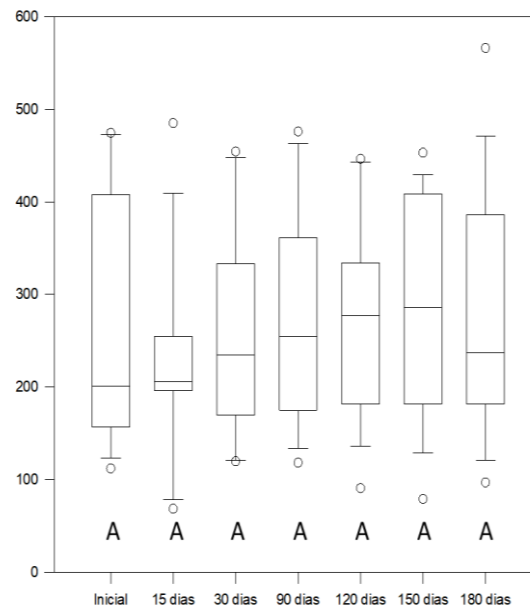
In Figures 1C and 1D it is possible to notice that there was a decrease in masticatory strength over time, mainly in the first months after application of botulinum toxin since it is the experimental group. There is a slight increase in the force values in both masseters as the time elapsed from the application of the drug on the 120th day after application, which demonstrates a temporary effect of the reduction of masticatory force within the experimental group.

**Figure 1C - Left Masseter- Botulinum Toxin. (Home X Follow-up Times).**



Graphs generated by the MathWorks statistics program - MATLAB software.

**Figure 1D** - Left Masseter- Botulinum Toxin. (Home X Follow-up Times).

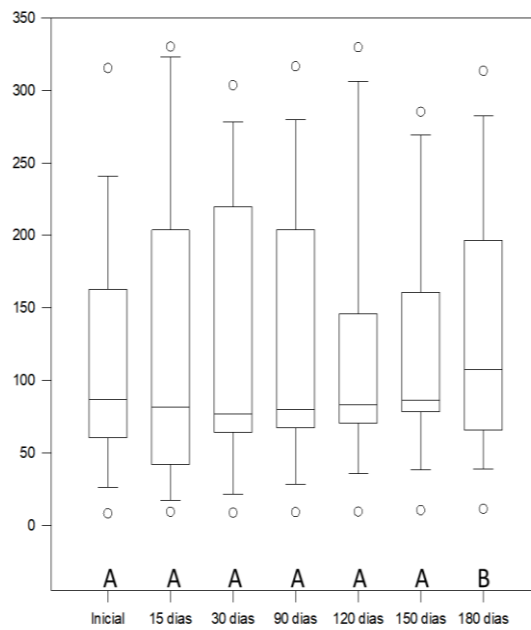


Graphs generated by the MathWorks statistics program - MATLAB software.

### 3.2 Evaluation of electromyography of the masseter muscle

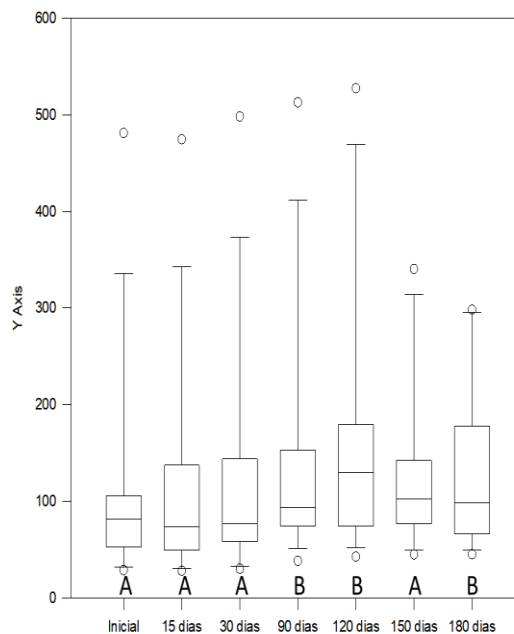
Measurements were performed only on the masseter muscle because of the risk of results being altered by the hair during the temporal muscle measurement. The analysis of the electromyographic activity of the right masseter muscle in the Control group revealed that when the baseline was compared to the other time intervals, the average values at baseline (81.6mV), at 30 days (73.8 mV), at 60 days (76.6 mV), at 90 days (93 mV), at 120 days (129 mV), at 150 days (102 mV) and 180 days (98 mV), difference was found to significant only between 90, 120 and 180 days ( $p < 0,05$ ) (Figure 2A and 2B).

**Figure 2A** - Left Masseter- Control. (Home X Follow-up Times).



Graphs generated by the MathWorks statistics program - MATLAB software.

**Figure 2B** - Right Masseter- Control. (Home X Follow-up Times).

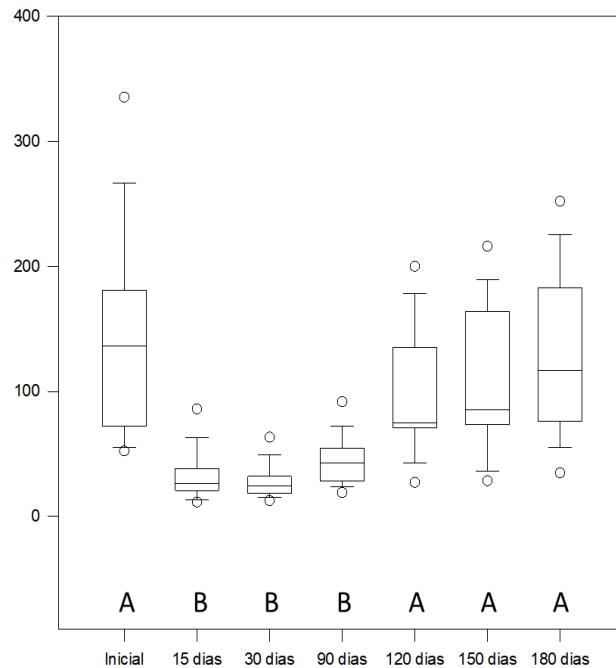


Graphs generated by the MathWorks statistics program - MATLAB software.

In Figures 2A and 2B, it is possible to note that there was no decrease in muscle electrical activity over time, since the control group did not apply the drug botulinum toxin. Maintaining constant electromuscular activity in both masseter muscles in the control group, and not even observing a possible placebo effect in patients in the control group.

The mean values of electromyographic activity of the left masseter muscle in the botulinum toxin group was found to be at baseline (140.33mV), at 30 days (31.46 mV), at 60 days (27.52 mV), at 90 days (44.18 mV), at 120 days (98.17 mV) at 150 days (101.74 mV) and 180 days (127.53 mV), and statistically significant differences were observed only between 15, 30, and 90 days ( $p < 0.05$ ) (Figure 2C).

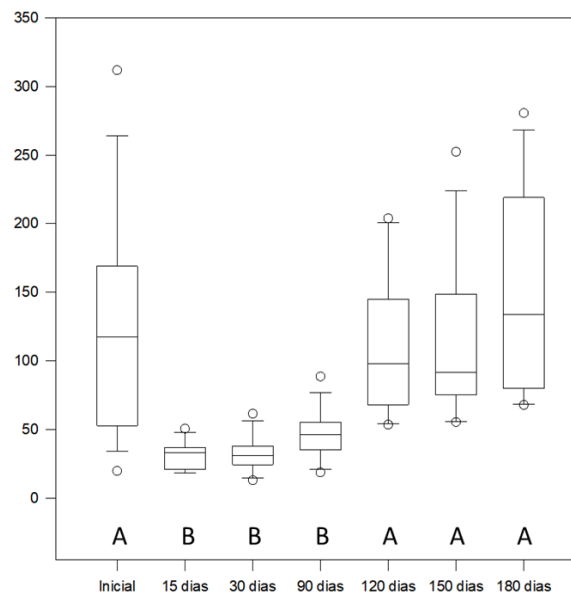
**Figure 2C** - Left Masseter- Botulinum Toxin. (Home X Follow-up Times).



Graphs generated by the MathWorks statistics program - MATLAB software.

The mean values of electromyographic activity of the right masseter muscle in the Botox group was found to be at baseline (117 mV), at 30 days (33 mV), at 60 days (30 mV), at 90 days (46 mV), at 120 days (97 mV) at 150 days (91 mV) and 180 days (133 mV), and statistically significant differences were observed only between 15, 30, and 90 days ( $p < 0.05$ ) (Figure 2D).

**Figure 2D** - Righ Masseter- Botulinum Toxin. (Home X Follow-up Times).



Graphs generated by the MathWorks statistics program - MATLAB software.

In Figures 2C and 2D it is possible to notice that there was a significant decrease in muscle electrical activity until the 120th day after application, which leads us to the right action that the drug butolinic toxin modulated the muscle electrical activities of the experimental group, directly decreasing the activity levels. . It is noted that after 120 days neuroelectromuscular activity began to show increases in activity levels, which refers to the temporary active effect of the drug's action.

The comparison between the Control and Paired Botox groups revealed that there was no statistical difference ( $p = 0.254$ ) at baseline for both groups. It was observed a statistically significant difference between groups at 30, 60 and 90 days ( $P < 0.05$ ). Decrease of electromyographic activity of the right masseter muscle was observed in the Botox group for the aforementioned periods (Table-1).

The analysis of the electromyographic activity of the left masseter muscle in the Control group, at different time intervals resulted in the following mean values at baseline (86.6 mV), at 30 days (81.4 mV), at 60 days (76.5 mV), at 90 days (79.7 mV), at 120 days (83 mV), at 150 days (86 mV), and at 180 days periods (107 mV). It was noted significant difference only at 180 days ( $p < 0.05$ ). The mean values of the electromyographic activity of the left masseter muscle in the Botox group were at baseline (136 mV), at 30 days (26 mV), at 60 days (24 mV), at 90 days (42.4 mV), at 120 days (74.8 mV), at 150 days (85.5 mV) and at

180 days (116.5 mV). Statistically significant differences were observed at 15, 30 and 90-day periods ( $p < 0.05$ ) (Table-1).

The comparison between the Control and Paired Botox groups for the left masseter muscle revealed no statistically significant difference ( $p > 0.05$ ) at baseline for both groups. Statistically significant difference occurred between groups at 30, 60 and 90 days ( $P < 0.05$ ). Decreased electromyographic activity of the left masseter muscle was observed in the Botox group for the aforementioned periods (Table-1).

**Table 1 – Electromyography.**

Electromyography:

Mean (standard deviation) and median (25%; 75%) values for the groups

		Controle	Botox	Valor de p
Left	Baseline	109,55 (77,88) 86,60 (60,50; 162,80)	140,33 (76,80) 136,50 (71,90; 181,00)	0.237
	30 days	118,45 (104,88) 81,40 (41,70; 203,70)	31,46 (18,30) 26,20 (20,80; 38,10)	0.002*
	60 days	114,84 (90,92) 76,51 (64,30; 219,90)	27,52 (12,49) 24,09 (18,30; 32,00)	<0.001*
	90 days	120,03 (87,82) 79,80 (67,41; 203,95)	44,18 (17,82) 42,42 (28,45; 54,81)	<0.001*
	120 days	125,22 (89,53) 83,08 (70,24; 146,08)	98,17 (46,93) 74,83 (70,70; 135,14)	0.590
	150 days	116,88 (76,31) 86,07 (78,24; 160,68)	101,74 (53,64) 85,55 (73,50; 163,80)	0.709
	180 days	130,81 (87,81) 107,16 (65,67; 196,63)	127,53 (60,66) 116,57 (75,88; 182,72)	0.740
	Right	Baseline	113,31 (113,64) 81,60 (52,80; 105,90)	128,24 (79,05) 117,40 (52,80; 169,00)
30 days		120,07 (115,05) 73,80 (49,30; 137,30)	32,02 (10,07) 33,20 (20,70; 36,70)	<0.001*
60 days		134,58 (126,11) 76,65 (58,57; 143,80)	32,39 (12,57) 30,94 (24,26; 37,95)	<0.001*
90 days		148,16 (128,56) 93,44 (74,33; 153,23)	46,87 (17,18) 46,40 (35,17; 55,02)	<0.001*
120 days		161,74 (136,92) 129,43 (74,33; 179,41)	111,32 (48,52) 91,82 (68,04; 144,98)	0.455
150 days		129,40 (85,07) 102,26 (77,04; 142,29)	113,96 (59,54) 91,72 (75,17; 148,40)	0.803
180 days		131,98 (87,75) 98,67 (66,02; 177,61)	144,46 (72,22) 133,53 (79,81; 219,00)	0.455

Comparative analysis between two groups with a 95% confidence interval. T test for when the data were considered parametric and Mann-Whitney Rank Sum Test for non-parametric data. \* It means difference between the control and botox groups for the same time of comparison ( $p < 0.05$ ).

Graphs generated by the MathWorks statistics program - MATLAB software.

Table 1 shows a co-relation of values of electromyographic activity between the control group and the experimental group. We can notice that the values of neuromuscular activity in the experimental group are significantly lower than in the control group until the 120th day. After this period, neuromodulatory activities lose their efficiency making the numerical values of gradation of neuromuscular autonomy similar for both study groups.

#### 4. Discussion

Botulinum toxin was firstly described in 1817 by Justinus Kerner, a German physicist, who began its use on animals. In 1897, microbiologist Emile Van Ermengem related the botulism epidemic to the bacteria found in food, thus isolating it and producing it in the laboratory (Goldstein, 2000; Guarda-Nardini et al., 2008; Majid, 2010). Botulinum toxin A has been used in recent years to help treat temporomandibular dysfunction, to reduce musculoskeletal pain and myofascial pain associated with bruxism (Freund, Schwartz & Symington, 1999; Guarda-Nardini et al., 2008; Canales, Câmara-Souza, Amaral, Garcia & Manfredini, 2017).

Regarding the treatment of TMJ dysfunction, there is still no therapy that permanently heals bruxism. Several issues regarding the subject are proposed and detailed in the literature.

Santos, Recco, Mota, Holanda & Junior (2017) conducted a review on the treatment of orofacial pain through acupuncture in patients with bruxism in order to prove the effectiveness of acupuncture in analgesia in patients with bruxism. They found that acupuncture causes endogenous release of chemical mediators such as opioids, cortisone and acetylcholine, improving pain. Thus, this therapy may be an alternative in the treatment of chronic and myofascial facial pain, such as those arising from bruxism.

Saletu et al., (2005) studied the pharmacotherapy of sleep bruxism to investigate the acute effects of clonazepam on bruxism. Their study included 10 patients who received previous treatment with bruxism splint. The authors found that clonazepam may reduce the symptoms of sleep bruxism by presenting good patient tolerability.

Another use of botulinum toxin is with occlusal appliances. Bruxism splint is the most commonly used therapy for the treatment of bruxism, although its mechanism of action is not well understood (Ommerborn et al., 2007). According to Harada, Ichiki, Tsukiyama & Koyano (2006), the use of occlusal splint, with or without occlusal coverage, was effective in the treatment of bruxism.

Literature reports confirm that cognitive behavioral therapy can be used in both types of bruxism, but its long-term application has no significant effect. Actually, it is possible that this therapy have more effect on wake bruxism due to the fact that factors psychological issues prove to be more important in this type of bruxism (Harada et al., 2006).

The use of catecholamine modulating neurochemical drugs, such as Diazepam and Methocarbamol, via dopaminergic route, have been effective as an auxiliary treatment for



bruxism, but at the risk of drug dependence over time (Bader & Lavigne, 2000; Ferrario et al., 2002). The prescription of propranolol, a beta-adrenergic agent was effective in the treatment of bruxism with its action related to direct sedative action due to its inhibition of trigeminal motoneurons (Bader & Lavigne, 2000; Aloé, 2009). The use of buspirone would cause a decrease in the number or sensitivity of presynaptic receptors, thus increasing the synapse for dopamine release, restoring motor modulation and disrupting muscle parafunctional activities (Bader & Lavigne, 2000; Goldstein, 2000; Aloé, 2009).

Botulinum toxin A is a presynaptic neuromuscular blocking agent, which inhibits the release of acetylcholine in neuromuscular junctions, thus reducing muscle contractions (Lew, 2002; Ommerborn et al., 2011)

Studies evaluating the efficacy of botulinum toxin A have yielded mixed results. Three studies reported that the use of the substance produced no benefit, while four reported that the use was beneficial (Nixdorf, Heo & Major, 2002; Von Lindern, Niederhagen, Bergé & Appel, 2003; Guarda-Nardini et al., 2008; Kurtoglu et al., 2008; Ernberg, Hedenberg-Magnusson, List & Svensson, 2011; Roldán-Barraza, Janko, Villanueva, Araya & Lauer, 2014). In the studies that reported a positive result for the use of botulinum toxin, some criticisms were observed, since most studies presented smaller sample size (Venancio, Alencar & Zamperini, 2009; Guarda-Nardini, Stecco, Stecco, Masiero & Manfredini, 2012; Jadhao et al., 2017). A short follow-up with a maximum of four months after drug application and verification of its action except that in our study the follow-up of patients was maintained over 6 months after application, presenting a relevant sample number for work to be developed (Kurtoglu et al., 2008; Venancio et al., 2009; Jadhao et al., 2017).

Studies reported the reduction of myofascial pain in patients with bruxism with reduced occlusion force in the masseter and temporal muscle after botulinum toxin A application (Guarda-Nardini et al., 2012). The maximum occlusal force was reduced after three months of botulinum toxin A application (Zhang et al., 2016). In the present study it was not possible to verify difference between the masseter muscle load cell intergroups nor between groups over time.

In the evaluation of the electromyographic activity (EMG) of the masseter muscle, there was a reduction of EMG activity in the experimental group at intervals of 15, 30 and 90 days after the single application of botulinum toxin A. These findings are compatible with the study of Lee, McCall, Kim, Chung & Chung (2010), who showed a reduction in EMG activity in the masseter muscle after injection of botulinum toxin, and the number of muscle contraction events was reduced from the fourth week and maintained for twelve weeks.

According to a randomized study, with twenty-four patients treated with injection of botulinum toxin into the masseter muscle, a reduction in EMG activity from the 14th day onwards with a return of the increase from the 28th day onwards was observed, as well as decreased pain scores (Von Lindern et al., 2003).

In the present study, an improvement in quality of life was found in the experimental group around 90 days after botulinum toxin injection. It was also possible to verify the correlation between the pain and time variables in the group that received the botulinum toxin, as well as the improvement of the quality of life over the follow-up time. In the study by Guarda-Nardinie et al., (2008) pain during chewing was reduced after 6 months, when patients with bruxism received botulinum toxin application compared to those who received placebo. This corroborates our results, regarding the improvement of pain in patients submitted to A-botulinum toxin (Botox®).

In a study by Ernberg et al. (2011), pain intensity was reduced at 30 and 90 days after application of A-botulinum toxin. Thus, one can stress out that the improvement of pain over time has a significant effect on improving the quality of life of the experimental group within 30, 60 90 and 120 days, after this period the effect of botulinum toxin begins to have its effect diminished and therefore new applications are necessary. These results are corroborated by Jadhao et al., (2017), who showed improvement in subjective resting and chewing pain parameters in the group treated with botulinum toxin A. In a prospective study of patients with chronic pain treated with injection of botulinum toxin in the temporal muscles and bilateral masseter masses, which were followed for 12 months, a reduction in pain measured by visual analog scale (VAS) and Physician Global Assessment (PGA) was reached (Baker & Nolan, 2017). When reviewing the scientific data available in the literature and the data obtained in this work, we suggest that A-botulinum toxin (Botox) may be indicated as an important aid for patients diagnosed with bruxism and orofacial pain, with periodic applications in the interval 4/4 months shown in this randomized trial.

## **5. Conclusion**

The use of A-botulinum toxin, applied to the masseter and temporal muscles bilaterally, in patients with bruxism and orofacial pain, proved to be an effective method to control masseter muscle hyperactivity in patients with bruxism, with its maximum peak of action until the ninetieth day after infiltration, with decreased muscle tension, improvement of

painful symptoms and, consequently, significant improvement in the quality of life of these patients.

The study shows that the effects produced by botulinum toxin A are temporary, with reversible effectiveness, requiring periodic applications to maintain long-term benefits, such as decreased muscle hyperactivity, decreased pain symptoms and improved quality of life of patients with bruxism and orofacial pain. Thus, it is a multifactorial chronic parafunctional condition that is difficult to control. Nevertheless, further studies are needed to refine the available knowledge on the subject.

In future studies, it would be of great importance for the literature to address conservative techniques for the treatment of myofacial pain and temporomandibular disorders with the application of butolinic toxin, such as the use of myo-relaxing plaques associated with the application of botulinum toxin or the adoption of multidisciplinary intervention associated with the use of botulinum toxin, and thus allow multiple viable alternatives in different scenarios.

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