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EVALUATION OF QUALITY OF LIFE IN PATIENTS WITH BRUXISM AND OROFACIAL PAIN AFTER TREATMENT WITH BOTULINUM TOXIN - RANDOMIZED, DOUBLE-BLIND CLINICAL TRIAL

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ABSTRACT

Introduction: Botulinum toxin is produced by the bacterium *Clostridium botulinum* and the clinical applications of this toxin have become common over the last 30 years with predictable results. **Objective:** To evaluate the improvement in the quality of life of bruxism patients with my ofascial pain after the application of botulinum toxin. **Method:** In this randomized, double-blind controlled clinical study, 30 female patients were selected aged between 18 and 40 years who presented bruxism with orofacial pain. The patients were classified into two groups: control and experimental groups that were not submitted or submitted to botulinum toxin application, r espectively. Later visual analog questionnaires correlating with pain, time, and quality of life were used. **Results:** No significant difference was observed regarding pain improvement over time and subsequent improvement in the quality of life in the control ($p = 0.127$) and experimental groups($p = 0.806$). However, a significant difference was observed regarding improvement in the quality of life in the experimental group due to the decrease in pain over time. **Conclusion:** The use of botulinum toxin A in bruxism patients with or of acial pain suggests that it could be an effective method in reducing pain symptoms and subsequent improvement in the quality of life of patients with such condition.

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INTRODUCTION

The botulinum toxin is one of the most potent neurotoxins produced by a gram-positive, sporulating, and strictly anaerobic bacterium *Clostridium botulinum* . It has seven different serotypes (A, B, C, D, E, F, and G) and is the first bacterial toxin to be used in the field of medicine. Its applicability was aimed at muscle problems at various levels (Sinclair, 2013).

Bruxism is defined as a parafunctional masticatory activity characterized by clenching and/or grinding of teeth, occurring during sleep and vigilance (Sener, 2007). Orofacial pain is a common symptom in the classical clinical characteristics of bruxism as well as hypertrophy and myalgia of masticatory muscles (mainly temporal and masseter); headache and pain in the temporomandibular joint are among the most commonly observed clinical manifestations (Laskin, 2018 and Sposito, 2009). The use of botulinum toxin has been very effective fortreating patients with bruxism dysfunction, offering a gain

in the quality of life due to the improvement in the painful symptomatology caused by this condition. Improvement is observed following the application of the botulinumtoxin in therapeutic doses at regular intervals of time (Von Lindern, 2001; Jadhao, 2017 and Zhang, 2016). Among the different serotypes, botulinum toxin type A has been the subject of pain control studies, including myofascial pain, neuralgia, and hyperesthesia, and is related to the mechanism of pain relief in the receptors of the neuromuscular junction as well as in the nociceptive receptor system (Aoki, 2004). Its side effects are rare, and even if they exist are transient and do not cause major problems in patients (Chung-Chih Yu, 2007). Herein, we aim to evaluate the effect of botulinum toxin type A on the improvement of pain symptoms in patients with bruxism and the subsequent impact on the quality of life improvement through a randomized, double-blind clinical trial conducted in female patients with a diagnosis of orofacial pain arising from bruxism.

MATERIALS AND METHODS

Ethical Criteria: This study was approved by the Human Research Ethics Committee of the University and registered on the national platform of clinical studies under number CAEEE64309416.1.0000.5152. All participants signed an informed consent form. The study was registered in the National Registry of Clinical Trials under number U1111-1217-7400.

Patient Selection: The study followed the CONSORT standards (Consolidated Standards of Reporting Trials). In this randomized, double-blind controlled clinical trial, 30 female patients aged 18 to 40 years who presented bruxism with orofacial painwere selected. Patients were recruited through referrals from dental surgeons in the city of Uberlândia, Minas Gerais, Brazil. The inclusion criteria were females aged between 18 and 40 years with bruxism and associated orofacial pain reported in the last 3 months. Exclusion criteria were patients with active psychosis, other active psychiatric disease or cognitive impairment; severe comorbid diseases; individuals exposed to botulinum toxin in the last 6 months; participation in another experimental therapeutic protocol; those with myasthenia gravis, amyotrophic lateral sclerosis, and other acute diseases; a history of dysphagia and/or botulism; and impairment of intellectual capacity, pregnancy, use of muscle relaxant plaques, and egg allergies.

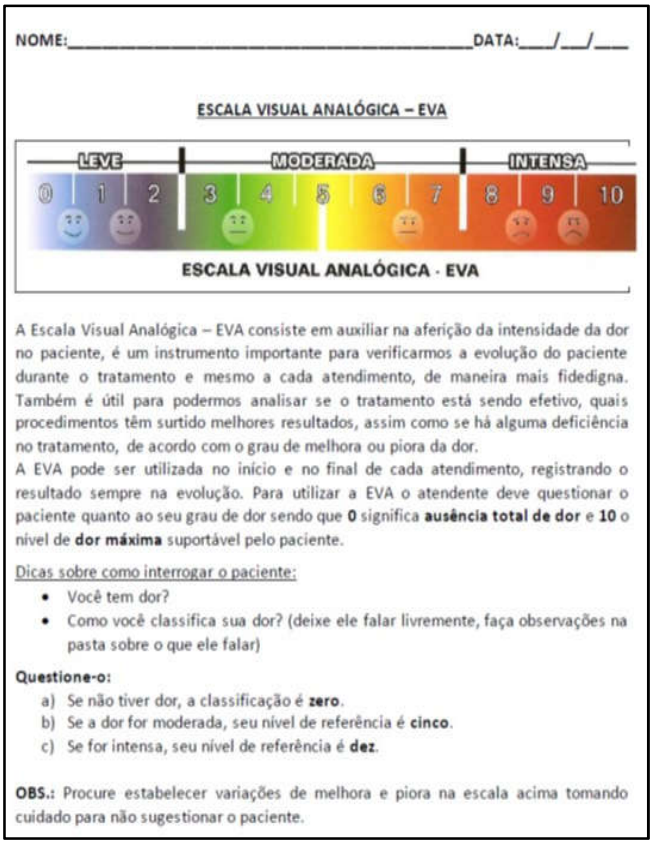
Experimental Protocol: In the first session (baseline), patients underwent a detailed examination of anamnesis, medical examination, and diagnostic system. A Visual Analogue Scale (EVA) (Figure 1) was appliedvia interview, for pain symptoms in the orofacial region, in which patients attributed values from zero to 10, wherein zero corresponded to no pain and 10 to the worst pain imaginable. Another quality of life EVA was applied to bruxism, wherein zero corresponded to the worst quality of life and 10 to the best quality of life. For the definition of the groups, the randomization list was created on the website www.sealedenvelope.comby operator one. The operator one placed syringes with saline solution or botulinum toxin inside envelopes with the identification of the corresponding patient (four syringes per envelope, one for each muscle) and without group identification to keep operator two blind. The operator two, responsible for the intervention, opened the envelope only during the procedure. Patients were randomized into two groups and were blinded as to which one they were assigned to:a) In the control group (n = 15), patients received 0.05ml of sterile saline solution applied to the anterior temporal muscle bundle and 0.2ml to each masseter muscle.b) In the experimental group (n = 15), patients received 20 U of botulinum toxin A (Botox®, Allergan Pharmaceuticals Ltd., Dublin, Ireland) applied to each masseter muscle and 5 U in the most anterior bundle of each temporal muscle. All the applications were performed on the same day by the previously calibrated blind operator two. Patients returned for reassessment after 30, 60, 90, 120, 150, and 180 days. During this period, they were submitted to EVA for pain and quality of life.

Statistical analysis

Data obtained from EVA for pain and quality of life were compared using the Friedman repeated measures and Dunnett's method for the experimental and control groups, considering the baseline as a reference during each evaluation period. Pearson's correlation was used to assess the correlation between time vs. pain and time vs. quality of life. All tests were performed using 95% confidence level and all analyses were performed using the Sigma Plot statistical package version 13.1 (Systat Software Inc, San Jose, CA, USA).

RESULTS

Comparisons between time, pain, and quality of life: When comparing time versus pain and quality of life in the control group, no statistically significant difference was observed (p = 0.127 and p = 0.806, respectively; Figure-2Aand 2B).


NOME:_____DATA:___/___/___

ESCALA VISUAL ANALÓGICA – EVA

LEVE MODERADA INTENSA

0 1 2 3 4 5 6 7 8 9 10

ESCALA VISUAL ANALÓGICA - EVA

A Escala Visual Analógica – EVA consiste em auxiliar na aferição da intensidade da dor no paciente, é um instrumento importante para verificarmos a evolução do paciente durante o tratamento e mesmo a cada atendimento, de maneira mais fidedigna. Também é útil para podermos analisar se o tratamento está sendo efetivo, quais procedimentos têm surtido melhores resultados, assim como se há alguma deficiência no tratamento, de acordo com o grau de melhora ou piora da dor.

A EVA pode ser utilizada no início e no final de cada atendimento, registrando o resultado sempre na evolução. Para utilizar a EVA o atendente deve questionar o paciente quanto ao seu grau de dor sendo que **0** significa **ausência total de dor** e **10** o nível de **dor máxima** suportável pelo paciente.

Dicas sobre como interrogar o paciente:

- Você tem dor?
- Como você classifica sua dor? (deixe ele falar livremente, faça observações na pasta sobre o que ele falar)

Questione-o:

a) Se não tiver dor, a classificação é **zero**.
b) Se a dor for moderada, seu nível de referência é **cinco**.
c) Se for intensa, seu nível de referência é **dez**.

OBS.: Procure estabelecer variações de melhora e piora na escala acima tomando cuidado para não sugestionar o paciente.

Figure 1. Visual Analogue Scale of pain presented to patients during the experiment

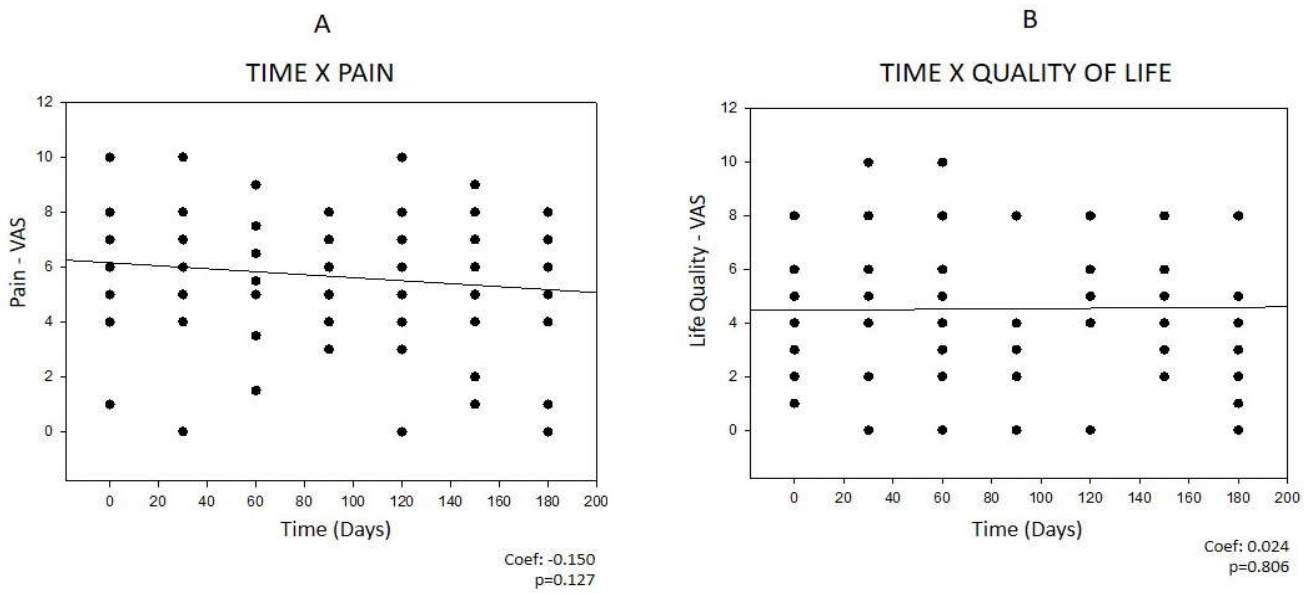


Figure 2A. Correlation graph between time and pain in the control group during the experiment, Figure-2B Correlation graph between time and quality of life of the control group during the experiment

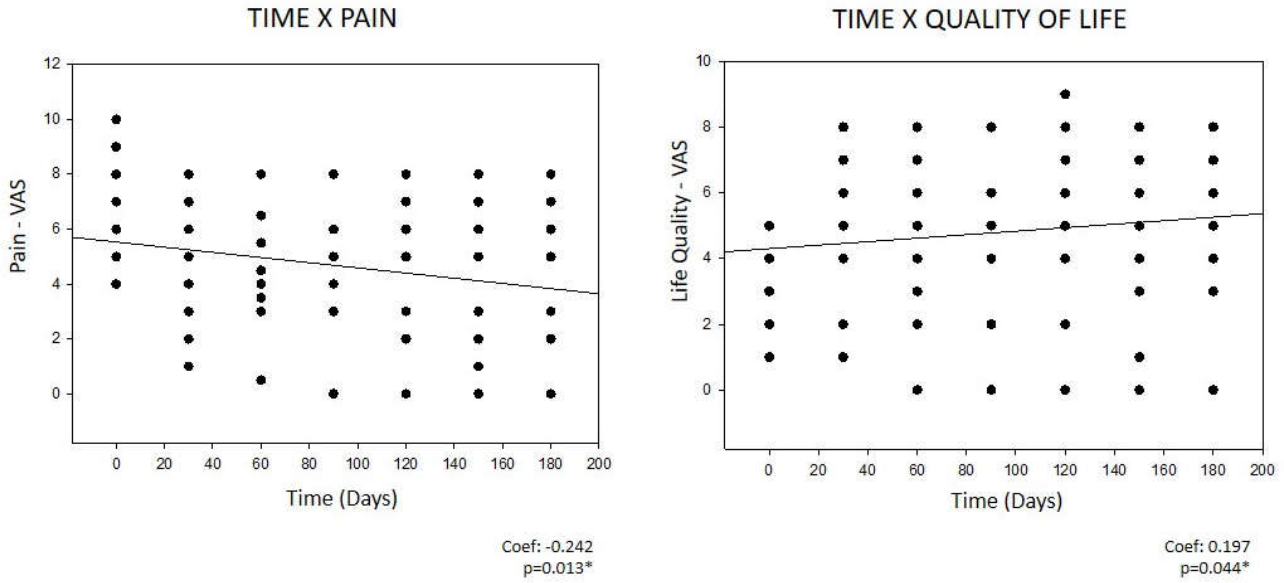


Figure 3A Correlation graph between time and pain of the experimental group during the research, Figure 3B. Correlation graph between time and quality of life of the experimental group during the research

However, the correlation in the botulinum toxin group between time and pain showed a decrease in pain over time, with a significant difference (p = 0.013) at intervals of 30, 60, 90, and 120 days (Figure-3A). Regarding the relationship between time and quality of life, aprogressive improvement was observed in the quality of life, which was measured after the application of botulinum toxin, with a significant difference (p = 0.044); Figure-3B).

DISCUSSION

Patients with bruxism present myofascial pain as one of the main symptoms caused by spasms of the masticatory muscles associated with an altered mandibular function that might be triggered by distension, contraction, or muscle fatigue (Amantéa, 2004). As its main cause, muscle hyperactivity has the practice of parafunctional habits like bruxism and nail-biting among others, which are aggravated and influenced by emotional stress (Sposito, 2009 and Murshed, 2012).

Pain is considered as a personal and subjective experience, and its perception is multidimensional. Pain is diverse in terms of quality and sensory intensity and is also influenced by affective-emotional variables (Scott, 1977). Although the evaluation of pain has a subjective component, it has been attempted to create instruments to standardize the monitoring of patients with diseases or injuries with pain characteristics. The instruments used comprise questionnaires and indices to quantify the intensity of pain, its impact on day-to-day activities, and quality of life, besides describing its other clinical characteristics. They can be classified as one-dimensional, e.g., the EVA, or multidimensional. The so-called one-dimensional instruments analyze only one characteristic, i.e., the intensity (Zhang, 2016 and Huskisson, 1974). The EVA is easy and can be rapidly applied, can be easily understood by the patient, and is an adequate way to estimate the intensity of pain. Therefore, it was used in the present study when referring to pain and quality of life. The botulinumtoxin was identified in 1817 when the first

description of botulism was published. Justinus Kerner associated deaths resulting from intoxication with a poison found in smoked sausages. Eight immunologically distinct serotypes have been identified, i.e., A, B, C1, D, E, F, and G (Petler, 2015). Botulinum toxin A has been used in the recent years for treatingtemporomandibular dysfunction and to reduce musculoskeletal pain and myofascial pain associated with bruxism (Freund, 1999 and Zhang, 2011). The mechanism of action of botulinum toxin is based on the high affinity for cholinergic synapses, causing a blockage in the release of acetylcholine from these nerve terminals without altering the neural conduction of electrical signals and/or the synthesis and storage of acetylcholine (Mejia, 2005). The muscular injection of botulinum toxin in an appropriate dose and location causes partial chemical de-nervation and contracture reduction, without causing complete paralysis (von Lindern, 2003). The action of botulinum toxin on the skeletal striated muscle begins in 2–5 days after application and extends in some cases, up to 2 weeks. Once installed, the effect lasts for 6 weeks to 6 months, on average 3–4 months. Histological examination reveals muscle atrophy and fiber changes during the period of the most intense effect (Dressler, 2002). The effect on the control of painful muscular symptomatology is temporary due to the reversibility of the condition.

The initial clinical studies on botulinum toxin were in myofascial pain and disorders in the temporomandibular joint region; thesestudies included a small number of cases and showed contradictory results (Chung-Chih Yu, 2007; Murshed, 2012; Zhang, 2011). The evidence for increased efficacy was recently obtained from placebo-controlled, double-blind studies with a random distribution of patients and a large number of cases, such as the present study. Regarding pain, several publications have reported the efficacy and safety of botulinum toxin fortreating myofascial pain. In the study by Ernberg *et al.*, pain intensity was reduced on days 30 and 90 after the application of botulinum toxin A (Zhang, 2016). Thus, the improvement in pain over time has a considerable effect on the improvement of the quality of life in the experimental group in 30, 60, 90, and 120 days. After this period, the effect of botulinum toxin begins to decrease; therefore, new applications are required. These results are corroborated by Jadhao *et al.* who showed improvement in the subjective parameters of pain at rest and during chewing in the group treated with botulinum toxin A (Ernberg, 1996) In a prospective study of patients with chronic pain treated with an injection of botulinum toxin into the temporal muscles and the bilateral masseters, who were followed up for 12 months, a reduction in pain was observed using EVA and Physician Global Assessment (Zhang, 2011). Considering the data from the available literature and those obtained from the present study, we suggest that the botulinum toxin A (Botox) can be indicated as an important aid in the control of pain for patients diagnosed with bruxism and orofacial pain, with four periodic applications in 4 months, as shown in the present randomized trial, wherein a significant improvement was observed in pain symptoms up to the fourth application, and subsequent positive progress in the quality of life.

Conclusion

The therapy with botulinum toxin type A is safe and well-tolerated in painful myofascial disorders, where pharmacotherapy regimens are known to cause side effects. It shows an improvement in the pain condition, and subsequent positive progress in the quality of life of patients undergoing the therapy. Although the effects of such applications are temporary, they have shown great efficacy in improving the symptomatological condition, allowing us to consider it as a basic treatment to routinely address myofascial pain in the medical and dentistry fields.

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