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Vitória de Oliveira Chami

TRATAMENTO DE PACIENTES COM DOR MIOFASCIAL E LIMITAÇÃO DE ABERTURA BUCAL ATRAVÉS DA LASERTERAPIA: ESTUDO CLÍNICO RANDOMIZADO DUPLO-CEGO

Santa Maria, RS
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Dissertação apresentada ao Curso de Mestrado do Programa de Pós-Graduação em Ciências Odontológicas, Área de Concentração em Odontologia, ênfase em Ortodontia, da Universidade Federal de Santa Maria (UFSM, RS), como requisito parcial para obtenção do grau de **Mestre em Ciências Odontológicas**.

Orientador: Prof. Dr. Vilmar Antônio Ferrazzo
Coorientadora: Prof. Dra. Mariana Marquezan

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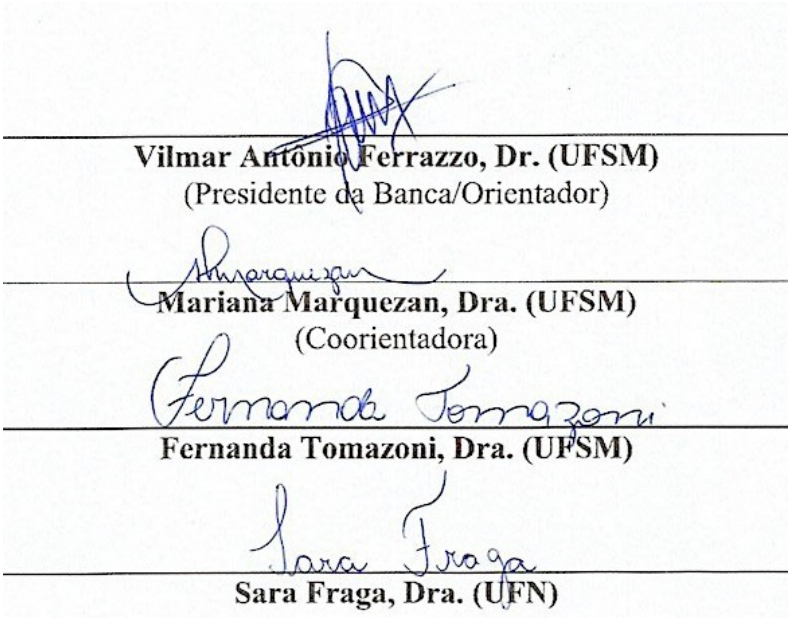

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Vitória de Oliveira Chami

RESUMO

TRATAMENTO DE PACIENTES COM DOR MIOFASCIAL E LIMITAÇÃO DE ABERTURA BUCAL ATRAVÉS DA LASERTERAPIA: ESTUDO CLÍNICO RANDOMIZADO DUPLO-CEGO

AUTORA: Vitória de Oliveira Chami
ORIENTADOR: Vilmar Antônio Ferrazzo
COORIENTADORA: Mariana Marquezan

Este ensaio clínico randomizado paralelo duplo-cego avaliou o efeito de um protocolo rápido de tratamento de laserterapia em baixa potência para pacientes com disfunção temporomandibular, diagnóstico de dor miofascial e limitação de abertura bucal. A amostra inicial foi composta por 384 pacientes avaliados por meio do *Research Diagnostic Criteria for Temporomandibular Disorders* e 20 deles incluídos no estudo. Os participantes foram randomizados e divididos em: grupo laser (n= 10) e grupo placebo (n= 10). O grupo laser recebeu duas sessões de laser em baixa potência, com intervalo de 48 horas, em pontos dolorosos musculares e articulares da face sensíveis à palpação manual, pré-estabelecidos. Foi utilizada a ponteira de laser infravermelho, em contato com a pele, perpendicular, imóvel, potência de 100 mW, fluência de 80 J/cm^2, durante 22 segundos por ponto. No grupo placebo, o protocolo foi o mesmo, porém a ponteira de laser regulada para não entregar energia ao tecido. Os pacientes foram avaliados quanto a sensibilidade dolorosa espontânea e durante os movimentos mandibulares antes do início do tratamento (T1), após a primeira sessão de laser (T2), 48 horas depois, antes (T3) e após (T4) a segunda sessão, 7 (T5) e 30 dias (T6) após T1. Os sujeitos foram avaliados também por meio do questionário de qualidade de vida *Oral Health Impact Profile for Tempormandibular Disorders* em T1 e T6. Pacientes, avaliadores e estatístico estavam cegos. Para avaliar as diferenças inter-grupos foram utilizados os testes t de *Student e Qui-quadrado*, e as mudanças intra-grupos foram avaliadas através do teste t Pareado. Durante o estudo, dois pacientes do grupo placebo foram excluídos (n= 8). Tanto o grupo laser quanto placebo apresentaram resultados similares durante o tratamento e acompanhamento para todas as variáveis analisadas no estudo. Comparando T1 com T6, houve um aumento significativo da máxima abertura bucal e melhora dos escores de qualidade de vida relacionado a saúde bucal apenas no grupo laser. Registro do ensaio: RBR-4w2gd8. Financiamento: Fundo de Incentivo à Extensão da Universidade Federal de Santa Maria (FIEX 2017).

Palavras-chave: Disfunção Temporomandibular. Dor Facial. Ensaio Controlado Randomizado. Laserterapia. Placebo. Qualidade de vida.

ABSTRACT

TREATMENT OF PATIENTS WITH MIOFASCIAL PAIN AND MOUTH OPENING LIMITATION THROUGH LASER THERAPY: DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL

AUTHOR: Vitória de Oliveira Chami
ADVISOR: Vilmar Antônio Ferrazzo
CO-ADVISOR: Mariana Marquezan

This randomized double-blind parallel clinical trial evaluated the effect of a rapid treatment protocol of low-level laser therapy in patients with temporomandibular disorder, myofascial pain and mouth opening limitation. A total of 384 adult patients were evaluated by Research Diagnostic Criteria for Temporomandibular Disorders, and 20 of them were included in the study. The participants were randomized and divided into laser group (n= 10) and placebo group (n= 10). The laser group received two sessions of laser therapy, with an interval of 48 hours, in painful muscular and articular sites of the face, sensitive to manual palpation, pre-established. The infrared laser tip was used in touch with the skin, perpendicular to, without moving it, 100 mW power, fluency of 80 J/cm^2, for 22 seconds per site. In the placebo group, the protocol was the same, but the tip regulated not to deliver energy to the tissue. The patients were evaluated for spontaneous pain sensitivity and during mandibular movements, before the treatment (T1), after the first laser therapy session (T2), 48 hours after, before (T3) and after (T4) the second session, 7 (T5) and 30 days (T6) after T1. Subjects were also assessed using the Oral Health Impact Profile for Temporomandibular Disorders questionnaire at T1 and T6. Patients, assessors, and statistician were blinded. To evaluate the inter-group differences, the Student's t-test and Chi-Square test were used, and intra-group changes were evaluated through the Paired t-test. During the study, two patients from the placebo group were excluded (n= 8). Both the laser and placebo groups presented similar inter-group results during the treatment and follow-up period for all variables analyzed in the study. Comparing T1 to T6, was a significant increase in the maximum mouth opening and improvement in the oral health related of quality of life scores only in the laser group. Trial registration: RBR-4w2gd8. Funding: Extension Incentive Fund of Federal University of Santa Maria (FIEX 2017).

Key words: Facial Pain. Laser Therapy. Placebo. Quality of Life. Randomized Controlled Trial. Temporomandibular Joint Disorders.

SUMÁRIO

1 INTRODUÇÃO

Disfunção temporomandibular (DTM) se refere a um termo coletivo usado para descrever um grupo de desordens músculo esqueletais que envolvem os músculos mastigatórios, a articulação temporomandibular (ATM) e estruturas orofaciais associadas, unidades que compõe o sistema estomatognático. Tal sistema está associado às funções de mastigação, fonação e deglutição (OKESON, 2013).

Os sintomas mais frequentemente relatados pelos pacientes com DTM são: dores na face, ATM e/ou músculos mastigatórios e dores na cabeça. Outros sintomas incluem as manifestações otológicas como zumbido, plenitude auricular e vertigem. Quanto aos sinais, encontram-se primariamente a sensibilidade à palpação dos músculos da face e ATMs, limitação de abertura bucal e/ou incoordenação de movimentos mandibulares, além de ruídos articulares (DE LEEUW e KLASSER, 2013).

Dados epidemiológicos demonstraram que 75% da população apresenta pelo menos um sinal de DTM e 33% pelo menos um sintoma, além de ser considerada a causa mais comum de dor não dentária na região orofacial (SCRIVANI, KEITH e KABAN, 2008). Dentre as DTMs, a dor miofascial apresenta a maior prevalência, em torno de 65%, quando associada a limitação de abertura bucal, corresponde a 18% deste total (WINOCUR *et al*., 2009). A amplitude de abertura bucal varia em média de 53 a 58mm, sendo menor em mulheres do que homens, além de diminuir ao passar dos anos (MEZITIS *et al.*, 1989). Considera-se que a abertura bucal normal não seja inferior a 40mm, o que já seria considerado uma limitação (DE LEEUW e KLASSER, 2013).

O sexo feminino apresenta o risco duas vezes maior do desenvolvimento de tais disfunções (BUENO *et al*., 2018). Os principais fatores de risco ou precipitantes desta condição são: aumento da demanda funcional (hábitos parafuncionais deletérios, por exemplo ranger de dentes, ou algum trauma na região), fatores emocionais negativos (ansiedade, estresse e depressão) e predisposição genética, como demonstrado em estudo prospectivo (SLADE *et al*., 2016). Um problema biológico pode ter antecedentes psicológicos e conseqüências comportamentais (CONTI *et al*., 2012).

Os conceitos atuais do tratamento de dor orofacial visam prevenir, curar ou aliviar os sinais e sintomas de morbidade dolorosa, bem como reduzir seu impacto sobre a qualidade de vida do paciente. Devido à etiologia multifatorial da DTM e à variedade de apresentações clínicas, os tratamentos deste distúrbio são diversos, incluindo várias abordagens, como: auto-manejo, mudança de hábitos do paciente, farmacoterapia, fisioterapia, calor, crioterapia,

anestesia local, agulhamento seco, acupuntura, placa oclusal estabilizadora, estimulação neural elétrica transcutânea, laserterapia em baixa potência (LBP) e cirurgia (LIST e AXELSSON, 2010). Entre a vasta gama de modalidades de tratamento das DTMs, o uso da LBP tem alcançado maior popularidade devido à sua natureza conservadora. Também foram demonstrados efeitos analgésicos, regenerativos e anti-inflamatórios no tecido alvo (DESIDERÁ *et al*., 2015; XU *et al*., 2018).

Em revisão sistemática para avaliar a efetividade de várias terapias físicas no tratamento de DTM, dentre elas, o laser de baixa potência, foi verificado que a aplicação de laser infravermelho nas ATMs e musculatura da face, reduziu a dor e aumentou a amplitude de abertura bucal (MEDLICOTT e HARRIS, 2006). Já em outra revisão com o intuito de examinar o efeito do LBP em DTMs, constatou-se que, apesar da maioria dos estudos selecionados mostrarem algum sucesso nas terapias, a heterogeneidade de metodologias dificulta a interpretação dos resultados. As fluências aplicadas, potências dos aparelhos, além do número de aplicações apresentam grande variação (CHEN *et al*., 2015).

Apesar do grande número de trabalhos que tentaram tratar os sinais e sintomas das DTMs por meio da LBP, não há consenso quanto a utilização. Além disso, ainda não se estabeleceu um protocolo ideal para irradiação quando diagnosticada tal enfermidade, nem as suas limitações.

Dessa maneira, o objetivo desse estudo foi avaliar o efeito de duas sessões de LBP no tratamento da dor miofascial e limitação de abertura bucal, além das possíveis mudanças na qualidade de vida relacionada a saúde bucal dos pacientes. A hipótese nula é de que tanto duas sessões de LBP, quanto a LBP placebo, tenham efeitos similares nos pacientes com o diagnóstico de dor miofascial e limitação de abertura bucal.

2 ARTIGO - LASER THERAPY AS RAPID TREATMENT OF MYOFASCIAL PAIN AND MOUTH OPENING LIMITATION: A RANDOMIZED CLINICAL TRIAL

Este artigo será submetido ao periódico Journal of Dental Research, Sage Journals, Qualis A1, Fator de Impacto 4.755. As normas para publicação estão descritas no Anexo A.

Laser therapy as rapid treatment of myofascial pain and mouth opening limitation: a randomized clinical trial

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Abstract

This randomized double-blind parallel clinical trial evaluated the effect of a rapid treatment protocol of low-level laser therapy (LLLT) in subjects with temporomandibular disorder diagnosed as myofascial pain with mouth opening limitation. A total of 384 adult patients were evaluated through Research Diagnostic Criteria for Temporomandibular Disorders, and 20 of them were included in the study. Participants were randomly divided into LLLT group (n=10) and placebo group (n=10). On LLLT group, two sessions were performed with a 48 hours interval, in pre-established painful muscular and articular sites of the face, sensitive to manual palpation. The infrared laser tip was used in touch perpendicular with the skin, without moving it, 100 mW power, fluency of 80 J/cm^2, for 22 seconds per site. In the placebo group, the protocol was the same, however the tip was regulated to do not deliver energy to the tissue. Patients were evaluated for spontaneous pain sensitivity and during mandibular movements, before (T1) and after the first LLLT session (T2), 48 hours after, before (T3) and after (T4) the second session, 7 (T5) and 30 days (T6) after T1. Subjects were also assessed using the Oral Health Impact Profile for Temporomandibular Disorders questionnaire at T1 and T6. Patients, assessors, and statistician were blinded. To evaluate the inter-group differences, the Student's t-test and Chi-square test was used, intra-group changes were evaluated through the Paired t-test. During the study, two patients from the placebo group were excluded. Both the LLLT and placebo groups did not present differences in inter-group results during the treatment and follow-up period for all variables analyzed in the study. Comparing T1 to T6, significant increase in the maximum mouth opening (p=0.04) and improvement in the oral health related quality of life scores (p=0.003) were observed only in the laser group. Trial registration: RBR-4w2gd8. Funding: Extension Incentive Fund of Federal University of Santa Maria (FIEX 2017).

Key-words: Facial Pain. Low-Level Light Therapy. Placebo. Quality of Life. Randomized Controlled Trial. Temporomandibular Joint Disorders.

1. Introduction

Temporomandibular disorders (TMD) is an umbrella term for pain and dysfunction involving the masticatory muscles and temporomandibular joints (TMJ). Prominent features include regional pain in the face and preauricular area, limitations in mandibular movements and noises of TMJ during excursions and opening (List, Jensen, 2017).

TMD affects up to 15% of adults and 7% of adolescents, and females have a two-fold increased risk of development (Bueno et al., 2018). Epidemiological data have shown that 75% of the population has at least one sign of TMD and 33% has at least one symptom, besides being considered the most common cause of non-dental pain in the orofacial zone (Scrivani et al., 2008).

Myofascial pain is a muscular disorder and can be associated with or without mouth opening limitation (Dworkin and Leresche, 1997). A retrospective study found that this condition is the most prevalence corresponding 65% of all TMDs, being 18% with mouth opening limitation and 47% without (Winocur et al., 2009).

Among the wide range of treatment modalities for TMDs, the use of low-level laser therapy (LLLT), also called photobiomodulation therapy, has achieved greater popularity due to its conservative nature. Studies have shown analgesic, regenerative and anti-inflammatory effects in the target tissue (Desiderá et al., 2015, Xu et al., 2018). Irreversible treatments should be avoided for TMD because the signs and symptoms of TMD may be fluctuating and self-limiting over time (Michelotti et al., 2005).

Despite the large number of clinical trials that attempted to treat the signs and symptoms of TMD through LLLT (Conti et al., 1997; Carrasco et al., 2010; Melchior et al., 2013; Demirkol et al., 2017; Magri et al., 2017), there is no consensus regarding its precise indications nor its limitations, or even an optimal protocol for irradiation (Chen et al., 2015). Thus, the objective of this study was to evaluate the effect of two LLLT sessions in the treatment of TMD myofascial pain with mouth opening limitation, and also to analyze changes in patients' oral health related quality of life (OHRQOL). The null hypothesis was that both LLLT and placebo present similar effects.

2. Methods

2.1. Trial design

A randomized double-blind parallel clinical trial was conducted. This study was performed after submission and approval of the Research Ethics Committee of the University of Santa Maria (protocol number: 74925717.6.0000.5346), registered in the Brazilian Registry

of Clinical Trials (ReBEC) of the Ministry of Health under registry number RBR-4w2gd8 and followed the criteria indicated by Consort 2010 for description of randomized controlled trials (Schulz et al., 2010).

2.2. Participants

The study sample was obtained from 384 participants referred to the Occlusion Clinic of the Federal University of Santa Maria by the screening sector of the Dentistry Course. The evaluations were carried out between January 2017 to January 2018.

Inclusion criteria for participation in the study were: patients of both sexes, between 18 and 60 years of age and diagnosis of myofascial pain with mouth opening limitation and no other diagnosis. This condition, recognized by the Axis I of Research Diagnostic Criteria for TMDs (RDC/TMD), is included in Group I of muscular disorders. For patients to be diagnosed of myofascial pain with mouth opening limitation, they had to present a complaint of pain in the mandible, temples, face, preauricular area or within the ears, at rest or during function; Pain on palpation in 3 or more of the 24 sites of face muscles and TMJs sites, and at least one of these sites had to be on the same side of the complaint; Pain-free during mouth opening measurement of less than 40 mm, and maximum assisted mouth opening (passive stretching) 5 mm greater than the unassisted painless opening (Dworkin and Leresche, 1992).

Participants with any other TMD diagnosis, acute traumatic injuries, patients who were completely or partially edentulous including the anterior region (since it would be difficult to accurately measure the mouth opening), and those undergoing treatment for TMD with other health professionals were excluded. Patients using analgesics and/or anti-inflammatories might suspend the medication at least 30 days before the study began (washout) and were instructed to do not use the medication during the treatment period.

2.3. Interventions

2.3.1. LLLT

The Gallium-Aluminum-Arsenide laser (GaAlAs) (Photon Lase III, DMC Equipamentos LTDA, São Carlos, SP, Brazil) was reviewed and calibrated by the manufacturer prior to the start of this study. Before each treatment, the amount of energy irradiated was checked by the laser sealer (LaserCheck, MMOptics, São Carlos, SP, Brazil), so that all patients in the treatment group received the same amount of radiation.

The treatment protocol was based on the recommendations of the appliance manufacturer, in the study of Pereira and collaborators (Pereira et al., 2004) and in the World

Association for Laser Therapy Guideline (Walt, 2006). The choice of LLLT sites on musculature and TMJs were pre-established through manual palpation of the 24 points identified by RDC/TMD. The sites that presented painful sensitivity were irradiated.

Two sessions of LLLT were performed with a 48 hours interval between them. The laser was used in continuous emission mode, in contact with the skin of the volunteers. During the application, the tip was positioned perpendicular to the irradiated area (Mazzetto et al., 2010; Melchior et al., 2013).

The parameters of the laser device used were: wavelength = 808 nm (infrared), power of 100 mW, fluency of 80 J/cm², 22 seconds per application, energy of 2.2 J per application, tip area (S) of 0.028 cm², power density of 3.57 W/cm² and a distance of at least 1 cm between each site.

2.3.2. Placebo

The subjects in the placebo group received the applications of a tip identical to the active one, with the same sound signal of time, but desactivated and without capacity to deliver energy to the tissue. In this way, it was not possible to identify the tips. During the laser sessions, the researchers and patients in both groups used protective goggles and obeyed biosafety standards.

2.4. Outcomes

In this study, several outcomes were considered, represented in a flowchart – Figure 1. Maximum mouth opening, right and left lateral excursion were Primary Outcomes and measured using a millimeter ruler (Jon Indústria de Produtos Odontológicos LTDA, São Paulo, SP, Brazil). Spontaneous pain sensitivity, pain sensitivity during mandibular right and left lateral and opening excursions, pain sensitivity through manual muscle and TMJ palpations, were Secondary Outcomes and assessed through a 0 to 4 pain scale, contained in RDC/TMD, reported by the patient. For the statistical analysis the result was dichotomized in presence and absence of pain. Six evaluations were performed: immediately before starting treatment - baseline (T1); immediately after the first laser session (T2); immediately before (T3) and after (T4) the second session; which was 48 hours after, 7 (T5) and 30 days (T6) after baseline.

The impact of treatment on OHRQOF, also considered a Secondary Outcome, was evaluated in T1 and T6 using a validated questionnaire - Oral Health Impact Profile for TMDs (OHIP/TMD) answered by the patient (Durham et al., 2011). This questionnaire had 7 domains and consisted of 22 questions, answered by a Likert scale of 5 options, with a maximum possible

score of 88 points. The higher scores of each questionnaire, the worse oral health related quality of life of the participant.

2.5. Sample size

The sample calculation was performed based on data of a pilot project containing 9 patients, being recommended to use 6 patients in each group (difference of mouth opening to be detected = 8.10 mm, standard deviation = 5.44, significance level of 5% and power of the test of 80%). Adding a 20% probability of loss, at least 8 patients were required per group. The sample was divided into two groups: LLLT group (LG) (n=10) and placebo group (PG) (n=10).

2.6. Randomization, allocation, implementation and blinding

Randomization and stealth allocation of the participants were performed by a researcher (M.M.) through the online tool called Research Randomizer (http://www.randomizer.org), via random lottery and generation of a random sequence in blocks of two.

The laser and placebo treatments were performed by another researcher (V.O.C.), different from the researchers (L.M.M. and G.S.) who performed the diagnoses and assessments of pain, maximum mouth opening, mandibular excursions, manual muscle and TMJ palpations, previously trained and calibrated by a professional experienced in the area (J.M.). The researchers (L.M.M and G.S.) and the volunteers only had access to information from the laser and placebo groups after the clinical trial was completed, thus characterizing a double-blind study. The statistician (F.T.) also did not know which group was each.

2.7. Statistical analysis

Data were analyzed using the STATA 14 program (Stata Corporation, College Station, TX, USA) and presented a normality distribution. A descriptive analysis was performed to present the characteristics of the sample. After that, the paired t-test was used for intra-group comparisons over time. In the intergroup comparisons (LG x PG) the t-test was used for the numerical variables and the chi-square test for the categorical variables. For all the statistical tests used, the significance level of 5% (alpha error, $p < 0.05$) was considered.

3. Results

3.1. Sample

Initially 384 participants were evaluated, and 20 patients (5.2%) of them, were included in the study's eligibility criteria and proposed to participate in the study. The random sample

was divided into two groups: Laser Group (n=10), Placebo Group (n=10). Two PG participants were excluded during the analyzes, one for taking anti-inflammatory medication, other for not attending the evaluation visit. The progression of the study was described in Figure 2.

The LG was composed of 60% women and with a mean age of 30.1 (10.90). PG had 87.5% of women and a mean age of 23.62 (4.06). The groups were similar at baseline, demographic distributions regarding skin color, schooling, employment, monthly income and marital status, beyond the clinical characteristics of the groups at the beginning of treatment are shown in Table 1.

3.2. Maximum mouth opening

At baseline, the mean of maximum mouth opening was 40 mm (3.21) in LG and 43.1 mm (5.4) in PG. During the follow-up period, at T6, the means increased, reaching 45.7 mm (6.6) in LG and 44.6 mm (7.4) in PG. Comparing the two groups, no change was considered statistically significant. The values of means, standard deviations and p value are shown in Table 2. According to Table 3, a significant increase was found only in LG (p =0.04).

3.3. Mandibular lateral excursion to the right and left

Measurements of right and left lateral excursions showed small variations in LG and PG, presenting no statistical significance (Tables 2 and 3).

3.4. Painful sensitivity reported by the patient

As for the presence of pain during mandibular lateral excursion to the right and left, mouth opening, and spontaneous pain, there were slight changes throughout the treatment, but without a statistically significant difference, according to Table 3. The number of sore points at manual palpation did not show significant difference inter-group or intra-group (Tables 2 and 3).

3.5. Oral health related quality of life

In T1, the mean scores of the OHIP/TMD questionnaire were 31.9 (13) for LG and 36 (15.9) points for PG. After 30 days, the mean decreased to 16.2 (7.5) points in LG and 19 (19.4) in PG, and there was no statistical difference when comparing the two groups (Table 2). When analyzed intra-group, the decrease in questionnaire scores was significant only in the laser group (p=0.003) (Table 3).

3.6. Harms

The volunteers in the placebo group, after completing the study, were invited to receive LLLT treatment according to the same protocol used in the laser group. In the case of pain maintenance and oral opening limitation after study completion, regardless of the group, participants were referred to the Temporomandibular Disorders Project of the Faculty of Dentistry of the Federal University of Santa Maria, where they received treatment with self-management and change of habits guidelines, occlusal splints and physiotherapy.

4. Discussion

The main results of this study when comparing LLLT treatment and placebo, were that changes did not present statistical differences and were similar during the treatment and follow-up period for all variables analyzed in the study. When analyzed intra-group, the outcomes of maximum oral opening and the impact of treatment on OHRQL showed significant improvement only in the laser group.

LLLT is a reversible, non-invasive, non-pharmacological, non-painful, safe and well accepted by patients as a therapeutic modality. A meta-analysis of twelve studies published in 2015 has shown that laser therapy has limited effectiveness in reducing pain in patients with TMD, but it promotes significant improvement in functional aspects, such as mouth opening (Chen et al., 2015). Within this perspective, this research demonstrated, as well, a significant increase in the amplitude of maximum mouth opening in patients who received active LLLT.

Regarding the reduction of pain sensitivity, no changes were observed comparing LG and PG. The divergent results of other clinical trials in systematic reviews (Maia et al., 2012, Petrucci et al., 2011, Melis et al., 2012) that present improvement in pain with laser therapy may be related to other dosages and methodologies of treatment application, and other TMD subtypes. In a recent clinical trial, both active laser therapy and placebo were able to reduce pain rates (Magri et al., 2017). Many factors may influence the patient's perception of pain intensity, as emotional factors being the most associated (Do Nascimento et al., 2014). At the beginning of the study, both LG and PG patients presented impairment in quality of life, discomfort, and psychological inability according to the OHIP/TMD questionnaire scores, and this could influence pain report.

Similar results in LG and PG could be explained by the placebo effect, defined as an improvement in health status that is not related to the direct biological effects of some therapeutic intervention and that can be performed by an inert agent (Colagiuri et al., 2015). Many factors can determine the magnitude of the placebo effect, such as individual differences,

psychological factors, expectancy of improvement, associations to previous experiences with the therapy tested, professional-patient relationship, sociocultural context, among others (Gourion et al. 2016). The use of state-of-the-art technology equipment, such as the laser device, may have amplified the placebo effect and influenced the magnitude of the results because it raises expectations for faster and more effective improvement.

The biomodulation capacity, analgesia and anti-inflammatory action of LLLT are explained by the induction of the cellular and systemic responses that the laser promotes when applied in specific regions, as already seen in the inflamed TMJs of rats (Desiderá et al., 2015). However, in humans, the cognitive, behavioral, and motivational aspects that permeate the placebo effect are as significant in the perception of pain improvement as biological tissue effects, as they are capable of leading to very similar clinical outcomes (Jakovljevic, 2014).

In a clinical trial with patients diagnosed with myofascial pain, there was a necessity to establish which of three protocols of different energy densities of LLLT and placebo would be most effective for reducing pain. The doses tested were: 25 J/cm², 60 J/cm², and 105 J/cm². The results showed that the three doses were effective, with superiority for lower energy density. However, the placebos groups of each dose also had similar effectiveness to active LLLT, demonstrating that placebo achieves the same clinical results obtained with active laser therapy (Carrasco et al. 2009), as also demonstrated in this clinical research.

The oral health related quality of life is determined by a variety of conditions that affect the individual's perception, their senses, and behaviors in the exercise of their daily activity. In a systematic review, it was verified that there is a direct correlation between TMD and lower quality of life (Bitiniene et al., 2018). In addition, mandibular functional limitations such as limitation of mouth opening have a strong influence (Almoznino et al., 2015).

Another systematic review analyzed the impact of therapeutic interventions for TMD on oral health related quality of life, the conclusion was that no one treatment modality can be advocated as the only approach for the treatment of TMDs, since there are several TMD subtypes and instruments used for the measurement of OHRQOL (Song et al., 2018). Thus, it is recommended to use specific questionnaires for TMD aiming at specific subtypes of the disorder, as was done in this study.

In a study that evaluated the effect of 8 sessions of LLLT on the improvement of the psychosocial aspects of patients with TMD, a significant reduction in the intensity of chronic pain and a decrease in the symptoms of depression in the patients were observed (Rodrigues et al., 2013). As in the present clinical trial, we found improvement in OHRQOL scores of patients with myofascial pain and mouth opening limitation after treatment with LLLT.

Important factors to consider are the number of LLLT sessions and the follow-up time of individuals undergoing laser therapy. According to some studies (Bezuur et al., 1988, Conti et al., 1997), the cumulative effect of the sessions may be responsible for the tendency to reduce pain and it is necessary to wait for the recovery period of the tissues. In the present study, we tested a rapid LLLT protocol, but the results were similar to more extensive protocols of 8 to 10 sessions (Carrasco et al., 2009, Mazzetto et al., 2010, Demirkol et al., 2017).

This study followed the recommendations of the Consensus agreement on the design and conduct of clinical studies with low level laser therapy and light therapy for musculoskeletal pain and disorders, approved by the World Association of Laser Therapy (Walt, 2006), in which studies should have a control group where patients receive placebo-LLLT, be based on Consort (Schulz et al., 2010) and registered on a clinical trial platform. Thus, the internal validity of this study are not compromised.

The limitation of this study was that a more extensive laser therapy protocol was not used to compare it to the rapid protocol. Other studies should be performed comparing different protocols (rapid versus extensive), LLLT and occlusal splint versus laser placebo and occlusal splints and laser only, besides comparing an untreated group, for patients with the same diagnosis. In addition, it is important to note that there is no consensus in the scientific literature on the doses and protocols of LLLT for the treatment of TMD, which makes it difficult to standardize the research and compare the results.

5. Conclusion

Based on the results of this clinical trial, it was concluded that the proposed treatment (LLLT in two sessions, with 48 hours interval) was similar when compared to placebo during the treatment and follow-up period for clinical, subjective, and painful sensitivity. After 30 days, there was a significant increase in the maximum mouth opening and improvement in the oral health related quality of life scores only in the laser group. The null hypothesis was partially rejected.

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7. Flowcharts and tables

Figure 1 – Flowchart representing the methodology and outcomes of this study.

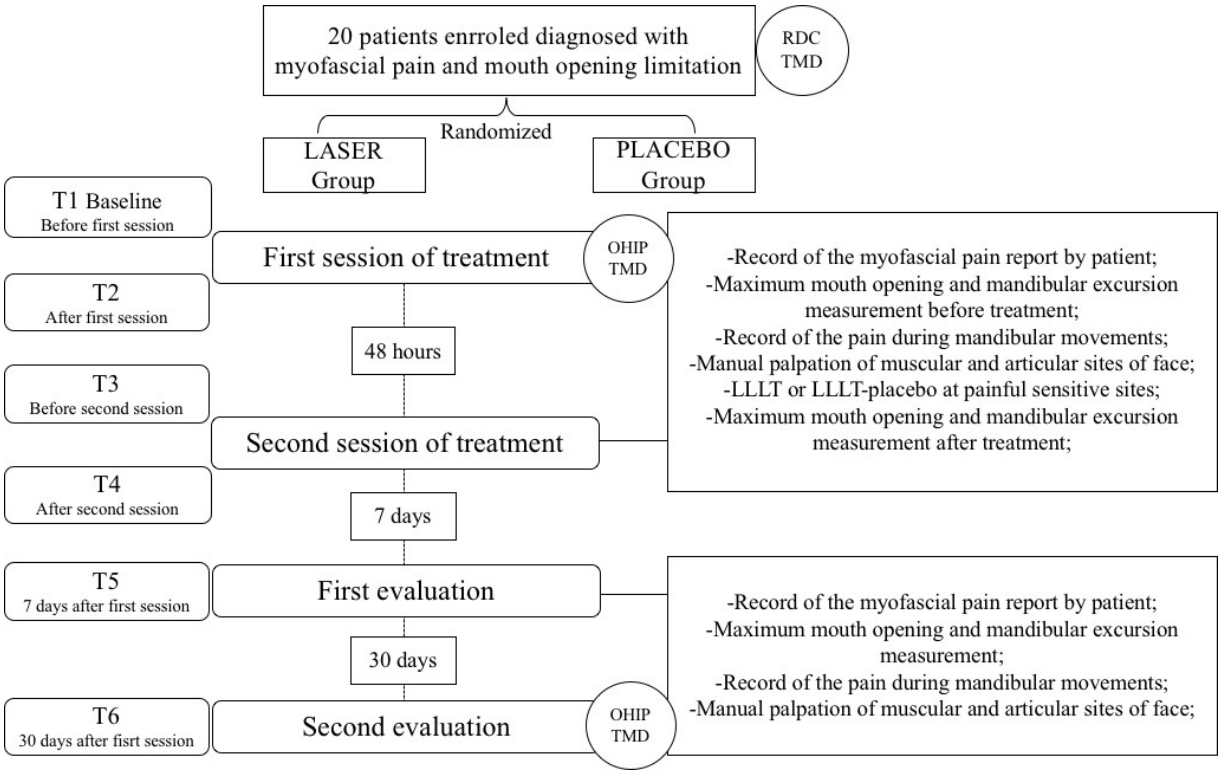

Figure 2 – Flowchart representing the study participants progress through all phases of the study.

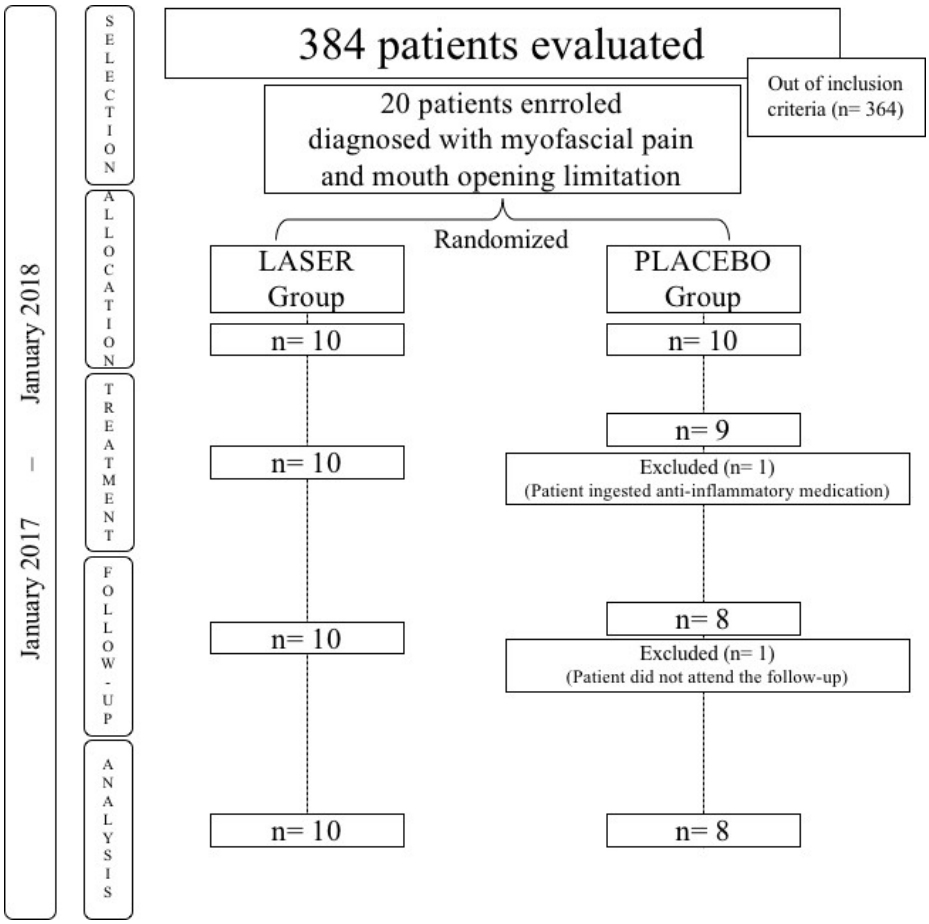

Table 1 - Sample data at the beginning of the study (T1), according to Student's t-test and Chi-square test.

	Laser Group	Placebo Group	
	Mean (SD) ou N (%)	**Mean (SD) ou N (%)**	***p* value**
Sex**			
Female	6 (60)	7 (87)	**1.67**
Male	4 (40)	1 (13)	
Skin color**			
White	8 (80)	7 (87)	**0.06**
Not White	2 (20)	1 (13)	
Schooling**			
Complete primary education	1 (10)	0 (0)	
Complete high school	2 (20)	2 (25)	**0.86**
Higher education	7 (70)	6 (75)	
Employment**			
Unemployed	2 (20)	0 (0)	
Employee	6 (60)	2 (25)	**8.22**
Studying	2 (20)	6 (75)	
Montly income**			
1 to 2 salaries	4 (40)	6 (68)	
2 to 3 salaries	3 (30)	1 (16)	**1.00**
More than 3 salaries	3 (30)	1 (16)	
Marital status**			
Not married		6 (60)	7 (87)
Married		4 (40)	1 (13) **1.67**
Age*	30.1 (10.9)	23,6 (4.0)	**0.06**
Mouth opening without pain (mm)*	28.1 (6.5)	28,7 (5.4)	**0.82**
Maximum mouth opening (mm)*	40 (3.1)	43,1 (5.4)	**0.09**
Mandibular right excursion (mm)*	8.9 (2.7)	7,7 (2.6)	**0.38**
Mandibular left excursion (mm)*	8.3 (2.1)	8,7 (2.4)	**0.68**
Number of sites sore to palpation*	9.2 (4.4)	10 (6.4)	**0.39**
OHIP/TMD Questionnaire*	31.9 (13)	36 (15.9)	**0.72**

*Student's t test
**Chi-square test

Table 2 - Comparison of outcome variables between the laser and placebo groups before, during and after treatments, according to Student's t-test and Chi-square test.

	Laser Group	**Placebo Group**	
	Mean (SD) or N (%)	**Mean (SD) or N (%)**	***p* value inter-groups**
Maximum mouth opening*			
T1 (before treatment)	40 (3.21)	43.1 (5.4)	**0.09**
T2 (after fist session)	41.9 (3.8)	44 (5.3)	**0.18**
T3 (after 48 hours, before second session)	41.7 (5.4)	42.3 (6.0)	**0.42**
T4 (after second session)	43.7 (6.4)	43.2 (5.2)	**0.57**
T5 (7 days after baseline)	43.9 (5.8)	43.8 (6.7)	**0.50**
T6 (30 days after baseline)	45.7 (6.6)	44.6 (7.4)	**0.63**
Mandibular right excursion*			
T1 (before treatment)	8.9 (2.7)	7.7 (2.6)	**0.38**
T3 (after 48 hours)	9.3 (2.4)	8.0 (2.5)	**0.29**
T5 (7 days after baseline)	9.3 (2.6)	8.6 (3.3)	**0.63**
T6 (30 days after baseline)	9.8 (2.5)	8.0 (2.3)	**0.14**
Mandibular left excursion*			
T1 (before treatment)	8.3 (2.1)	8.7 (2.4)	**0.68**
T3 (after 48 hours)	8.1 (2.0)	9 (2.7)	**0.43**
T5 (7 days after baseline)	8.4 (2.1)	8.7 (2.4)	**0.75**
T6 (30 days after baseline)	8.8 (2.3)	8.8 (2.4)	**0.95**
Sites sore to palpation*			
T1 (before treatment)	9.2 (4.4)	10 (6.4)	**0.39**
T3 (after 48 hours)	7.5 (2.8)	7.9 (7.4)	**0.44**
T5 (7 days after baseline)	7.2 (3.6)	8.6 (5.6)	**0.28**
T6 (30 days after baseline)	5.9 (3.6)	6.8 (5.7)	**0.35**
OHIP/TMD Questionnaire*			
T1 (before treatment)	31.9 (13)	36 (15.9)	**0.72**
T6 (30 days after baseline)	16.2 (7.5)	19 (19.4)	**0.66**
Pain at mandibular excursion**			
T1 (before treatment)	4 (40)	5 (62.5)	**1.00**
T3 (after 48 hours)	3 (30)	5 (62.5)	**0.60**
T5 (7 days after baseline)	2 (20)	5 (62.5)	**0.28**
T6 (30 days after baseline)	2 (20)	4 (50)	**0.50**
Pain at mouth opening**			
T1 (before treatment)	4 (40)	6 (75)	**0.67**
T3 (after 48 hours)	5 (50)	5 (62.5)	**0.60**
T5 (7 days after baseline)	4 (40)	5 (62.5)	**1.00**
T6 (30 days after baseline)	3 (30)	6 (75)	**0.34**
Spontaneous pain**			
T1 (before treatment)	6 (60)	4 (50)	**0.67**
T3 (after 48 hours)	3 (30)	2 (25)	**0.81**
T5 (7 days after baseline)	3 (30)	2 (25)	**0.81**
T6 (30 days after baseline)	2 (20)	2 (25)	**0.80**

*Student-s t test
**Chi-square test

Table 3 - Intra-group comparisons of outcome variables before and 30 days after application of treatments, through Paired t-test.

	Before tretament	**30 days after treatment**	
	Mean (SD)	**Mean (SD)**	***p* value intra-group**
Maximum mouth opening			
Laser Group	40 (3.1)	45.7 (6.6)	**0.04***
Placebo Group	43.1 (5.4)	44.6 (7.4)	**0.61**
Mandibular right excursion			
Laser Group	8.9 (2.7)	9.8 (2.5)	**0.46**
Placebo Group	8.7 (2.4)	8.8 (2.6)	**0.92**
Mandibular left excursion			
Laser Group	8.3 (2.1)	8.8 (2.3)	**0.62**
Placebo Group	7.7 (2.6)	8 (2.3)	**0.84**
Sites sore to palpation			
Laser Group	9.2 (4.4)	5.9 (3.6)	**0.11**
Placebo Group	10 (6.4)	6.8 (5.7)	**0.25**
OHIP/TMD Questionnaire			
Laser Group	31.9 (13)	16.2 (7.5)	**0.003***
Placebo Group	36 (15.9)	19 (19.4)	**0.07**

*Statistical significance according to Paired t-test, $p<0.05$

3 CONCLUSÃO

Com base nos resultados desse ensaio clínico, pode-se concluir que para pacientes diagnosticados com dor miofascial e limitação de abertura bucal duas sessões de laserterapia em baixa intensidade ativa ou placebo, com intervalo de 48 horas, não apresentaram diferenças significativas durante o período de tratamento e acompanhamento para desfechos clínicos, subjetivos e de sensibilidade dolorosa. Houve aumento significativo na amplitude máxima de abertura bucal e melhora nos escores de qualidade de vida relacionado a saúde bucal apenas no grupo laser. Com isso, a hipótese nula foi parcialmente rejeitada.

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ANEXO A – NORMAS PARA PUBLICAÇÃO NO PERIÓDICO JOURNAL OF DENTAL RESEARCH.

The *Journal of Dental Research (JDR)* adheres to the CSE (8th Edition) editorial style. All submitted manuscripts should be formatted in this style

The *Journal of Dental Research* (*JDR*) is a peer-reviewed scientific journal dedicated to the dissemination of new knowledge and information on all science relevant to dentistry and to the oral cavity and associated structures in health and disease. The *Journal of Dental Research*'s primary readership consists of oral, dental and craniofacial researchers, clinical scientists, hard-tissue scientists, dentists, dental educators, and oral and dental policy-makers. The *Journal* is published monthly, allowing for frequent dissemination of its leading content. The *Journal of Dental Research* also offers OnlineFirst, by which forthcoming articles are published online before they are scheduled to appear in print. Authors of all types of articles should be aware of the following guidelines when submitting to JDR.

ONLINE SUBMISSION

Submissions to the *Journal of Dental Research* are only accepted for consideration via the SAGETrack online manuscript submission site at http://mc.manuscriptcentral.com/jdr. Authors who do not have an active account within the system are required to create a new account by clicking, "Create Account," on the log-in page. The system will prompt the authors through a step by step process to create their account. Once created authors can submit their manuscripts by entering their "Author Center" and clicking the button by "Click Here to Submit a New Manuscript."

If any difficulty is encountered at anytime during the account creation or submission process, authors are encouraged to contact the *Journal of Dental Research* Publications Coordinator, Kourtney Skinner, at kskinner@iadr.org

MANUSCRIPT REQUIREMENTS BY TYPE

The *Journal of Dental Research* accepts the following types of manuscripts for consideration:

Original Research Reports: These manuscripts are based on clinical, biological, and biomaterials and bioengineering subject matter. Manuscripts submitted as research reports have a limit of 3,200 words (including introduction, materials, methods results, discussion and; excluding abstracts, acknowledgments, figure legends and references); a total of 5 figures or tables; 40 references; and must contain a 300 word abstract.

Letters to the Editor*: Letters must include evidence to support a position about the scientific or editorial content of the *JDR*. Manuscripts submitted as a letter to editor have a limit of 250 words. No figures or tables are permitted. Letters on published articles must be submitted within 3 months of the article's print publication date.

Guest Editorials*: A clear and substantiated position on issues of interest to the readership community can be considered for this manuscript type. Guest Editorials are limited to 1,000 words. No figures or tables are permitted.

Discovery!: Essays that explore seminal events and creative advances in the development of dental research are considered for the "Discovery!" section of the
journal. Manuscripts submitted for "Discovery!" have a limit of 2,500 words and a total of 2 figures or tables. Manuscripts are to be submitted by invitation only.

Critical Reviews in Oral Biology & Medicine: These manuscripts should summarize information that is well known and emphasize recent developments over the last three years with a prominent focus on critical issues and concepts that add a sense of excitement to the topic being discussed. Manuscripts are to be submitted by invitation only. Authors interested in submitting to this section must contact the Editor of *Critical Reviews in Oral Biology & Medicine*, Dr. Dana Graves, at dgraves@iadr.org for submission approval and instructions.

Manuscripts submitted as Critical Reviews have a limit of 4,000 words; a total of 6 figures or tables; 60 references; and must contain a 300 word abstract.

Additional Instructions for Critical Reviews*:* -It is important to include several illustrations or diagrams to enhance clarity.

Manuscripts that lack figures or diagrams typically receive a low priority score.

-Summarize important concepts in tables or flow charts or show critical data in the form of figures. NOTE: authors will need to obtain permission to reproduce a previously published figure or table.

-Due to the broad readership, abbreviations commonly recognized in one field may not be readily apparent to those in a different field. Keep abbreviation use to a minimum.

-The cover page, abstract, text, summary, figure legends, and tables should be combined into a single Word document. Figures should be submitted as a separate document.

All submissions must include a title page and be accompanied by a cover letter and list of suggested reviewers. Cover letters should certify the research is original, not under publication consideration elsewhere, and free of conflict of interest. Title pages should include: abstract word count, total word count (Abstract to Acknowledgments), total number of tables/figures, number of references, and a minimum of 6 keywords. Keywords cannot be words that have been included in the manuscript title. Key words should be selected from Medical Subject Headings (MeSH) to be used for indexing of articles. See: http://www.nlm.nih.gov/mesh/MBrowser.html for information on the selection of key words. Please submit the names and email addresses of four preferred reviewers when prompted by the SAGETrack system. Preferred reviewers cannot be colleagues at the contributors' institution or present or former collaborators.

TITLES

Titles can consist of a maximum of 75 characters (including spaces). Titles do not normally include numbers, acronyms, abbreviations or punctuation. The title should include sufficient detail for indexing purposes but be general enough for readers outside the field to appreciate what the paper is about.

ACKNOWLEDGMENTS

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Fonts

Limit fonts used in any figure to Times, Times New Roman, Arial, Frutiger, and Sabon. Other fonts cannot be guaranteed to reproduce properly.

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REFERENCES

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Additional supporting data may be referenced as a supplemental appendix for publication online only. All supplemental appendix files must be submitted with the manuscript for review. Supplementary files will be subjected to peer-review alongside the article.

Supplementary files will be uploaded as supplied. They will not be checked for accuracy, copyedited, typeset or proofread. The responsibility for scientific accuracy and file functionality remains with the authors. A disclaimer will be displayed to this effect with any supplementary material published. Supplemental files may include additional figures or tables that exceed the Journal's limit. Material intended for the supplemental appendix must have "supplemental" or "appendix" in the file name upon upload. When formatting your supplemental files, please follow these instructions:

- Authors should provide a single Word file with all Appendix content. Figures and tables should be included in the main Appendix file so they can appear immediately alongside their captions. High resolution figures may also be supplied separately if authors wish, but they also must be copied into the Word file so everything can be kept together.
- Be sure to run spell check and proofread the text.
- Remove all highlighting/other colors. Use one font throughout.
- The Appendix should include the title of the article and all authors. Page numbers are recommended.
- Figures and Tables should be labeled Appendix Figure/Table 1, Appendix Figure/Table 2, etc. Avoid labeling as S1, S2, and so forth.
- All table footnotes and figure legends should be included.
- Preferably, authors shouldn't label separate parts as "Appendix 1", "Appendix 2", etc.; just use section heads as in a regular article.

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Manuscript submission guidelines for the *Journal of Dental Research* follow the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" set forth by the International Committee of Medical Journal Editors (ICMJE). For additional information please visit the ICMJE web site at http://www.icmje.org/.

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Manuscripts reporting a randomized clinical trial are required to follow the CONSORT guidelines. The Journal requires authors of pre-clinical animal studies submit with their manuscript the Animal Research: Reporting In Vivo Experiments (ARRIVE) guidelines.

Authors of human observations studies in epidemiology are required to review and submit a STROBE statement. When uploaded to the SAGETrack system, any checklists completed by authors should be given a supplementary file designation. Authors who have completed the ARRIVE guidelines or STROBE checklist should include as the last sentence in the Methods section a sentence stating compliance with the appropriate guidelines/checklist.
Additional guidance on compliance with various research guidelines can be found on the Guideline Information - Enhancing the Quality and Transparency of Health Research: www.equator-network.org.
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mc.manuscriptcentral.com/societyimages/jdr/CONSORT+2010+checklist%5b1%5d.doc
The *Journal of Dental Research* requires authors to register their clinical trials in a public trials registry. Authors of manuscripts describing such studies are asked to submit the name of the registry and the study registration number prior to publication. Authors are asked to include their clinical trial registration number at the end of their abstracts. In accordance with the aforementioned "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," clinical trials will only be considered for publication if they are registered.

INSTITUTIONAL REVIEW BOARD AND WRITTEN INFORMED CONSENT

For protocols involving the use of human subjects, authors should indicate in their Methods section that subjects' rights have been protected by an appropriate Institutional Review Board and written informed consent was granted from all subjects. When laboratory animals are used, indicate the level of institutional review and assurance that the protocol ensured humane practices.

ANEXO B – APROVAÇÃO NO COMITÊ DE ÉTICA EM PESQUISA

UNIVERSIDADE FEDERAL DE SANTA MARIA/ PRÓ-REITORIA DE PÓS-GRADUAÇÃO E

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Tratamento da limitação de abertura bucal em pacientes com disfunção temporomandibular através da laserterapia: um estudo clínico randomizado duplo-cego

Pesquisador: Mariana Marquezan
Área Temática:
Versão: 3
CAAE: 74925717.6.0000.5346
Instituição Proponente: Universidade Federal de Santa Maria/ Pró-Reitoria de Pós-Graduação e
Patrocinador Principal: Financiamento Próprio

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_978735.pdf	29/03/2018 13:17:40		Aceito
Cronograma	Cronograma.pdf	29/03/2018 13:15:26	Mariana Marquezan	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	29/03/2018 13:15:00	Mariana Marquezan	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoPlataforma2018.docx	03/12/2017 19:47:27	Mariana Marquezan	Aceito
Outros	xtermodeconfidencialidade.jpeg	22/11/2017 13:09:50	Mariana Marquezan	Aceito
Outros	gap.pdf	20/08/2017 23:54:31	Mariana Marquezan	Aceito
Orçamento	Orcamento.docx	15/08/2017 18:26:13	Mariana Marquezan	Aceito
Declaração de Instituição e Infraestrutura	AutorizacaoDpto.jpeg	15/08/2017 13:05:56	Mariana Marquezan	Aceito
Declaração de Pesquisadores	DeclaracaoPesquisadores.jpeg	15/08/2017 13:05:21	Mariana Marquezan	Aceito
Folha de Rosto	Folhaderosto.pdf	15/08/2017 13:04:34	Mariana Marquezan	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SANTA MARIA, 03 de Abril de 2018

Assinado por:
CLAUDEMIR DE QUADROS
(Coordenador)

ANEXO C – APROVAÇÃO NO REGISTRO BRASILEIRO DE ENSAIOS CLÍNICOS

HOME / SUBMISSÕES / SUMÁRIO / TRIAL: RBR-4W2GD8 TRATAMENTO DA LIMITAÇÃO DE ABERTURA BUCAL EM PACIENTES COM PROBLEMAS NA ARTICULAÇÃO TEMPOROMANDIBULAR ATRAVÉS DA LASERTERAPIA

Submissões

NOVA SUBMISSÃO

Data	Título	Situação
2017/05/15 17:04	Tratamento da limitação de abertura bucal em pacientes com disfunção temporomandibular através da laserterapia	aprovado