Study Protocol

Randomized, Placebo, Controlled Clinical Trial Protocol of Mandibular Mobilization in Individuals with Anterior Disc Displacement with Magnetic Resonance Imaging Assessment.

ABSTRACT

Objective: To assess the influence of mandibular mobilization on the positioning of the articular disc, using magnetic resonance imaging (MRI) in participants with anterior displacement of the disc with and without reduction, immediately, 3 and 6 months after treatment.
Study design: Controlled, randomized clinical trial with blinded evaluators and participants.
Methodology: Individuals aged 18-45 years with an MRI-confirmed diagnosis of anterior disc displacement.
Intervention: Two groups: GA (intervention) and GB (placebo) will receive 12 treatment sessions. Main outcome measures: Disc positioning assessed by MRI before and after the last session and at 3 and 6-month follow-ups.
Analysis: The statistical analysis will use linear mixed models based on the intention to treat. The significance level will be set at 5%.
Results: To determine the success of the intervention protocol, a 30% improvement in the difference between the parameters measured in the MRI at pre- and post-treatment moments will be considered, in addition to clinical improvement in mandibular movement.

Keywords: Temporomandibular Joint Disorders, Anterior Disc Displacement, Magnetic Resonance Imaging, Musculoskeletal Manipulations.

1. INTRODUCTION

Temporomandibular disorder (TMD) involves changes that affect the temporomandibular joint (TMJ), masticatory muscles, and structures related to the head and neck. TMD, of multifactorial etiology, can be of joint, muscular, or mixed origin, associated with pain, jaw dysfunction, and structural changes [OROFACIAL PAIN et. al, 2015, LA TOUCHE, R. et. al, 2020, SLADE, G. D. et. al, 2016, YIN, Y. et. al, 2020].

Joint-related TMD refers to intra-articular disorders, including disc displacements. Anterior disc displacement refers to an abnormal geometric relationship between three TMJ components (i.e. temporal bone, disc, condyle). Anterior disc displacement with reduction

(DDWR) refers to the anterior position of the disc when the mouth is closed and during opening the disc is recaptured adopting a posterior position. It is the most prevalent internal derangement of TMJ (41% worldwide), with 33% of the population being asymptomatic. [POLUHA, R. L. et. al, 2019].

The literature points to anatomical, biomechanical factors, and parafunctional habits as possible etiologies [LA TOUCHE, R. et. al, 2020, MIERNIK, M. & WIĘCKIEWICZ, W. et. al, 2015]. Disc displacement without reduction (DDwoR) refers to the constant anterior position of the disc, limiting mandibular function, and maybe the last phase of condyle-disc dysfunction after episodes of joint noises [DI PAOLO, C. ET. AL, 2023, MACRÌ, M., MURMURA, G., SCARANO, A. & FESTA, F, 2022].

The diagnosis of disc position is obtained through clinical evaluations(Diagnostic Criteria for TMD – DC/TMD) and imaging exams, with magnetic resonance imaging (MRI) being the reference exam to identify the position of the disc, with high specificity~~ies~~ (88-90%) and sensitivity~~ies~~ (78 -83.3%) [LA TOUCHE, R. et. al, 2020, SCHIFFMAN, E. & OHRBACH, R, 2019]. However, treating anterior disc positioning is challenging. Raising patient awareness about their condition and preventing exacerbated activities are often recommended [POLUHA, R. L. et. al, 2019]. Although there is no standard treatment for such conditions, conservative approaches such as manual therapy, photobiomodulation, intraoral medications and devices are priorities [POLUHA, R. L. et. al, 2019, BOUCHARD, C., GOULET, J.-P., EL-OUAZZANI, M. & TURGEON, A. F, 2017]. Invasive procedures such as TMJ arthrocentesis, arthroscopies, and surgical techniques should be considered in case of failed attempts at conservative interventions due to the associated risks[LALUE-SANCHES M, GONZAGA AR, GUIMARÃES AS, RIBEIRO EC, 2015]. The main objective of treatment is to improve mandibular function and remodel the soft tissues of the joint [DI PAOLO, C. et. al, 2023, MACRÌ, M., MURMURA, G., SCARANO, A. & FESTA, F, 2022].

Despite the amount of work in the literature on the use of MRI to evaluate internal disorders [DIAS, I. M., COELHO, P. R., PICORELLI ASSIS, N. M. S., PEREIRA LEITE, F. P. & DEVITO, K. L, 2012, OHNUKI, T. et. al, 2006] of the TMJ and treatments [AKTAS, I., YALCIN, S. & SENCER, S, 2010,EMARA, A. S., FARAMAWEY, M. I., HASSAAN, M. A. & HAKAM, M. M, 2013, HASEGAWA, Y. et. al, 2011, HUANG, I.-Y. *et al*,~~2011, ZAUGG~~2011, ZAUGG, B., HÄMMERLE, C. H. F., PALLA, S. & GALLO, L. ~~M.,~~M, 2012, ZHANG, S. et. al. 2010, ZHU, Y., ZHENG, C., DENG, Y. & WANG, Y, 2012], there is a gap in the literature regarding the evaluation of imaging findings after the physiotherapeutic intervention. Therefore, the present study will aim to evaluate the influence of mandibular mobilization on the positioning of the articular disc, using MRI in individuals with anterior displacement of the

Comment [hi1]: Is there a supplementary method that can be combined with MRI to increase the sensitivity and specificity of the diagnosis?

Comment [hi2]: I believe that since the aim of the study is to assess the pre and post MRI image after joint mobilization, a short introduction of the physiotherapeutic therapy is due in the introduction.

disc. The hypothesis of the present study will be to demonstrate whether joint mobilization influences the position of the anteriorly displaced joint disc.

2. METHODOLOGY

Ethical aspects

This protocol follows specific research guidelines for human subjects and was approved by the University's Research Ethics Committee (CAAE: 36854714.7.0000.5511).Individuals who agree to participate in the research will sign the Informed Consent Form. The protocol will be ~~develop ped~~developed, and it was registered at ClinicalTrials.gov (NCT02294799) This study will be carried out at the University's Musculoskeletal Research Center (NUPEM).

Design

This study is a randomized, double-blind clinical trial, following the recommendations of the Consolidated Standards of Reporting Trials (CONSORT), as shown in Figure 1 [BUTCHER et. al, 2022]. This protocol will follow the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [CHAN et. al, 2013].

Figure 1: Study design flowchart according to CONSORT.

Participants

Study participants did not participate in formulating the research design or its objectives. The design and goals of this project were established by the research team and subsequently subjected to review by ad hoc advisors from the entity that finances MRI exams.

Eligibility Criteria

Individuals aged between 18 and 45 years old, both genders, diagnosed with anterior disc displacement with or without reduction will be included. Individuals with exclusively muscular TMD will be excluded; who have systemic diseases that affect the joints and/or masticatory muscles; neuromuscular diseases; with condylar hypo/hyperplasia; who use any type of dental prosthesis; are undergoing orthodontic and/or physiotherapeutic treatment; that present the absence of dental elements except their third molars; those with neurological or behavioral disorders that make it impossible to undergo MRI and/or with a history of previous temporomandibular joint surgery. Participants will be instructed not to use pharmacological analgesics while participating in the study but will be encouraged to report their use if unavoidable.

Randomization and blinding

After they sign the formal consent, a physical therapist will assess them to determine eligibility. Participants will be randomized into two groups: Group A (intervention) and Group B (placebo), using the randomization.com program. Three physiotherapists will be part of the protocol. One will be responsible for pre and post-intervention assessments and will be blind to the type of intervention. The second physiotherapist will be responsible for the intervention phase in the intervention group (GA) and will be blind to the assessments. The third physiotherapist will be responsible for the intervention phase in the placebo group (GB), who will be blind to the evaluations. A radiology technician will perform the MRI examination, a laboratory radiologist will provide the report, and 3 dentists specialized in radiology will analyze the disc positioning pre and post-intervention, being blinded to the type of intervention received by the participants. A tenth collaborator will process and analyze the collected data, being blinded to the type of intervention received by the participants.

Comment [hi3]: Are the physiotherapist of the same experience and qualifications? Since the observation may be biased due to the subjectiveness of the physiotherapist.

Intervention

GA*:* With the individual in the supine position on the stretcher, non-specific mandibular mobilization will be carried out by an experienced and previously trained therapist, using disposable gloves, positioning the thumb on the last molar, the patient will lightly press the thumb of the physiotherapist with the upper and lower arch during grade III mobilization. Five repetitions of 1 minute will be performed [MAITLAND, GD, 2001]' between repetitions, mouth opening will be performed fifteen times with the tongue on the incisive papilla [EL HAGE, Y. et. al,2013]. The mandible will be mobilized bilaterally. The therapist will remain standing on the opposite side of the mandibular mobilization, performing millimeter oscillatory movements. The treatment will last 6 weeks, twice a week, 12 sessions in total.

Figure 2. Nonspecific mandibular mobilization technique

Figure 3. Mouth opening exercise with tongue on the incisive papilla

GB*:* The positioning will be identical to Group A, for both the therapist and the patient. However, mobilization will not be performed, the therapist will position the thumb on the last molar, flex and extend the interphalangeal joint slightly for 1 minute, without generating movements in the TMJ, and five repetitions will be performed. The treatment will last the same as GA.

Treatment Protocol for TMD:

Physiotherapy is considered a conservative and effective approach in the treatment of temporomandibular disorders (TMDs) and has demonstrated significant efficacy in reducing symptoms, in addition to presenting lower costs and risks to patients [VAIRA & De RIU, 2023; WADHOKAR & PATIL, 2022; ARMIJO-OLIVO et al., 2016]. Through interventions such as therapeutic exercises and manual therapy, physiotherapy can manage symptoms and improve function in patients with TMD [ARMIJO-OLIVO et al., 2016; MEDLICOTT & HARRIS, 2006; ASQUINI et al., 2021]. TMJ mobilization is usually included in combination with other interventions. Evidence on the immediate effects of TMJ mobilization is scarce, and evidence supporting its use is inconclusive [BRONFORT et al., 2010; BUTTS et al., 2017]. Therefore, evaluating the effects of a single technique can help avoid bias due to the influence of other factors on the outcomes to be studied.

Primary outcome measures

Diagnostic Criteria forTemporomandibular Dysfunction (DC/TMD): It is a biaxial diagnostic instrument. Axis I consists of two questionnaires, demographic data, and a clinical examination, including palpation of structures, measurement of mandibular range of motion, and verification of the presence of joint noises, among others. And Axis II is composed of a pain drawing instrument and 8 questionnaires. Each of these questionnaires presents its interpretation. The diagnostic decision diagram offers 9 diagnostic possibilities, with more than one diagnosis possible for each joint. Diagnoses of intra-articular disorders and degenerative joint disorders require imaging examination for confirmation [SCHIFFMAN, E. L. et. al, 2014].

Magnetic Resonance: The magnetic resonance equipment that will be used is the Philips Multiva, 1.5 tesla, manufactured in 2019. The distance between the chin and the sternal notch will be measured in the first examination and maintained in the final examination, to ensure the same examination conditions (pre- and post-intervention).

TMJ image acquisition will be performed in two moments: mouth closed, with the tongue on the incisive papilla without tooth contact, and mouth open to 80% of the maximum opening (submaximal), previously measured. In the open mouth examination, overlapping toothpicks will be placed between the right and left premolars to ensure submaximal opening and maintenance of mouth opening. The images will be taken in T1, T2, and DP, in sagittal and coronal sections, by a single radiological technician, ensuring consistency in the scanning method and parameters.

Magnetic Resonance Analysis: The MRI exams will be analyzed by 3 independent dental radiologists, considering parameters established in a previous meeting, in two different mandibular positions: closed mouth and open mouth. For a quantitative and precise assessment, a tracing will be made in the most central and superior region of the mandibular fossa, extending to the most posterior portion of the articular disc band (figure 4). These parameters will be compared pre and post-treatment for both groups.

Figure 4:Protocol for measuring the articular disc on magnetic resonance imaging, (A) closed mouth, (B) open mouth.

Secondary outcome measures

World Health Organization Quality of Life Abbreviated (WHOQOL-BREF):To assess the quality of life, the WHOQOL-BREF will be used, an abbreviated version of the WHOQOL-100, consisting of 26 questions, 2 referring to global and general health and the others divided into four domains: physical, psychological health, social relationships, and environment. In the end, values equal to or close to 0 will present an unfavorable quality of life, and close to or equal to 100 will present a favorable quality of life [FLECK, M. P et. al, 2000].

Patient-specific functional scale: It is a global scale and can be used for any region of the body. The patient is asked to identify up to 3 activities that they are unable to perform or present some difficulty with, the higher the average score (0-10) the better the patient's ability to perform the activities [HORN, K. K et.al, 2012].

Numerical Pain Scale (NPS): This is an easy-to-apply scale, where the individuals will be asked to respond, in a numerical sequence from 0 (o pain) to 10 (worst pain), how intense their pain is [FERRERA-VALENTE et.al, 2011].

Sample size

The sample size was calculated according to the data presented by Emara, et al. (2013) considering the difference in the mean (0.62 ± 0.27) of the disc displacement before and after intervention with botulinum toxin. Considering the mean and standard deviation of the pre- and post-intervention conditions for each clinical outcome [primary]. For the calculation, the values $\alpha = 0.05$ [5% chance of type I error] and $1-\beta = 0.95$ [% of sample power], which was the evaluation of the disc position after treatment with nonspecific mandibular mobilization, 6 participants per group will be necessary. The sample size was calculated using the G*POWER software [FAUL et. al, 2007].

Comment [hi4]: Why is there an intervention with botox?

Statistical analysis

The normality of data related to outcome measures will be verified using the Shapiro-Wilk test. Descriptive statistics will be used to characterize the participants, and the groups (GA and GB) will be compared using either the independent t-test or the Mann-Whitney test, and possible differences between groups will be tested using linear mixed models, considering the moments before, after 12 treatment sessions, after 3 months of treatment, and after 6 months of treatment. The differences between the groups [treatment effects] and their respective confidence intervals (95%CI) will be calculated through the construction of linear mixed models [TWISK et. al, 2003] using interaction terms of treatment groups versus time, with all models adjusted to initial estimates. If the data do not present a normal distribution, Friedman's ANOVA with Dunn's post hoc test will be used. The statistical significance considered will be $p<0.05$.

Cohen *d* and the partial eta squared ($_p^2$) will be used to calculate the effect size of the results [COHEN et. al, 1998], and the interpretation will be based on the values established by Cohen: low effect (*d* =0.2 and $_p^2$ =0.01); moderate effect (approximately *d* =0.5 and $_{p2 = 0.06}$); and large effect (from: *d* =0.8 and $_p^2$ =0.14). These analyses were performed using SPSS 20.0 software [SPSS Inc., Chicago, USA].

3.Results

The protocol of the current study is innovative and unprecedented as it will assess the behavior of the anterior disc displacement through MRI after mandibular mobilization. To determine the success of the intervention protocol, a 30% improvement in the difference between the parameters measured in the MRI at pre- and post-treatment moments will be considered or the mean differences between the coordinates of each of anterior point of the disc and the posterior point of the disc pre- and post mobilization in the 0.62 and 0.83 [EMARA et.al, 2013], in addition to clinical improvement in mandibular movement.

4. DISCUSSION

In the present study, we will only address anterior disc displacements with or without reduction with a specific focus on disc positioning after joint mobilization.

Conservative approaches are in most cases the first therapeutic option for individuals with disc displacements. This strategy encompasses medication administration, the use of intra-oral devices, joint infiltrations, use of jaw exercises, and manual therapy, including joint mobilizations to improve disc positioning in the joint [LA TOUCHE, R. et. al, 2020, MIERNIK, M. & WIĘCKIEWICZ, W. et. al, 2015, BOUCHARD, C., GOULET, J.-P., EL-OUAZZANI, M. &

TURGEON, A. F et. al, 2017, ATARAN, R et. al, 2017] . However, despite these consolidated approaches, the literature still lacks robust investigations that evaluate the direct impact of joint mobilizations on disc positioning.

An important contribution of this research is to encourage other clinical trials that provide interventions for disc displacement, as the present study is the first investigation with the explicit purpose of showing possible changes in the positioning of the articular disc in individuals with anterior disc displacement. The results will be measured using MRI, the reference standard for evaluating this specific joint.

5. CONCLUSION

This study will evaluate how the anteriorly displaced disc will behave after mandibular mobilization. It will be possible to determine the effects of mobilization through MRI.This protocol seeks to determine whether mandibular mobilization can help rehabilitate anteriorly displaced disc in the TMJ and thus be included in therapeutic planning.

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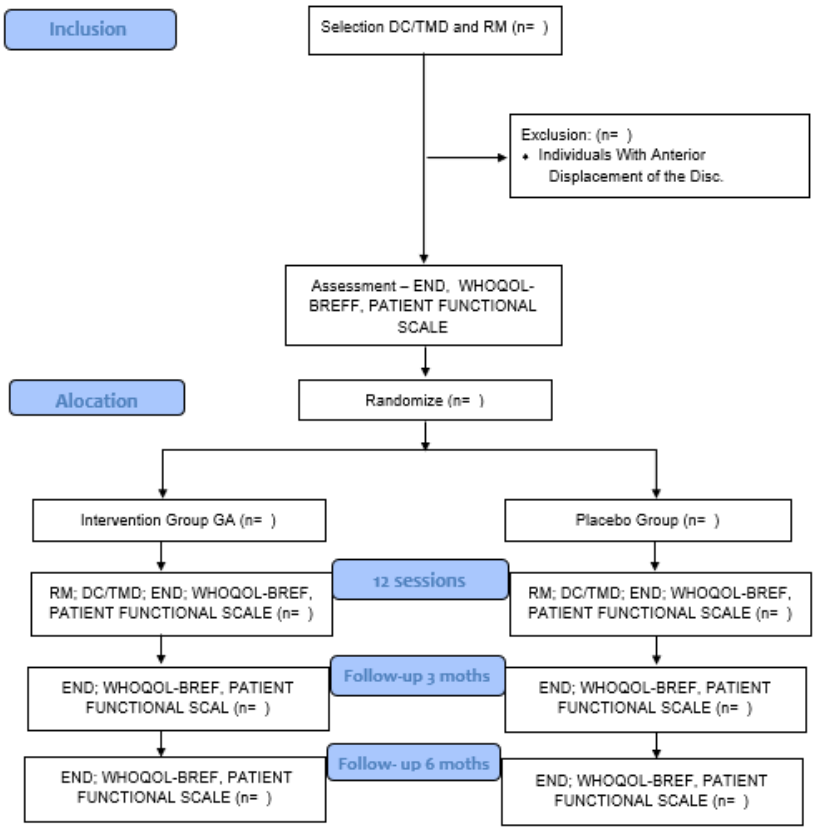

Figure1: Study Design Flowchart according to CONSORT

Figure 2: Nonspecific mandibular mobilization technique

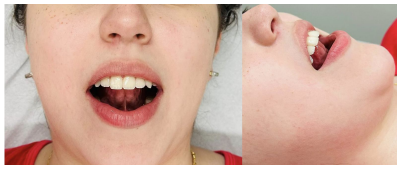

Figure 3: Mouth opening exercise with tongue on the incisive papilla

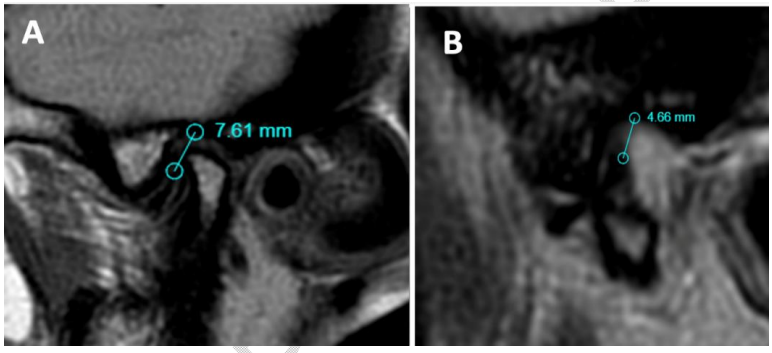

Figure 4. Protocol for measuring the articular disc on magnetic resonance imaging, (A) mouth closed, (B) mouth open