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RESEARCH ARTICLE

Remodeling dental anatomy vs sham therapy for chronic temporomandibular disorders. A placebo-controlled randomized clinical trial☆

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ABSTRACT

Background: Evidence regarding the etiology or effective treatments for chronic orofacial pain, the majority diagnosed as temporomandibular disorder (TMD), is limited.
Purpose: To investigate whether occlusal equilibration therapy (ET) and decreasing the (higher) angle of the lateral guidance on the nonworking-side leads to a reduction in chronic TMDs intensity.
Methods: It was conducted a randomized, explanatory, single blind with blinded assessment, placebo-controlled trial with strong protection against bias involving patients with chronic TMDs. Participants were randomly assigned to receive equilibration therapy or sham therapy. ET in this study consisted of minimal invasive occlusal remodeling to obtain balanced occlusion with reduction of the steeper angle of lateral mandibular movement with respect to the Frankfort plane. The primary outcome was a change in the pain intensity score (on a 0–10 point scale, with 0 indicating no pain and 10 the worst possible pain) at month 6. Secondary outcomes include maximum unassisted mouth opening and psychological distress.
Results: A total of 77 participants underwent randomization, 39 of whom received ET and 38 sham therapy. The trial was stopped early for efficacy, according to preestablished rules when 67 participants (n = 34, n = 33, respectively) had completed the analysis. At month 6, the mean unadjusted pain intensity score was 2.1 in the ET and 3.6 in the sham therapy group (adjusted mean difference, −1.54; 95% confidence interval [CI] −0.5 to −2.6; P = 0.004; ANCOVA model). The mean increase in maximum unassisted mouth opening (main secondary outcome) was significantly higher in the real therapy group (adjusted mean difference 3.1 mm, 95% CI 0.5–5.7, p = 0.02).
Conclusion: ET significantly reduced the intensity of facial pain associated with chronic TMDs and increased maximum unassisted mouth opening, as compared with sham therapy, over the course of 6 months. There were no serious adverse events.

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1. Introduction

1.1. Background

Chronic orofacial pain conditions (the most frequent cause of which are temporomandibular disorders [TMDs]) can be particularly difficult to diagnose and treat because of their complexity and the limited understanding of the mechanisms underlying their etiology

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and pathogenesis (NASEM, 2020; Sessle, 2021). The overall prevalence of TMD in elderly adults has been reported to be approximately 31% (Valesan et al., 2021). Although the female sex may not be a major risk factor for TMDs (Widmalm et al., 1994; Slade et al., 2016a,2016b), the majority of patients seeking treatment are women (NASEM, 2020). Recently, peripheral risk factors (Cooper, 2011; Nguyen et al., 2017, 2021; Walton and Layton, 2021; Kucukguven et al., 2022; Tervahauta et al., 2022; Keil et al., 2023; de Abreu et al., 2023) and also a number of biopsychosocial-central risk factors (Fillingim et al., 2011; Slade et al., 2016a,2016b; NASEM, 2020) for suffering from functional disorders of the stomatognathic system have been identified. However, these studies did not provide new information on the main causes of TMDs and their implications for the management of these patients (Svensson and Exposto, 2020). Therefore, a wide variety of treatments, mostly conservative, have been proposed and carried out over the last decades (Stohler and Zarb, 1999; Feng et al., 2019; Al-Ani, 2020; Penlington et al., 2022). Recently, because of the low evidence base for conservative treatments, a management pathway has been proposed that shows an escalation from conservative to invasive treatment (Al-Moraissi et al., 2020; Al-Moraissi et al., 2022; Tran et al., 2022).

One of the most debated treatments has been occlusal adjustment (OA) (Al-Ani, 2020; Solow, 2021). The authors are unaware of any study showing that conventional OA (aimed at eliminating interference and obtaining canine disclusion) (Dawson, 1989), mainly performed during the 80s - 90s (Solow, 2021) has provided better outcomes than a placebo. The lack of clinical evidence has allowed the role of occlusion in TMDs to be refuted (Alanen, 2002). However, scientific evidence contradicting an occlusal causal role in functional disorders is lacking (Kirveskari et al., 1998; Alanen, 2002; Alanen et al., 2012; Alanen and Kirveskari, 2012; Solow, 2019; de Abreu et al., 2023).

1.2. Study rationale

The rationale of the present randomized clinical trial was based on the following evidence:

- The presence of premature contacts leads to deflective jaw closure (Dawson, 1989; Cordray, 2016; Kattadiyil et al., 2021; Cao, 2022; de Abreu et al., 2023).
- Joint overloads can contribute to TMDs, and is dependent of the occlusal scheme (Tanaka et al., 2008; Pérez del Palomar et al., 2008; Commisso et al., 2014; Sagl et al., 2021). Most authors prefer canine disclusion for fully dentate individuals despite this concept is not supported by scientific evidence (Thornton, 1990). When canine disclusion occurs during lateral mandibular movements, the stomathognatic system acts as a class III lever and the temporomandibular joints (TMJs) receive loads (the forces applied by the coactivation of elevator muscles are located between the TMJS [fulcrum] and the canines [resistance]). These loads can be reduced if during these lateral movements upper and lower teeth keep in contact (balanced occlusion; GPT-9, 2017), which permits distribution of muscular forces throughout the dental arch. According to Minagi et al. (1990), adequate tooth contacts on the nonworking-side protect TMJs from overloading and reduce the risk of suffering TMDs. This balanced occlusal scheme is well tolerated by patients (Santana and Mora, 1995). It was therefore chosen for this investigation in those cases where it could be achieved without the enamel removal needed to eliminate contacts on the nonworking-side when a canine disclusion is intended.
- The affected side is the usual chewing side and the side where the lateral guidance angle (LGA) is lower (Fig. 1a) (Ferrario et al., 1996; Reinhardt et al., 2006; Yalçın Yeler et al., 2017; Santana-Mora et al., 2013, 2021). LGA was defined in this research as frontal plane lateral mandibular movement with respect to the Frankfort horizontal plane. Using only one side for chewing alters the asymmetry of the facial (Heikkinen et al., 2022) and articular structures (Dibbets, Dijkman, 1997; Fanghänel and Gedrange, 2007; Jiang et al., 2015; Santana-Mora et al., 2013, 2021; Nickel et al., 2018; Ma et al., 2021; Ma et al., 2022; Tran et al., 2023). During mastication, on the non-working side, the condyle moves forth and back, allowing lubrication of the articular surfaces and proper metabolism. On the working side the condyle remains mostly static (Miyawaki et al., 2001). This could explain why this is the side where the symptoms tend to be located when masticatory alternation dysfunctions occur.

Accordingly, it was hypothesized that in selected patients, an individualized ET can be implemented to treat chronic TMDs. ET in this study includes the following:

- Balancing the occlusion during jaw closure, eliminating occlusal prematurity.
- Obtaining balanced occlusion (GPT-9, 2017) during lateral jaw motion where possible to minimize enamel elimination and protect the TMJs.
- Reducing the highest LGA (Fig. 1b) on the side not usually used for chewing expecting to recover chewing on the non-used side.

1.3. Intervention design

To test the hypothesis that ET would be effective in treating patients with chronic painful TMDs, this randomized clinical trial was designed as the most appropriate method of objectively assessing the efficacy of a new treatment.

2. Methods

2.1. Ethics statement

This trial was approved by the Regional Human Ethics Committee of Galicia, Spain (approval number 2009/017, updated November 29, 2013). All participants provided written informed consent before enrollment, consistent with the information provided in this article.

2.2. Trial design and oversight

This explanatory randomized clinical trial, single blind with blinded assessment, was placebo-controlled, parallel, and carried out in a single center. It compared an ET with a placebo (sham-control) therapy.

The prospective protocol (available in Supplementary data 1), the investigation, and the reporting of this study were carried out in accordance with standard guidelines (Schulz et al., 2010; Dworkin et al., 2010; World Medical Association, 2013; Chan et al., 2013). An independent Data and Safety Monitoring Board (DAMOCLES Study Group, 2005) approved the protocol before study began and monitored the trial in real time using a certified online database (OpenClinica®), implemented to ensure the transparency and accuracy of the trial's progress; only the data manager of the Oral and Maxillofacial Surgery Service of A Coruña University Hospital was able to enter data in OpenClinica, which was inaccessible to the researchers.

2.3. Eligibility and recruitment

Patients who visited a trial clinician for jaw pain were considered for trial recruitment. After receiving brief information about the trial, written permission for an initial assessment was obtained. Patients considered to be elegible were those who were diagnosed

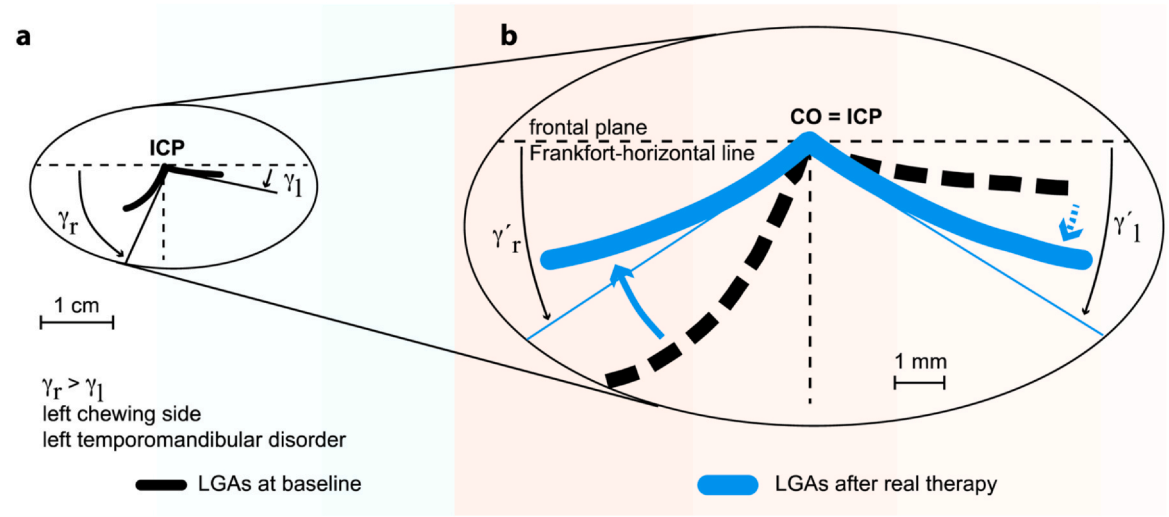

Fig. 1. Kinesiographic recordings. Frontal plane lateral mandibular movement, and angles with respect to the horizontal line. **a**, diagnosis: a lower left angle ($\gamma_l < \gamma_r$) is associated with ipsilateral involvement and habitual chewing. **b**, therapeutic operationalization of the γ angles (blue line; $\gamma'_r \cong \gamma'_l$). Slopes of right and left gamma angles, with respect to Frankfort line, of frontal plane lateral mandibular movements recordings (K7 Myotronics) were calculated in first 2 mm of motion from ICP. ICP, maximal intercuspal position; CO, centric occlusion; TMD, temporomandibular disorder. R, right; L, left.

with TMDs according to DC/TMD Axis 1 (Schiffman et al., 2014), TMD myogenous and/or TMD arthrogenous, which can be aligned with the ICOP (2020) of myofascial orofacial pain and/or TMJ pain, respectively, were fully dentate (except third molars) and had clinically normal or quasi-normal (Angle Class I, stable) occlusion. Experienced pain (reported by the participant) of moderate to severe intensity (scores ≥4 and ≤9) on a of 0–10 scale (where 0 = no pain and 10 = worst possible pain), and chronic (at least during the previous 6 months) were considered eligible. The full list of inclusion and exclusion criteria can be found in the study protocol (Item 10 in Supplementary appendix 1). All participants had previously been provided with occlusal device therapy; most had also received other conservative or minimally invasive treatments.

After a complete evaluation, a trial clinician adequately informed them of the trial characteristics and invited all qualified patients to participate. Once they had consented to participate, they were enrolled, and were registered in OpenClinica. The research team was notified, and the patients were called for treatment 2–4 weeks later; this period served as a washout period for current therapies and reminded them to follow the instructions for participants.

2.4. Randomization and blinding

An independent senior statistician created the random assignment sequence and the treatment code (A/B). The sequence was sent to the data manager (A Coruña Hospital), who distributed it consecutively in opaque white envelopes. The therapy code was sent to the therapy provider, who, in turn, sent it in a sealed envelope to the chairman of the monitoring committee. All the trial clinicians (except the therapy provider, who did not participate in the evaluations or data analysis), committee members, statisticians, and participants were unaware of the trial-group assignments during the study period until the results were written up and approved.

2.5. Interventions

The trial regimen consisted of a real therapy (ET) or a similar placebo. The ET therapy, as previously mentioned, was designed to eliminate premature contacts, to obtain balanced occlusion, and to alter the LGA. LGA alterations were operationalized by attempting to satisfy the following equation (Santana-Mora et al., 2021):

right CPA × left LGA = left CPA × right LGA

The recording and measurement of the parasagittal plane condylar path angles (CPAs) with respect to the Frankfort plane and LGAs were carried out following the method described by Santana-Mora et al. (2013). Usually, the highest guidance was reduced. However, when the canine on the usual working side showed severe wear (usually associated with bruxism), lateral guidance was increased by adding restorative material.

ET also attempted to obtain a "functional" class I ratio of canines on both sides during lateral mandibular movements (working side). The ET procedure was systematized and is thoroughly described in Supplementary appendix 2 to allow for reproducibility of the study. Typically, the adjustment required 90 min and was carried out by the head of the Occlusion and Prosthodontics service. The therapy was refined in a second session one to two months later and typically required 30 min. Placebo treatment was performed identically to ET but using a non-cutting rotary instrument that did not remove any enamel. Intraoral photographs of all participants can be seen in Figshare (Data Citation1) (Data not shown). Adjustments outside the trial and the use of occlusal splints were not permitted. Other concomitant therapies were strongly discouraged.

2.6. Outcomes and data collection

The primary outcome was reduction in the mean intensity of the 30-day jaw pain score, from baseline at the 6-month assessment on a numerical pain-rating scale from 0 to 10 (with 0 indicating no pain and 10 the worst possible pain). Secondary outcomes were an increase in maximum unassisted mouth opening (MMO) and an improvement in psychological distress by assessing the scores of the global severity index (GSI) item of the SCL-90-R questionnaire (Derogatis et al., 1976), higher scores indicate greater distress. Three data collection periods were used: baseline, 3 months (secondary time for the main variable), and 6 months (primary time for all variables) after therapy.

2.7. Concealment allocation

At the start of therapy at the University Dental Clinic (Santiago de Compostela, Spain), the therapy provider requested the therapy code

by telephone from the data manager of the University Hospital (A Coruña, Spain). The therapy code was registered with OpenClinica, and the name of the participant was written on the envelope, which was resealed and stored for subsequent verification.

2.8. Statistical methods

The statistician determined that a total of 88 participants (44 per group) would be required to provide 80% power to detect a difference of 1.5 points (considered clinically important) in the jaw pain intensity score. A standard deviation (SD) of 2.4 was assumed for the jaw pain intensity score at 6 months according to an earlier pilot trial (cliniclatrials.gov NCT00899717).

It has been established that 2/10 points is a clinical important difference withing a individual; however, clinically important between-group differences are lower (Smith et al., 2020), and usually established as 1.5/10 in similar trials on chronic pain (Mathieson et al., 2017; Williams et al., 2018).

For the primary outcome of change in self-reported jaw pain intensity from baseline to 6 months, analysis of covariance (ANCOVA) was used, adjusting for baseline jaw pain intensity and including treatment group as an explanatory variable. The distribution of change in jaw pain intensity from baseline to 6 months was examined and found to be approximately normally distributed. The same approach was used for the secondary continuous outcomes of change in maximum unassisted mouth opening from baseline to 6 months and change in psychological distress from baseline to 6 months. The change in the habitual chewing side was reported descriptively. All analyses were conducted using the strict intention-to-treat approach (I-T-T).

The study used an interim analysis plan with a single interim analysis after 70% of participants had completed the six-month follow-up visit. Using the Lan-DeMets version of the O'Brien-Fleming stopping rule, the critical value for statistical significance at the interim analysis (under both intention-to-treat and per-protocol sets) was + 2.438, corresponding to a nominal two-sided p-value of 0.0146. The Data and Safety Monitoring Board was responsible for activating early stopping.

The null hypothesis was that no difference would be found in the studied variables between the ET (real therapy) and the sham therapy (placebo) groups.

3. Results

3.1. Trial population

From August 2014 through June 2018, a total of 77 participants (74 white, 3 black) were randomly assigned, 39 to the real treatment group and 38 to the placebo group. (Fig. 2).

The characteristics of the participants at baseline are presented in Table 1. Both groups had similar demographic and clinical characteristics. At baseline, in both groups, the main symptom was arthralgia. The mean (SD) jaw-pain intensity score at baseline was 6.6 (1.4) in the real therapy group and 6.5 (1.1) in the placebo group. Raw data are available at Dryad digital repository (Data citation 2) (data not shown).

3.2. Efficacy

3.2.1. Primary efficacy outcome

The trial was halted prematurely for efficacy on June 11, 2018, as the interim analysis conducted by the monitoring committee showed a highly significant difference (p = 0.01) between the two groups when 67 participants (A group N = 34, B group N = 33) had completed the trial, implying that one of the two treatments was more effective. This report is based on the findings in all the participants who underwent randomization (N = 77) before June 11, 2018.

Mean pain intensity decreased from 6.6 at baseline to 2.1 at month six in the real treatment group; in the sham-placebo group it decreased from 6.5 to 3.6 points, respectively. The mean difference between the two trial groups in the chronic TMD-pain intensity score was significant at month 6 (adjusted mean difference −1.54, 95% confidence interval [CI], −0.5 to −2.6, p = 0.004) (Table 2, Fig. 3). A highly statistically significant mean difference at 6 months was also observed in the per protocol (modified I-T-T) population (adjusted mean difference 2.0; 95% CI 1.0–3.0; p < 0.001).

3.2.2. Secondary efficacy outcomes

The mean increase in MMO from baseline to six months was significantly higher in the ET group (adjusted mean difference 3.1 mm, 95% CI 0.5–5.7, p = 0.02) (Table 2). Considering the subgroup of participants with limited maximum aperture (< 40 mm) at baseline, it increased from 33.0 to 42.2 mm in the ET group (n = 15) and from 34.4 to 39.0 mm in the sham therapy group (n = 11). The minimal clinically important difference between the groups has not yet been established.

No evidence of a difference between the groups was found in change in psychological distress or in chewing side (Table 2). Additional information on the results can be seen in Supplementary appendix 3.

3.3. Safety

There were no serious adverse events. Three participants in the real therapy group reported hypersensitivity, which was successfully treated with topical fluoride application.

4. Discussion

4.1. Main findings

The study data support the rejection of the null hypothesis. The present trial showed that ET therapy was more effective (clinically and statistically) than a sham-placebo in reducing jaw-pain intensity in participants with moderate-to-severe chronic jaw pain with a diagnosis of TMD over the course of six months. ET therapy was also more effective than a placebo in increasing maximum non-assisted mouth opening (Table 2). No serious adverse effects were detected.

4.2. Strengths and limitations

The main strength of this study was a design that provided strong protection against bias (Dworkin et al., 2010; Schulz et al., 2010; Chan et al., 2013). The trial had very high adherence. Two participants in the ET group did not receive treatment due to initial hypersensitivity, and all randomized participants completed the analysis except one who dropped out after three months (the treatment could not be completed due to hypersensitivity during the actual treatment, and they refused a composite to increase the lower LGA; she continued to have the same pain intensity after 3 months).

This study has several limitations. Only a minority of participants were male; furthermore, arthrogenous pathology (persistent, and refractory to other treatments) was the most common TMD in this study (Table 1). Both characteristics, which are not in themselves a limitation of the study, are common characteristics of patients referred to tertiary level centers (Stohler and Zarb, 1990). This seems a priori to limit the extrapolation of these results to other patient groups with different characteristics. The standardization of treatment over two visits, for methodological reasons (as the therapy provider had extensive experience in performing ET successfully), probably led to an underestimation of the actual treatment effect in

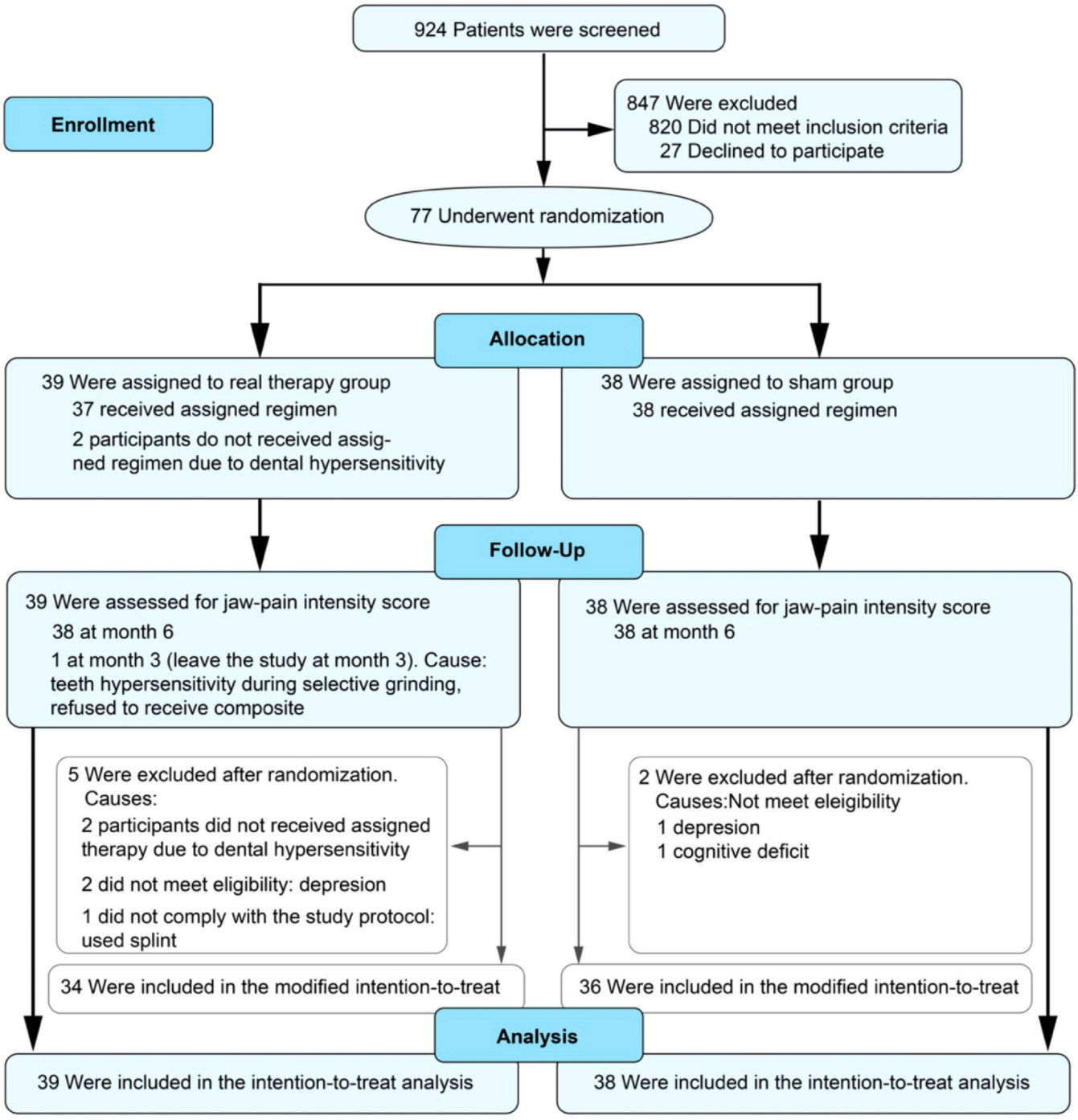

Fig. 2. CONSORT flow diagram. Screening, randomization, and follow-up.

this trial; in clinical practice, certain patients often receive treatment in a greater number of visits to achieve the greatest therapeutic benefit. The change from habitual side chewing to alternate chewing was reported by the majority of participants in both groups. This outcome should be interpreted with caution, as the participants were aware of the purpose of the assessment of this variable at the six-month visit, precluding an objective assessment of this variable.

4.3. Comparisons with other studies

The results of this study were not consistent with those of relevant systematic reviews (Al-Moraissi et al., 2020, 2021; Solow, 2021) which concluded that conservative therapies or ordinary OA were no more effective than other treatments or a placebo, although it is striking that these reviews reported a lack of high-quality studies on this topic. The different therapeutic goals and methods, ordinary OA (Dawson, 1989) vs ET, may explain the positive results obtained in this trial. Both ET and OA procedures require the elimination of interferences or occlusal disharmonies. Therefore, other features of ET should explain the different results they provide. First, the reduction of the LGA on the unaffected side (to equalize both LGAs or to become slightly lower than that on the opposite side), was consistently performed (except in two participants). Secondly, OA typically requires canine disclusion (Dawson, 1989), while ET preserved contacts (non-interference) on the non-working side during mandibular laterality excursions. This made it possible, first,

Table 1
Characteristics of the participants at baseline.

Characteristic	Real therapy group (N = 39)	Placebo group (N = 38)
Female sex — no. (%)	36 (92.3)	35(92.1)
Median age (IQR) — yr	29 (22–38)	30 (25–40)
Affected side/s — no. (%)		
Right	10 (25.6)	8 (21.1)
Left	16 (41)	13 (34.2)
Both	13 (33.3)	17 (44.7)
Median symptoms chronicity (IQR) — months	36 (18–120)	45 (24–79)
Arthralgia (with or without myalgia) — no. (%)	33 (84.6)	29 (76.3)
Myalgia (without arthralgia) — no. (%)	4 (10.3)	7 (18,4)
Internal joint derangement		
Disc displacement with reduction — no. (%)	8 (20.5)	5 (13.2)
Disc displacement without reduction — no. (%)	4 (10.3)	5 (13.2)
Disc degeneration or absence — no. (%)	2 (5.1)	2 (5.3)
Degenerative joint disease — no. (%)	2 (5.1)	1 (2.6)
Condyle hypoplasia — no. (%)	4 (10.3)	1 (2.6)
Jaw-pain score (indistinctly, NRS or VAS)		
Median — (IQR)	7 (5–8)	7 (6–7)
Mean — (SD)	6.6 (1.4)	6.5 (1.1)
Mouth opening		
Limited mouth opening — no. (%)	16 (41)	12 (31.6)
Maximum unassisted jaw opening (mm)	41.5 ± 8.4	43.9 ± 7.8
Habitual chewing side— no. (%)		
Right	16 (41.0)	14 (36.8)
Alternate	8 (20.5)	13 (34.2)
Left	15 (38.5)	11 (28.9)
Mean Global Severity Index — (SD)	0.9 (0.6)	0.8 (0.5)
Headache		
Prevalence in this trial — no. (%)	34 (87.2)	30 (78.9)
Median intensity NRS — (IQR)	7 (5–8)	5.8 (1–7.6)
Neuropathic facial pain — no. (%)	13 (36.1)	12 (34.3)
Condylar path angles in relation to Frankfort Plane. Mean — (SD) (degrees)		
Right side — (SD)	50.5 (10,7)	47.3 (8.1)
Left side — (SD)	50.1 (10.5)	49.3 (8.6)
Lateral guidance angles in relation to Frankfort Plane — (SD) (degrees)		
Right side — (SD)	41 (11.6	40.1 (12.5)
Left side — (SD)	38 (10.4)	37.3 (10.6)

IQR, interquartile range; SD, standard deviation; NRS, 0–10 numerical pain-rating scale; VAS visual analogue scale.

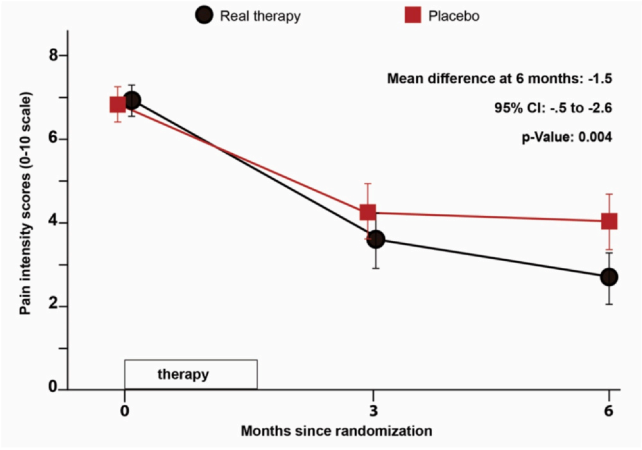

Fig. 3. Pain intensity scores across the trial according to trial group. Mean changes from baseline were baseline-adjusted; 95% confidence intervals (I bars) and p-values were from analysis of covariance models adjusting for baseline values in the intention-to-treat approach. The placebo group was used as the reference group (as control group). Negative values of jaw-pain of mean change favors the real therapy group.

to protect the TMJ, which is speculated (as it is not possible to measure loads on TMJs because they require invasive procedures), to be in agreement with the findings of Minagi et al. (1990); Pérez del Palomar et al. (2008); Commisso et al. (2014); Sagl et al. (2021); secondly, it minimized the removal of tooth enamel, since if canine disclusion were to be achieved, it would require more wear to remove all contacts during mandibular laterality, except for the contacts of the canine on the working side (Dawson, 1989). It was therefore inferred that providing adequate contacts on the non-working-side (balanced occlusion) may have contributed to the effectiveness of the ET treatment.

The a priori hypothesis that therapeutic reduction of the LGA on the non-working side facilitates chewing on this side could not be assessed with the present study design. This would require withholding information from patients, which would violate the integrity of the doctor-patient relationship. However, it seems to be supported by previous studies which showed an association between a lower LGA and habitual (preferred) chewing side (Ferrario et al., 1996; Santana-Mora et al., 2021). No modification was performed in the placebo group, which could explain the difference in results between the two groups in the study.

The ET performed in this trial is original and novel, and the authors are unaware that it has been evaluated before. The rationale of this study emerges after more than 35 years of clinical experience

Table 2
Outcomes at 6 months.

	Real therapy group (N = 39)	Placebo group (N = 38)	Mean Difference[a] (95% CI)	p value
Jaw-Pain score[b]				
Mean (SD) change from baseline	-4.4 (2.0)	-2.9(2.7)	-1.5 (−2.6, −0.5)	0.004
Maximum mouth opening-mm				
Mean (SD) change from baseline	6.2 (6.5)	2.5 (0.3)	3.1 (0.4, 5.7)	0.02
Global Severity Index				
Mean (SD) change from baseline	-0.4 (0.4)	-0.3 (0.3)	-0.05 (−0.21, 0.11)	0.54
Habitual chewing side-N(%)				
Change in chewing side— N(%)	27 (69.2)	20 (52.6)	1.32[c] (0.91, 1.90)	0.14
Perceived Improvement— N(%)	37 (94.9)	23 (67.7)	1.40[c] (1.10, 1.79)	0.002
Headache Intensity				
Mean (SD) change from baseline	-3.0 (3.2)	-1.2 (3.5)	-0.73 (−1.99, 0.52)	0.25
Neuropathic Pain— N(%)	2 (5.4)	4 (11.4)	0.47[c] (0.09, 2.42)	0.36

[a] mean difference, 95% confidence intervals and p-values from analysis of covariance models adjusting for baseline values;
[b] for change in jaw-pain score a negative number indicates a reduction in pain;
[c] risk ratio and 95% CI.

and hinges on the contribution of Ferrario et al. (1996) as well as other research (Santana and Mora, 1995; Santana-Mora et al., 2013, 2021), which demonstrated the association between a side with a lower LGA, the same habitual chewing side, and the same affected side. Although no prospective study has shown that the asymmetry of LGAs triggers or aggravates TMDs, the information provided by these studies made it possible to reasonably speculate that lowering the highest LGA should be an appropriate treatment for TMDs.

This study emphasizes the importance of peripheral factors on TMDs (including anatomy, biodynamics, and function of the stomatognathic system) in the diagnosis of TMD.

The population of the present study was homogeneous in terms of dental condition (fully dentate, with normal or quasi-normal occlusion, and stable). This characteristic has not been typically considered in other studies on TMDs approached from the biopsychosocial model point of view (Fillingim et al., 2011; Slade et al., 2016a,2016b; NASEM, 2020). However, it was an essential inclusion criterion in this trial, as teeth are major agents of mastication; this was a crucial aspect of this study. The results of this trial should not be extrapolated to patients with different dental conditions.

Two participants required further readjustment after the trial; both had severe nasal obstruction. Nasal obstruction is a risk for TMDs (Slade et al., 2016a,2016b) and should be explored during the diagnosis of TMDs and, until corrected by a specialist, should be an exclusion criterion in future TMD clinical trials.

4.4. Future directions

Pragmatic clinical trials are needed to determine the efficiency of ET in a more generalized context. Prospective studies should investigate whether a cause-effect relationship exists between the asymmetry of the LGAs, a common side of chewing, and TMDs. Due to ethical concerns (“do no harm”) and to avoid inadequate irreversible grinding, ET therapy should be administered by experienced clinicians.

5. Conclusions

In comparison with a sham-placebo, the real therapy ET was more effective in treating chronic orofacial pain (with a diagnosis of TMD) and improving maximum unassisted mouth opening over a six-month period.

Ethical statement

The study was approved by the Autonomic Research Ethics Committee of Galicia: CAEI approval number 2009/017; updated on November 29, 2013. Informed consent was obtained during each screening visit to perform the diagnostic procedures. All methods were performed in accordance with the Declaration of Helsinki. Information presented here is consistent with the consent obtained.

CRediT authorship contribution statement

Urbano Santana-Penín: Conceptualization, Funding acquisition, Investigation, Writing - Original draft. **Urbano Santana-Mora:** Conceptualization, Methodology, Investigation, Writing - Original draft. **Alicia López-Solache**: Methodology, Data curation, Visualization. **María J. Mora**: Conceptualization, Methodology, Funding acquisition, Resources, Validation, Visualization. **Tymoti Collier:** Formal analysis. **Stuart Pocock:** Formal analysis. **Fernanda Lorenzo-Franco**: Investigation. **Pablo Varela Centelles**: Methodology, Investigation, Supervision, **José López-Cedrún:** Conceptualization, Methodology, Funding acquisition, Investigation, Resources, Project administration. All of the authors reviewed the manuscript for important intellectual content. The corresponding author had full access to all the data in the study and takes responsibility for the integrity and transparency of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data Availability

Data citation 1. Urbano Santana et al. Composite pictures from the two study groups of the MAP Trial. Figshare 2020. https://doi.org/10.6084/m9.figshare.13107953.v1. Data citation 2. Urbano Santana-Penin et al. Dryad Digital Repository 2022. MAP Trial raw data. https://doi.org/10.5061/dryad.zkh189370.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Compliance with ethics requirements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Informed consent was obtained from all patients included in the study.

Transparency statement

The manuscript’s guarantor (U. S-P) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any deviations from the study as originally planned (and, if relevant, registered) have been explained.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.aanat.2023.152117.

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