Study Protocol and Statistical Analysis Plan

ClinicalTrials.gov Study Document

Official Title: Comparative Evaluation of Occlusal Splint Therapy, Botulinum Toxin Type A Injection, and Combined Medical-Splint Therapy in Bruxism-Related Temporomandibular Disorder Symptoms: A Prospective Non-Randomized Open-Label Controlled Trial

Brief Title: Occlusal Splint, Botulinum Toxin Type A, and Medical-Splint Therapy for Bruxism-Related TMD Symptoms

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Study Setting: Department of Prosthodontics, Faculty of Dentistry, Recep Tayyip Erdogan University, Rize, Türkiye

This document summarizes the study protocol and statistical analysis plan for the above ClinicalTrials.gov record. No names or identifying information of research participants are included.

Study Protocol

1. Background and rationale

Bruxism-related temporomandibular disorder (TMD) symptoms may include masticatory muscle pain, restricted mandibular function, joint sounds, and parafunctional tooth contact. Conservative and minimally invasive treatment options include occlusal splint therapy, botulinum toxin type A injection, and combined conservative approaches. Comparative clinical data evaluating these treatment modalities within the same study framework remain limited.

2. Objectives

The primary objective of this study was to compare the 3-month treatment outcomes of occlusal splint therapy, botulinum toxin type A injection, and combined medical-splint therapy in patients with bruxism-related TMD symptoms. Treatment response was assessed using changes in the Fonseca Anamnestic Index (FAI) score from baseline to the 3-month follow-up.

3. Study design

This study was designed as a 3-month prospective, non-randomized, open-label, controlled, parallel-arm clinical trial. Participants were assigned to one of three active treatment arms according to clinical indication, symptom profile, shared decision-making, and patient preference. Because of the nature of the interventions, blinding of participants and clinicians was not feasible.

4. Study setting

The study was conducted at the Department of Prosthodontics, Faculty of Dentistry, Recep Tayyip Erdogan University, Rize, Türkiye.

5. Sample size

An a priori sample size calculation was performed using G*Power software. The calculation was planned for a three-arm comparison of treatment response, with total FAI change score defined as the primary outcome. Assuming a medium effect size, an alpha error probability of 0.05, statistical power of 80%, and three parallel treatment arms of equal size, the minimum required sample size was estimated as 60 participants in total, corresponding to 20 participants per arm.

6. Eligibility criteria

Inclusion criteria

- Adults aged 18 years or older.
- Presence of bruxism-related temporomandibular disorder symptoms.
- Self-reported sleep or awake bruxism based on clenching or grinding awareness.
- Clinical signs compatible with bruxism, including dental attrition, cupped-out wear facets, or shiny occlusal surfaces.
- Absence of known systemic conditions that could interfere with treatment or outcome assessment.
- Ability to provide written informed consent.

Exclusion criteria

- Age younger than 18 years.
- Presence of systemic or neurological disorders.
- Uncontrolled psychiatric conditions.
- Infection or inflammatory lesions at the planned injection sites.
- History of maxillofacial surgery or severe trauma in the relevant orofacial region.
- Inability or unwillingness to provide written informed consent.

7. Treatment arm assignment

After baseline clinical examination and eligibility assessment, participants were assigned to one of three parallel treatment arms: occlusal splint therapy, botulinum toxin type A injection, or combined medical-splint therapy. Treatment assignment was non-randomized and based on clinical indication, symptom profile, shared decision-making, and patient preference.

- Participants with pronounced occlusal wear and parafunctional tooth contact were assigned to the occlusal splint therapy arm.
- Participants with marked masticatory muscle hyperactivity, masseter hypertrophy, or restricted opening associated with muscle overactivity were assigned to the botulinum toxin type A injection arm.
- Participants with diffuse myofascial pain requiring short-term symptom control in addition to occlusal stabilization were assigned to the combined medical-splint therapy arm.

8. Interventions

Arm 1: Occlusal splint therapy

Participants received custom-made maxillary stabilization splints. Hard acrylic splints were adjusted to obtain simultaneous bilateral posterior contacts in centric relation and canine guidance during eccentric movements. Participants were instructed to wear the splints during sleep for at least eight hours per night during the follow-up period.

Arm 2: Botulinum toxin type A injection

Participants received a single session of intramuscular botulinum toxin type A injections. Dysport was reconstituted with 2 mL of sterile 0.9% saline immediately before injection. A total dose of 160 U Dysport was administered per participant, consisting of 60 U into each masseter muscle and 20 U into each temporalis muscle. Injections were performed intramuscularly under aseptic conditions using a standardized protocol.

Arm 3: Combined medical-splint therapy

Participants received a custom-made maxillary stabilization splint using the same design and adjustment protocol as the occlusal splint therapy arm. In addition, a short-term pharmacological regimen consisting of thiocolchicoside 8 mg/day and tenoxicam 20 mg/day was prescribed for 7 to 10 days for acute symptom control. Participants continued nocturnal splint use during the follow-up period.

9. Outcome measures

Primary outcome

The primary outcome was the change in total Fonseca Anamnestic Index score from baseline to the 3-month follow-up. The FAI is a 10-item symptom-based questionnaire used to assess TMD-related symptom severity. Total scores range from 0 to 100, with higher scores indicating more severe symptoms. Change was calculated as pre-treatment total score minus post-treatment total score; therefore, higher positive change values indicate greater symptom improvement.

Secondary outcomes

- Change in selected FAI sub-item scores from baseline to the 3-month follow-up. Selected items assessed mouth opening difficulty, masticatory muscle fatigue or pain during chewing, temporomandibular joint clicking, and teeth clenching or grinding habit. Each selected item is scored from 0 to 10, with higher scores indicating more severe symptoms.
- Change in FAI severity category from baseline to the 3-month follow-up. Total FAI scores were categorized as absence of symptoms (0-15), mild symptoms (20-40), moderate symptoms (45-65), or severe symptoms (70-100).
- Treatment-related adverse events during the 3-month follow-up period.

10. Follow-up schedule

The FAI was administered at baseline before treatment and at the 3-month follow-up. Adverse events were monitored during the follow-up period. The 3-month follow-up was selected to evaluate early clinical response and to allow sufficient time for neuromuscular adaptation to splint therapy and for the expected clinical effect of botulinum toxin type A.

11. Safety monitoring

Participants were questioned about possible adverse events associated with each intervention, including injection-site pain, bruising, chewing weakness, facial asymmetry, dysphagia, or other local symptoms after botulinum toxin type A injection; gastrointestinal symptoms, dizziness, or drug-related intolerance after pharmacological treatment; and discomfort, mucosal irritation, or occlusal changes associated with splint use. Serious adverse events were defined as events requiring urgent medical care, hospitalization, treatment discontinuation, or resulting in persistent functional impairment.

12. Ethical considerations and consent

The study protocol was approved by the Institutional Ethics Committee of Recep Tayyip Erdogan University (Date: July 18, 2024; Approval No: 2024/194). The study was performed in accordance with the principles of the Declaration of Helsinki. All participants received written and verbal information about the study procedures, treatment options, and potential risks, and written informed consent was obtained before treatment.

Statistical Analysis Plan

1. Analysis population

The analysis population included all enrolled participants who were assigned to a treatment arm and had available baseline and 3-month follow-up data for the relevant outcome. Participants were analyzed according to the treatment arm to which they were assigned. No imputation of missing data was planned.

2. Descriptive statistics

Continuous variables were summarized as mean ± standard deviation or median (minimum-maximum), as appropriate. Categorical variables were summarized as number and percentage.

3. Assumption checks

The normality of continuous variables was assessed using the Shapiro-Wilk test. Homogeneity of variances was evaluated using Levene's test.

4. Within-arm comparisons

Within-arm pre- and post-treatment comparisons were performed using paired samples t-tests or Wilcoxon signed-rank tests depending on data distribution and measurement level. Because selected FAI sub-item scores and FAI severity categories were ordinal, Wilcoxon signed-rank tests were used for their intra-arm comparisons.

5. Between-arm comparisons

Between-arm comparisons of baseline scores, post-treatment scores, and change scores were performed using one-way analysis of variance. Change scores were calculated as pre-treatment score minus post-treatment score. Bonferroni-corrected post-hoc tests were used for pairwise comparisons when the overall test was significant. Sex distribution was compared using the Pearson chi-square test.

6. Effect size estimation

Effect sizes were reported using Cohen's d for pairwise comparisons and eta-squared (η^2) for analysis of variance. For Wilcoxon signed-rank tests, r was used as the effect size measure.

7. Longitudinal adjusted analysis

A Generalized Estimating Equations (GEE) model was used to account for repeated measurements within participants and to adjust for age and sex. The model included time, treatment group, time-by-treatment interaction terms, age, and sex as predictors. A Gaussian distribution with an identity link function and an exchangeable working correlation structure was used. Robust standard errors were reported.

8. Statistical significance

A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 27.0.

9. Adverse event analysis

Treatment-related adverse events were summarized descriptively by treatment arm. Serious adverse events were tabulated separately if observed.