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The Impact of botulinum toxin type A for facial aesthetics on psychological stress and periodontal disease therapy

Submission date 14/04/2025	**Recruitment status** Not yet recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 15/04/2025	**Overall study status** Ongoing	
Last Edited 14/04/2025	**Condition category** Oral Health	

Plain English summary of protocol

Background and study aims
Periodontitis (“gum disease”) is a chronic inflammatory disease of the supporting structure of teeth and the main cause of adult tooth loss, with negative impact on the quality of life (QoL). Approximately 20 to 50 % of the worldwide population suffers from periodontal disease, and the risk of developing this disease is increased with ageing and an inefficient immune response. In addition, psychological-stress and negative mood are also significantly associated to the aggravation of the disease. Generally, periodontitis, ageing, stress, and immune system are interconnected, and overall leading to an increase of inflammation mediators. In order to retain the teeth and delay the signs of ageing appearance, the ageing population often combines nonsurgical periodontitis treatment (NSPT) and procedures to improve facial aesthetics. Botulinum toxin type A (BoNTA) has been used in facial rejuvenation, and it has been linked to an improvement in the QoL. The mechanisms behind BoNTA actions remain poorly studied, but the power of BoNTA highlights the importance of clarifying what happens when we inject BoNTA for facial aesthetics in patients suffering from periodontal disease and receiving standard treatment. This study will describe for the first time the biological, psychological and clinical effects of combining NSPT and the popular BoNTA for facial aesthetics, or a placebo.

Who can participate?
Female participants, between 18 and 65 years old, with upper face expression wrinkles, suffering from periodontitis stage II who attend Egas Moniz University dental clinic in Portugal.

What does the study involve?
Participants will be allocated to one of two groups. Those in the first group will undergo NSPT and BoNTA intramuscular injections into the upper face. Those in the second group will receive NSPT and saline solution injections mimicking BoNTA treatment.
The study will last 6-weeks in total and participants will be monitored after treatment, 2-weeks (remotely) and 4-weeks (on-site).
Participants will be asked to give blood, saliva and gingival crevicular fluid (GCF) samples at the

beginning and at the end of the study (before and 4-weeks after the treatment) to test for inflammation biomarkers and stress hormones. Participants will also complete questionnaires and clinical assessments during the study period.

What are the possible benefits and risks of participating?
There will be direct benefit to oral health and facial aesthetics to those taking part. The results of this study will explore the role of BoNTA in the Dentistry field, considering the impact that such interventions can have to people´s QoL, which may improve dentists and patient´s choices. It may improve our knowledge on how drugs may influence inflammatory processes and consequently impact on periodontitis standard therapies and potentially antibiotic prescribing practices.
Possible risks and adverse effects may occur, although they tend to be mild in severity, self-limited and often avoidable, mostly related to BoNTA injection and local events such as pain, bruise, oedema, inflammation, infection, bleeding, swelling, asymmetry, drooping of the brow or eyelid, headache, allergies. Regarding NSPT, it may temporarily increase tooth sensitivity and mobility, gum bleeding or inflammation. To note that phlebotomy procedures is an invasive procedure, but none of these will not have any negative effect on general health.

Where is the study run from?
The study is being run by the Faculty of Dental Medicine, University of Porto (FMDUP) and Egas Moniz Center for Interdisciplinary Research (CiiEM); Egas Moniz School of Health & Science and will take place in Egas Moniz University dental clinic.

When is the study starting and how long is it expected to run for?
January 2022 to October 2028

Who is funding the study?
The Foundation for Science and Technology (FCT), Faculty of Dental Medicine, University of Porto (FMDUP), Egas Moniz Center for Interdisciplinary Research (CiiEM); Egas Moniz School of Health & Science (Portugal).

Who is the main contact?
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Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
The Foundation for Science and Technology (FCT) Doctoral Scholarship: 2023.00543.BD; Ethics committee Egas Moniz: 1524

Study information

Scientific Title
The Impact of botulinum toxin type A for facial aesthetics on psychological stress, periodontal inflammation and periodontal disease therapy – a prospective clinical trial

Acronym
BBToxPP

Study objectives
Clinical dilemma: if the nonsurgical periodontitis treatment (NSPT) provided simultaneously with botulinum toxin type A (BoNTA) aesthetic intervention into the upper face leads to non inferior results as NSPT with a placebo. We hypothesised that such approach may have no significant deleterious results and may even enhance aesthetic outcomes, patient-reported outcome measurements and localised chronic inflammation with potential traceable anti-inflammatory levels and stress biomarkers.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 18/12/2024, Egas Moniz Ethics Committee (Egas Moniz Center for Interdisciplinary Research (CiiEM); Egas Moniz School of Health & Science, Campus Universitário, Quinta da Granja, 2829-511 Caparica, Almada, Portugal, Almada, 2829-511, Portugal; +351 212 946 700; egasmoniz@egasmoniz.edu.pt), ref: 1524

Study design
Single-centre double-blind 6-week parallel-group non-inferiority randomized controlled trial

Primary study design
Interventional

Study type(s)
Quality of life, Treatment

Health condition(s) or problem(s) studied
Periodontal disease/periodontitis stage II

Interventions
Participants will be randomly assigned to one of the following groups: (i) treatment or (ii) control-placebo group:
Single session for the administration of (i) BoNTA or (ii) saline solution (0.9% NaCL) intramuscular injections into frontalis, corrugator, and orbicularis oculi muscles, both combined with NSPT (1st phase and 2nd phase), consisting of oral hygiene instructions and risk factors control, professional mechanical plaque removal (PMPR) and subgingival instrumentation of disease sites with periodontal pocket depth (PPD) ≥ 4mm, with hand or ultrasonic instruments, under local anaesthesia. The administration of BoNTA and placebo starts immediately after the NSPT 2nd phase session.

Randomization will be performed using an internet randomizer. To ensure balanced group sizes, the method to be used is permuted blocks with stratification on participants characteristics capable to interfere with periodontal treatment such as sex, grade modifiers (smoking and diabetes type II) and control of oral hygiene. Participants will be randomly assigned by a third-party at a 1:1 ratio to 1 of the 2 arms of the study. The treatment for each patient will be recorded and placed in a sealed opaque envelope. The participants, investigators, and healthcare team will be blind to the allocation sequence. Allocation concealment will be ensured, as the person who generates the allocation sequence will not determine eligibility and entry of patients. Therefore, another researcher, will open the sealed envelope, and prepare the syringes according to the subject's distribution.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Botulinum toxin type A (BoNTA)

Primary outcome(s)
Bleeding on probing (BOP) and periodontal pocket depth (PPD) measurements, at baseline and 4 weeks post-treatment, which will allow to evaluate the difference among groups for the percentage of volunteers achieving a stable treatment response (whole mouth BOP<10%, PPD ≤4mm and no BOP), in remission (whole mouth BOP>10%, PPD ≤4mm and no BOP), or unstable response (PPD ≥ 5mm, or ≥ 4mm and presence of BOP).

Key secondary outcome(s))
1. Post-operative change in global levels of inflammation, neurogenic inflammation and periodontal inflammation, through inflammatory mediators' biomarkers, 2 weeks after baseline and 4 weeks following intervention:
1.1. Collected from saliva – cytokines IL-6, IL-1β, TNF-α
1.2. Collected from gingival crevicular fluid (GCF) - IL-6, IL-1β, TNF-α
1.3. Collected from blood/systemic - C-reactive protein (CRP) and calcitonin gene-related peptide (CGRP).
2. Psychological-stress levels measured at baseline or 2 weeks after baseline and 4 weeks following intervention:

2.1. Collected from saliva - cortisol and dehydroepiandrosterone (DHEA) levels (2weeks after baseline and 4 weeks after intervention)
2.2. Portuguese validated version of Perceived Self Stress Scale (PSS) (baseline and 4 weeks after intervention)
2.3. Portuguese version validated FACE-Q scales (baseline and 4 weeks after intervention)
3. Periodontal tissues clinical parameters measured by calibrated examiners at baseline and 4 weeks following intervention:
3.1. full mouth bleeding score (FMBS) - The % FMBS score will be measured by the number of surfaces positive for BS X 100 divided by the total number of teeth X 4.
3.2. full mouth plaque score (FMPS) – The % FMPS score will be measured by the number of surfaces positive for PS X 100 divided by the total number of teeth X 4.
3.3. clinical attachment level (CAL) - measured with probe in millimeters (probing pocket-depth (PPD) plus distance from top gingival margin to Cemento Enamel Junction (CEJ) [+, - or =])
3.4. radiographic parameters.
4. Skin objective analysis: change in wrinkles, furrows, folds, and creases assessed with 2D/3D imaging skin analysis, measured at baseline and 4 weeks following intervention.
5. Changes in patient reported outcome measurements (PROMs) measured at baseline and 4 weeks following intervention with Portuguese validated versions of:
5.1. Perceived Self Stress Scale (PSS)-10
5.2. Oral Health Impact Profile 14 (OHIP-14-PT)
5.3. Oral health-related quality of life (EuroQoL-5D)
5.4. FACE-Q scales.

Completion date
01/11/2027

Eligibility

Key inclusion criteria
1. Systemically healthy
2. females
3. ≥ 18 years old and < 65 years of age
4. Psychologically healthy individuals
5. with desire to improve facial aesthetics
6. Naïve to BoNTA.
7. Willingness to read and sign a copy of the Informed Consent Form after reading the Patient Information Sheet, and after the nature of the study has been fully explained.
8. Clinical evidence of periodontitis (STAGE-II): Radiograph bone loss (coronal third – 15-33%), at least with one interdental area of periodontal pocket depth (PPD) ≤ 5 mm, bleeding on probing (BOP), and attachment loss (CAL) 3-4 mm, in any area of their mouth (excluding third molars and distal of second molars).
9. Clinical evidence of upper face hyperdynamic lines, GLOGAU scale I-IV.
10. Full mouth (marginal) bleeding and plaque scores (FMBS and FMPS) – no restrictions.
11. No non-surgical periodontal treatment or facial aesthetic interventions completed within 6 months prior to assessment for eligibility.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
65 years

Sex
Female

Key exclusion criteria
1. Medical history that includes diabetes type 1 or hepatic or renal disease, or other serious medical conditions (e.g., Compromise respiratory function, neuromuscular disorders) or transmittable diseases (e.g. cardiovascular disease or AIDS).
2. Antibiotic or anti-inflammatory therapy during the month preceding the baseline exam.
3. Calcium channel blockers, anticholinergic, cyclosporine, aminoglycosides, or any drug that can interfere with neuromuscular transmission.
4. Chronic treatment (>2 weeks) with anticoagulants, corticosteroids or other medications that can severely impact on bone formation.
5. History of alcohol or drug abuse.
6. Smoking ≥10 cigarettes a day.
7. Self-reported pregnancy or lactation.
8. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or product administration or may interfere with the interpretation of trial results and, in the judgement of the investigator, would make the subject inappropriate for entry into this trial.
9. Patients with known hypersensitivity to Botulinum Toxin or any constituents of the commercially available formulations, including reconstitution diluent.
10. Presence of active infection at the injection-site.
11. Clinical evidence of STAGE-I, III, IV periodontitis.

Date of first enrolment
01/05/2026

Date of final enrolment
01/11/2026

Locations

Countries of recruitment
Portugal

Study participating centre
Egas Moniz Center for Interdisciplinary Research (CiiEM); Egas Moniz School of Health & Science
Campus Universitário, Quinta da Granja
Almada

Portugal
2829-511

Sponsor information

Organisation
Universidade do Porto

ROR
https://ror.org/043pwc612

Organisation
Egas Moniz Center for Interdisciplinary Research (CiiEM); Egas Moniz School of Health & Science

Funder(s)

Funder type
Government

Funder Name
Fundação para a Ciência e a Tecnologia (FCT)

Funder Name
Faculty of Dental Medicine, University of Porto

Funder Name
Egas Moniz Center for Interdisciplinary Research (CiiEM); Egas Moniz School of Health & Science

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes