

# INPLASY PROTOCOL

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**Review Stage at time of this submission:** Data analysis.

**Conflicts of interest:**  
The authors declare that they have no conflicts interest.

## Does enamel matrix derivate application provide additional clinical benefits in the treatment of upper gingival recessions Class I and II of Miller? A systematic review and meta-analysis

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**Review question / Objective:** Focus Question - In the surgical treatment of patients with Miller Class I and II or Cairo type I gingival recessions in upper teeth, which is the efficacy of the association of EMD with CAF+CTG or with CAF in comparison with CAF+ CTG or CAF alone, in terms of GR reduction, in randomized clinical trials? PICO - Population: Patients with Miller Class I and II or Cairo type I gingival recessions in upper teeth; Intervention: Root coverage procedure with the adjunctive use of EMD with CTG or CAF; Comparison: Root coverage procedures with CAF + CTG + EMD or CAF + EMD vs CAF + CTG or CAF alone; Outcome: GR reduction (primary outcome variable), CAL gain and KTW gain (secondary variables) at 6 and 12 months. Study design: Randomized clinical trials.

**Condition being studied:** Gingival recession (GR) is pathological apical shift of the gingival margin, exposing the root surface. The GR can be caused by intrasulcular restorative/prosthetic cervical margin placement, orthodontic treatment and strong evidences shows that an improper tooth brushing may lead to a buccal GR. Some of the injury caused by the GR are, hypersensitivity, esthetical loses in smile, root caries, and disharmony of gingival margin.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 October 2020 and was last updated on 14 October 2020 (registration number INPLASY2020100048).

### INTRODUCTION

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patients with Miller Class I and II or Cairo type I gingival recessions in upper teeth, which is the efficacy of the association of EMD with CAF+CTG or with CAF in

comparison with CAF+ CTG or CAF alone, in terms of GR reduction, in randomized clinical trials? PICO - Population: Patients with Miller Class I and II or Cairo type I gingival recessions in upper teeth; Intervention: Root coverage procedure with the adjunctive use of EMD with CTG or CAF; Comparison: Root coverage procedures with CAF + CTG + EMD or CAF + EMD vs CAF + CTG or CAF alone; Outcome: GR reduction (primary outcome variable), CAL gain and KTW gain (secondary variables) at 6 and 12 months. Study design: Randomized clinical trials.

**Rationale:** To the best of our knowledge, this is the first systematic review to report the use of EMD in upper teeth. In our review we only choose studies that evaluated the use of EMD in patients with Miller Class I and II or Cairo type I gingival recessions in upper teeth. Due, that maxillary teeth show significantly greater mean root coverage and complete root coverage than teeth in the mandible.

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## METHODS

**Search strategy:** Medline (Pubmed) (((“Gingival recession” OR Recession OR “Gingival atrophy” OR “Periodontal atrophies” OR “Gingival atrophies” OR “Root coverage” OR “Root cover” OR “Surgical flaps” OR “Gingival surgery” OR “Periodontal plastic surgery” OR “Mucogingival surgery” OR “Coronally advanced flap” OR “Periodontal surgery” OR "gingival graf" OR "connective tissue graft") AND (“Enamel matrix derivate” OR EMDOGAIN OR amelogenin OR “Dental Enamel Proteins” OR EMD))) EMBASE

(((“Gingival recession” OR Recession OR “Gingival atrophy” OR “Periodontal atrophies” OR “Gingival atrophies” OR “Root coverage” OR “Root cover” OR “Surgical flaps” OR “Gingival surgery” OR “Periodontal plastic surgery” OR “Mucogingival surgery” OR “Coronally advanced flap” OR “Periodontal surgery” OR "gingival graft" OR "connective tissue graft") AND (“Enamel matrix derivative” OR EMDOGAIN OR amelogenin OR “Dental Enamel Proteins” OR EMD))) Scopus ( "Gingival recession" OR recession OR "Gingival atrophy" OR "Periodontal atrophies" OR "Gingival atrophies" OR "Root coverage" OR "Root cover" OR "Surgical flaps" OR "Gingival surgery" OR "Periodontal plastic surgery" OR "Mucogingival surgery" OR "Coronally advanced flap" OR "Periodontal surgery" OR "gingival graft" OR "connective tissue graft" ) AND ( "Enamel matrix derivative" OR emdogain OR amelogenin OR "Dental Enamel Proteins" OR emd ) AND ( trial OR trials ) Web of science (((“Gingival recession” OR Recession OR “Gingival atrophy” OR “Periodontal atrophies” OR “Gingival atrophies” OR “Root coverage” OR “Root cover” OR “Surgical flaps” OR “Gingival surgery” OR “Periodontal plastic surgery” OR “Mucogingival surgery” OR “Coronally advanced flap” OR “Periodontal surgery” OR "gingival graft" OR "connective tissue graft") AND (“Enamel matrix derivative” OR EMDOGAIN OR amelogenin OR “Dental Enamel Proteins” OR EMD))).

**Participant or population:** Patients with Miller Class I and II or Cairo type I gingival recessions in upper teeth.

**Intervention:** Root coverage procedure with the adjunctive use of enamel matrix derivate (EMD) with connective tissue graft (CTG) or coronally advanced flap (CAF).

**Comparator:** CAF + CTG + EMD or CAF + EMD vs CAF + CTG or CAF alone.

**Study designs to be included:** Randomized clinical trials.

**Eligibility criteria:** Randomized clinical trial that included individuals without systemic diseases with at least 6 months of follow up.

**Information sources:** The grey literature in the System for Information on Grey Literature in Europe (<http://www.opengrey.eu>) and The New York Academy of Medicine Grey Literature Report (<http://www.greylit.org>) were screened electronically, as recommended by the high standards for systematic reviews (AMSTAR guideline).

**Main outcome(s):** GR reduction - CAF+EMD versus CAF - At 6 months, the random effects meta-analyses showed a GR reduction favoring CAF + EMD (MD = -0.29; 95% CI -0.54 – -0.04; p-value=0.02), showing low heterogeneity (Q test p-value=0.03; I<sup>2</sup> = 40%). A sensitivity analysis was conducted to test the robustness of estimation, excluding a concern study because of the presence of tobacco as effect modifier. It was observed a statistical significant trend for better RG favoring CAF+EMD group still remains (MD= -0.33; 95% CI -0.59 – -0.06; p-value=0.02), in a context of low heterogeneity (Q test p value=0.27; I<sup>2</sup>=40%); CTG+EMD versus CTG - At 12 months, the random effects meta-analyses did not show differences in GR reduction between the groups (MD = -0.27; 95% CI -0.97 – 0.44; p-value=0.46), showing high heterogeneity (Q test p-value=0.02; I<sup>2</sup> = 69.56%). A sensitivity analysis was conducted to test the robustness of estimation and to explore sources of high heterogeneity, excluding a study because of the presence of tobacco as effect modifier. It was observed a statistical significant trend for better RG favoring CTG+EMD comparison (MD=-0.66; 95% CI -1.14 – -0.18; p-value=0.01). This findings are observed in a context of low heterogeneity (Q test p value=0.81; I<sup>2</sup>=0.18%).

**Quality assessment / Risk of bias analysis:** Two reviewers appraised the risk of bias on the selected studies using the Cochrane risk-of-bias tool, RoB 2 (version 2, available at: <https://www.riskofbias.info/welcome/>

rob-2-0-tool/current-version-of-rob-2). Cases of disagreement were solved by a third reviewer. The authors from this systematic review decided to access the result related to “assignment to intervention (the intention to treat effect)” and five domains were examined: bias from the randomization and allocation concealment process, bias due to deviations from intended interventions that involve masking of participants and researchers team, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Based on the responses to signaling questions and algorithms from this tool, we will judge each domain to be “low risk of bias”, “some concerns relating to the risk of bias” or “high risk of bias”. Studies have been categorized as being at low risk of bias (all domains were at low risk of bias), high risk of bias (one or more domains were at high risk of bias), some concerns (if one or more domains have some concerns).

**Strategy of data synthesis:** Statistical data handling was performed by one author. Random-effects meta-analyses are conducted at 6- and 12-months follow-up. Forest plots were created to illustrate the effects of the meta-analyses results. The effect size between test and control groups are summarized as mean differences (MD) in millimeters, and its respective 95% confidence intervals (CI). The results of mucogingival surgery procedures might be affected by either clinical (age, sex, surgery, clinical expertise, etc.) and methodological aspects inherent to clinical trials conduction. A Sidik-Jonkman (Hartung- Knapp- Sidik- Jonkman) random-effects model is carried out because provides adequate type I error rates and is more robust to changes in the heterogeneity variance estimates, especially in meta-analyses that contain few studies. Between-study heterogeneity was visually inspected in the forest plots and by calculating the  $\tau^2$  (absolute heterogeneity) and the I<sup>2</sup> statistics (relative heterogeneity) and the corresponding nullity statistical Q-test were calculated. The I<sup>2</sup> index defines the proportion of total

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variability in the result explained by heterogeneity, but not chance. Heterogeneity was roughly categorized as low, moderate, and high to I2 values of 25%, 50%, and 75%. Publication bias was investigated by visual inspection of the funnel plot; The Egger test is conducted in datasets having at least 10 studies. In the case of high heterogeneity, a sensitivity analysis is conducted to sought high heterogeneity sources and test the robustness of estimations against potential risk populations (e.g. smokers). A two-sided level of significance of 5% ( $\alpha=0.05$ ) was established. The Stata/SE version 16.1 for Mac (StataCorp LP, College Station, TX, USA) was used for quantitative synthesis.

**Subgroup analysis:** Subgroup analysis was not performed.

**Sensibility analysis:** In the case of high heterogeneity, a sensitivity analysis is conducted to sought high heterogeneity sources and test the robustness of estimations against potential risk populations (e.g. smokers). A two-sided level of significance of 5% ( $\alpha=0.05$ ) was established.

**Country(ies) involved:** Brazil and Spain.

**Keywords:** Connective tissue graft; Enamel matrix derivate; Gingival recession, Meta-analyses.

**Contributions of each author:**

**Author 1 - Jonathan Meza-Mauricio -** Performed the search in the database, data collection, evaluated the risk of bias of included studies and drafted the manuscript.

**Author 2 - Camila Pinheiro Furquim -** Performed the search in the database, data collection, evaluated the risk of bias of included studies and drafted the manuscript.

**Author 3 - Willy Bustillos -** Selection of included papers.

**Author 4 - David Soto-Peñaloza -** Performed statistical data handling and drafted the manuscript.

**Author 5 - David Peñarrocha-Oltra -** Evaluated the risk of bias of included studies and drafted the manuscript.

**Author 6 - Belen Retamal-Valdes -** Performed the data collection, writing review and editing of the current manuscript.

**Author 7 - Marcelo Faveri -** Selection of included papers, writing review and editing of the current manuscript.