CLINICAL TRIAL PROTOCOL

STUDY NUMBER: Fibro-Gide

STUDY TITLE: Treatment of multiple gingival recession defects with a coronally advanced flap or a modified tunnel technique and a volume stable three-dimensional xenogenic collagen matrix: a monocentric randomized clinical trial.

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1. SYNOPSIS

TITLE	Treatment of multiple gingival recession defects with a coronally advanced flap or a modified tunnel technique and a volume stable three-dimensional xenogenic collagen matrix: a monocentric randomized clinical trial.
TRIAL LOCATION	**PI**: Prof. Massimo de Sanctis Dipartimento di Odontoiatria – Ospedale San Raffaele Direttore: Prof. Enrico Felice Gherlone
STUDY OBJECTIVES	To compare the outcomes of two muco-gingival surgery techniques, the modified coronally advanced flap (MCAF) for multiple recession defects (Zucchelli & de Sanctis 2000) and the modified coronally advanced tunnel technique (MCAT) (Aroca 2013), performed in the Department of Periodontology of San Raffaele Hospital with the results reported in the literature. Secondarily, the study will evaluate whether patients report a preference in terms of discomfort and perception of aesthetics between the two surgical techniques.
STUDY DESIGN	Single center, National study, Comparative, Randomized, Open label
STUDY POPULATION	**Main selection criteria:** patients requiring root coverage procedures from the Dental Clinic of San Raffaele Vita-Salute University will be enrolled in the study. **Inclusion criteria**: multiple (i.e., at least 2) Miller Class I and/or II gingival recessions located in the maxillae, good general health, healthy periodontal conditions (FMPS and FMBS <25%). **Exclusion criteria**: smoking >10 cigarettes/day, nursing and pregnant female, contraindication against oral surgical interventions and against use of Fibro-Gide **Total expected number of patients**: 36 (18 for each group)
STUDY PROCEDURES	Recessions will be randomly treated by means of MCAF + CM or MCAT technique + CM. The following measurements will be recorded at baseline (prior to surgery), at 90, 180 and 360 days: Gingival recession depth (REC in mm), Keratinized tissue width (KTW in mm), Gingival thickness (GT in mm), Pocket probing depth (PPD in mm), BoP (Bleeding on Probing, PI (Plaque Index).
STUDY DEVICE	Fibro-Gide
STATISTICAL CONSIDERATIONS	**Hypothesis tested**: no statistically significant differences are observed with respect to the clinical parameters CRC, at 12 months between the two treatment modalities (i.e., MCAF + CM or MCAT technique with CM). **Sample size calculation**: the needed number of patients to be enrolled in this study is 17 for the test group MCAF + Fibro-Gide and 17 for the MCAT + Fibro-Gide. However, the number of patients will be increased of 1 patient for each arm considering the possibility of dropout, so the required number will be 18 for each group. **Primary method of analysis**: the significance of the difference within each group and between groups before and after treatment will be evaluated with the paired samples t-test or two independent samples t-test, as appropriated, regarding all numerical data (REC, KTW, GT, PPD, percentage of root coverage and VAS scale). Fisher's exact test will be applied for categorical data (frequency of complete root coverage). Differences will be considered statistically significant when the p-value was <0.05.
DURATION OF STUDY PERIOD	**Global**: 2 years **Per patient**: 1 years

2. FLOW-CHART

	Screening phase	Study phase						End of study
Evaluation	**Screening**	**Surgery**	**Post treatment follow-up**					
		Day 0	**Day 7±2**	**Day 14±4**	**Day 30±7**	**Day 90±15**	**Day 180±30**	**Day 360±60**
Demographic data	X							
Inclusion/Exclusion criteria	X							
Previous medical history	X							
Informed consent	X							
Clinical examination	X							
PPD, BoP, PI	X					X	X	X
REC, KTW, GT	X					X	X	X
Oral hygiene instructions	X	X		X				
Treatment								
Randomization		X						
Mucogingival surgery		X						
Use of Fibro-Gide		X						
Compliance			X	X	X	X	X	X
Suture removal				X				
Photography		X	X	X	X	X	X	X
Pain assessment (VAS)			X					

3. INTRODUCTION AND RATIONALE

Gingival recession is defined as the exposure of the root surface due to the displacement of the gingival margin apical to the cement-enamel junction (CEJ) (Armitage 1999; Wennstrom 1996). It was estimated that >20% of the population presents one or more tooth surfaces exhibiting recessions (Albandar and Kingman,1999). The development of gingival recessions can often be associated with mechanical factors (trauma caused by excessive tooth brushing, orthodontic therapy or piercing), or inflammatory periodontal disease (Graziani 2014). The exposed root surfaces are frequently associated with esthetic complaints, root hypersensitivity and difficulties in achieving optimal plaque control (Cairo 2017).

The progression of gingival recessions should be evaluated in individuals with a high level of plaque control (Matas 2011).

Furthermore, a recent systematic review assessed the prognosis of untreated gingival recessions and found that only 21.9% of sites with gingival recession at baseline did not increase in recession severity during a 2-year follow-up period, and that 79.3% of patients showed an increase in the number of recession defects (Cairo 2017; Chambrone 2016).

Results from systematic reviews indicate that at single Miller (Miller, 1985) Class I and II gingival recessions complete root coverage (CRC) can predictably be obtained when using the modified coronally advanced flap (MCAF) technique, with and without soft tissue grafting and/or biologic agents, such as an enamel matrix derivative (Cairo 2014; Chambrone 2010).

On the other hand, the treatment of multiple gingival recessions appears to be more challenging for the clinician and due to limited evidence, no recommendation can be made to support the selection of one technique over another (Tonetti 2014); but modified CAF and tunnel approaches show higher level of complete root coverage (CRC) (Graziani 2014).

During the discussion of a recent meta-analysis, Graziani reported that despite the “ideal” treatment is not yet identified, there are some indirect suggestions from the analyzed data that, in comparison to the traditional CAF approach, the use of additional grafting, modifications of the flap technique or tunnel variation with connective tissue graft (CTG) may improve clinical results (Graziani 2014).

Findings from a long-term study, suggest that, in patients with a high standard of oral hygiene, enrolled in a regular maintenance care program, shallow recessions may further deteriorate over a period of 10 to 27 years. On the other hand, treatment of contra-laterally located recessions by means of gingival-augmentation techniques showed long-term stability and a tendency for coronal displacement of the gingival margin with a reduction in recession depth (Agudio 2009). These results are in line with those from a 5-year follow-up split mouth study comparing the clinical outcomes of the modified coronally advanced flap (MCAF) alone, versus the coronally advanced flap plus connective tissue graft (CAF + CTG) in the treatment of multiple gingival recessions (Pini-Prato 2010). Over a short period (e.g., up to 6 months), both treatments resulted in comparable outcomes in terms of root coverage. However, at the 5-year follow-up, the sites treated with CAF alone demonstrated an apical relapse of the gingival margin, whereas the sites grafted with CTG showed not only stability, but even a coronal improvement of the gingival margin, as compared to the 6-month results (Agudio 2009; Pini-Prato 2010).

CTG harvesting is often associated with increased patient morbidity, prolonged surgical time and the possibility of postoperative complications such as bleeding, numbness and sensibility changes at the donor area (Aroca 2013; Buff 2009; Reiser 1996). Various allografts or replacement biomaterials have been developed instead of a connective tissue graft in order to reduce patient morbidity (Aroca 2013; Thombre 2013 Cordaro 2012; Aroca 2009). A newly developed porcine-derived bio-resorbable

collagen matrix (CM) (Fibro-Gide) has been recently introduced as an alternative to CTG in periodontal plastic surgery.
These mucogingival surgical techniques are routinely used to treat recessions by clinicians of Department of Periodontology of Dental Clinic of San Raffaele Hospital and they are present in the list of dental services provided with code "ODCMCM".

4. STUDY OBJECTIVES

The aim of this study will be to compare the outcomes of two muco-gingival surgery techniques, the modified coronally advanced flap (MCAF) for multiple recession defects (Zucchelli & de Sanctis 2000) and the modified coronally advanced tunnel technique (MCAT) (Aroca 2013), performed in the Department of Periodontology of San Raffaele Hospital with the results reported in the literature. Secondarily, the study will evaluate whether patients report a preference in terms of discomfort and perception of aesthetics between the two surgical techniques.

4.1. Primary outcome

- percentage (%) of complete root coverage (CRC) at 12 months

4.2. Secondary outcomes

- percentage of root coverage (RC %) at 3, 6 and 12 months
- keratinized tissue width (KTW) at 3, 6 and 12 months
- gingival thickness (GT) at 3, 6 and 12 months
- post-surgical pain (PP),
- amount of drug intake after surgery
- patient perception of aesthetics at 6 and 12 months
- color match (blending), contour (correct outline of the gingival margin at adjacent teeth), contiguity (evaluated based on the visible confluence between the treated area and the adjacent soft tissues), degree of keloid formation scored at the 1-year post-surgical evaluation will be measured by an expert periodontist.
- duration of surgery (from anesthesia to last suture).

5. STUDY DESIGN

5.1. Description of the protocol

The present research is a monocentric prospective parallel randomized controlled clinical trial.
Patients presenting multiple gingival recessions in the maxillae will be enrolled in the study after having signed an informed consent. Recessions will be treated by means of two mucogingival surgery techniques: modified coronally advanced flap (MCAF) and modified coronally advanced tunnel technique (MCAT), in association with the use of a collagen matrix (CM).
An allocation sequence by means of a computer-generated random list will be created and a sealed opaque envelope will contain the type of treatment assigned to each patient. The opaque envelope will be opened immediately after performing anesthesia.

5.2. Duration of study

Each patients will be followed for 12 months after surgery.

6. SELECTION OF PATIENTS

The present study will be reported according to the CONSORT statement for improving the quality of reports of parallel-group randomized trials (http://www.consort-statement.org/). This will be a parallel monocentric prospective randomized controlled clinical trial.
Patients requiring root coverage procedures from the Department of Periodontology of San Raffaele Hospital will be enrolled in the study.

6.1. Inclusion criteria

Subjects must be males and females of at least 18 years of age with:

- multiple (i.e., at least 2) Miller Class I and/or II gingival recessions located in the maxillae, with an apico-coronal extension (i.e., defect depth > 1 mm with at least one defect > 2 mm) and with at least 1 mm of residual keratinized tissue,
- good general health, with no systemic diseases that could influence the outcome of the therapy,
- healthy periodontal conditions (i.e., no presence of sites ≥ 4 mm and/or presence of intra-bony defects in the selected sites),
- adequate oral hygiene (full mouth plaque score (FMPS) of <25% at baseline (following initial oral hygiene instructions and prophylaxis),
- an adequate control of inflammation (full mouth bleeding score [FMBS]) of <25% at baseline (following initial oral hygiene instructions and prophylaxis).

Subjects must have voluntarily signed the informed consent before any study related action and must be committed to the study and the required follow-up visits.

6.2. Exclusion criteria

- subjects who currently smoke >10 cigarettes/day,
- female subjects who are nursing, pregnant, or plan to become pregnant,
- contraindication against oral surgical interventions,
- contraindication against use of Fibro-Gide (acute infection in the area of surgery and patient with collagen allergy)

7. STUDY PROCEDURE

7.1. Pre-treatment procedures

Cause-related therapy will be completed on all patients prior to surgery. In particular, patients will receive oral hygiene instructions (roll technique) to eliminate the wrong habits related to the etiology of the recession at least 2 months before surgery.

7.2. Surgical procedures

Two experienced practitioners (M.d.S. and S.A.) will perform the surgical session according to the technique as presented by Zucchelli & de Sanctis 2000 and Aroca et al. 2013.
- Modified coronally advanced flap (MCAF)

After local anesthesia, a horizontal incision is made to include one tooth on each side of the teeth to be treated. The horizontal incision of the envelope flap consists of oblique sub-marginal incisions in the interdental areas, incisions which continue with the intra-sulcular incision at the recession defects. Each surgical papilla (SP) is dislocated with respect to the anatomic papilla by the oblique sub-marginal interdental incisions; in particular, the surgical papilla mesial to the flap midline are dislocated more apically and distally, while the papilla distal to the mid-line are shifted in a more apical and mesial position.
The envelope flap is raised with a split-full-split approach in the coronal-apical direction: the surgical papilla is dissected in a split-thickness manner, while gingival tissue apical to the root exposures is raised in a full-thickness manner (to provide that portion of the flap critical for root coverage with more thickness). Finally, the most apical portion of the flap is elevated in a split-thickness manner to facilitate the coronal displacement of the flap.
The portion of the root exposure with loss of clinical attachment (gingival recession plus probeable gingival sulcus/pocket) are mechanically treated with the use of curettes and EDTA is applied for 2 minutes.
The remaining tissue of the anatomic interdental papilla is de-epithelialized to create connective tissue beds to which the surgical papilla are sutured.
A sharp dissection into the vestibular lining mucosa is then carried out to eliminate muscle tension. Flap mobilization is considered "adequate" when the marginal portion of the flap is able to passively reach a level coronal to the CEJ at each single tooth in the surgical site. The flap, in fact, should be stable in its final position even without the sutures.
The porcine-derived bio-resorbable collagen matrix (CM) (Fibro-Gide) is now prepared for placement on the interested areas: the width of the matrix must be reduced to 3-4 mm and the matrix has to adapt to the receiving tissues, when placed, a suture (6/00) must be used to hold it in position.
Sling sutures (6/00) are performed to accomplish a precise adaptation of the buccal flap on the exposed root surfaces and to stabilize every single surgical papilla over the interdental connective tissue bed.
- <u>Modified coronally advanced tunnel technique (MCAT)</u>
Immediately before surgery, composite stops are placed at the contact points to prevent collapse of the future suspended sutures into the inter-proximal spaces.
After local anaesthesia, root planing of the exposed root surface is performed by means of hand instruments. Ethylenediaminetetraacetic (EDTA) is applied on the sites.
Subsequently, intra-sulcular incisions were placed and muco-periosteal flap separation are raised using sharp tunnel elevators. The muco-periosteal dissection is extended beyond the muco-gingival junction (MGJ) and under each papilla, to allow passive, tension-free mobilization in coronal direction. Muscle fibres and any remaining collagen bundles on the inner aspect of the flap alveolar mucosa are cut using Gracey curettes with extreme care in order to obtain a passive coronal positioning of the flap and the papilla and to avoid perforation of the flap.
The porcine-derived bio-resorbable collagen matrix (Fibro-Gide) is now prepared for placement on the interested areas: the width of the matrix must be reduced to 3-4 mm, then it can be inserted under the CAMT by starting at the deepest recession. Then, the site is rinsed with saline solution to remove any clot. The matrix has to be held in position using a suture (6/00).
Finally, the flap is positioned coronally to CEJ by means of suspended sutures (6/00) around the contact points.
At surgery, the duration of the full procedure will be evaluated (from anesthesia to suture).

7.3. Study device

Fibro-Gide, a porcine, porous, resorbable and volume-stable collagen matrix, will be used for this investigation. It is a class III medical device according to the Medical Device Directive 93/42 EEC's definition: 1.1. long term implant, 1.2. implantable and rules 8 (resorbable) and 17 (animal origin). The material is weakly cross linked using EDC ((1-ethyl-3-3-dimethylaminopropyl) carbodiimide).
CE certificate G7 1607 39446 073 for Geistlich Fibro-Gide® was issued on 12.08.2016 for the intended use of soft tissue augmentation in the oral cavity.
All matrices will be provided by Geistlich as a contribute to the project.

7.4. Post-operative procedures

Post-surgically, all patients will be given antibiotics for 6 days and were instructed to rinse their mouth with a 0.2% chlorhexidine solution, three times a day for 1 min. for 1 months.
Patients will be instructed to avoid brushing in the operated area until 2 weeks after surgery and instructed in mechanical tooth cleaning using a soft toothbrush.
All patients will be recall after 1, 2 and 4 weeks. They will be further recalled 3, 6 and 12 months after surgery for professional oral hygiene procedures and measurements.

7.5. Follow-up

Patients will be followed for 12 months after surgery.
At 7 ± 2 days post-surgery – general examination, photographic picture of the treated site questionnaire about post-operative pain.
At 14 ± 4 days post-surgery – suture removal, photographic pictures of the treated site
At 1 month ± 7 days post-surgery – general examination, photographic picture of the treated site
At 3 months ± 15 days post-surgery - general examination, photographic picture of the treated site, measurements of the following parameters: Gingival recession depth (REC in mm), Keratinized tissue width (KTW in mm), Gingival thickness (GT in mm), Pocket probing depth (PPD in mm), BoP, PI.
At 6 ± 1 months post-surgery - general examination, photographic picture of the treated site, evaluation of the aesthetic outcome, measurements of the following parameters: Gingival recession depth (REC in mm), Keratinized tissue width (KTW in mm), Gingival thickness (GT in mm), Pocket probing depth (PPD in mm), BoP, PI.
At 12 ± 2 months post-surgery - general examination, photographic picture of the treated site, evaluation of the aesthetic outcome, measurements of the following parameters: Gingival recession depth (REC in mm), Keratinized tissue width (KTW in mm), Gingival thickness (GT in mm), Pocket probing depth (PPD in mm), BoP, PI.

7.6. Investigator training

Five subjects not involved in the study, each showing a pair of single-rooted contra-lateral teeth with recessions > of 2 mm on the mid-buccal aspect of each tooth, will be used to calibrate the examiner. The examiner will evaluate the subjects on two occasions 24 h apart. Calibration will be accepted if 90% of the recordings could be reproduced within a difference ≤ 0.5 mm (Aroca 2010).

8. STATISTICAL CONSIDERATIONS

8.1. Sample size calculation

The range of mean root coverage percentage of the two mucogingival techniques which can be found in literature varies between 85% and 95%. While the value of variability (SD) obtained in previous articles is 10%. On the basis of these settings, the sample dimension has been calculated using a = 0.05 and the power (1-b) of 80%. The minimal significant value considered is 10%.
So, the needed number of patients to be enrolled in this study is 17 for the test group MCAF + Fibro-Gide and 17 for the MCAT + Fibro-Gide. However, the number of patients will be increased of 1 patient for each arm considering the possibility of dropout, so the required number will be 18 for each group.

8.2. Null hypothesis

H0: No statistically significant differences are observed with respect to the clinical parameters CRC, at 12 months between the two treatment modalities (i.e., MCAF + CM or MCAT technique with CM).

8.3. Statistical Methods

Statistical analysis will be performed using commercially available software (STATA) or R environment (www.r-project.org). Both patient- and tooth-level analysis will be performed for each parameter. Therefore, mean values and standard deviations (SD), as well other descriptive statistics, for the clinical variables will be calculated for each patient per treatment.
A mixed model will be built to take into account the variability due to patient and tooth factors differentially.
Accordingly, the significance of the difference within each group and between groups before and after treatment will be evaluated with the paired samples t-test or two independent samples t-test, as appropriated, regarding all numerical data (REC, KTW, GT, PPD, percentage of root coverage and VAS scale).
Fisher's exact test will be applied for categorical data (frequency of complete root coverage).
P-values will be computed by means of permutation methods to avoid any distributional assumptions or asymptotical approximation. Differences will be considered statistically significant when the p-value was <0.05.

9. ETHICAL AND REGULATORY CONSIDERATIONS

This clinical trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice.
This clinical trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country in which the clinical trial is performed, as well as any applicable guidelines.

9.1. Informed consent

The investigator (according to applicable regulatory requirements), or a person designated by the investigator, and under the investigator's responsibility, should fully inform the Patient/Subject of all pertinent aspects of the clinical trial. All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.
Prior to a patient's/subject's participation in the clinical trial, he/she MUST signed the written Informed Consent Form.
It must also be made clear to the patient/subject that he/she can withdraw from the study at any time without giving reasons and that he/she will not be in any way disadvantaged by this.

The Informed Consent Form must be approved by Independent Ethics Committee.
Any Informed Consent will be part of Investigator's file and retained with it. A copy of the signed and dated written Informed Consent Form must be provided to the patient/subject.

9.2. Independent Ethics Committee Approval (IRB/IEC)

This clinical trial protocol as well as the Informed Consent are to be submitted to the appropriate Ethics Committee, and it is mandatory to obtain the written and dated approval/ favorable opinion, signed by the chairman with ethics committee(s) composition.
The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, Informed Consent Form, Investigator's Brochure, investigator's CV, etc.), the list of voting members and their qualifications and the date of the review should be clearly stated on the written ethics committee approval/favorable opinion.

9.3. Responsibilities of the investigator(s)

The investigator(s) undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, ICH /Good Clinical Practice and the applicable regulatory requirements.
The investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study required procedures. The investigator agrees to provide all information requested in the Case Report Form (CRF) in an accurate and legible manner.
Furthermore, the investigator commits to give immediate notice of any Adverse Event and/or Serious Adverse Event (AE/SAE).

10. DATA MANAGEMENT

10.1. Source Documents

According to the ICH /Good Clinical Practice, the monitoring team must check the Case Report Form entries against the source documents.

10.2. Case Report Forms (CRFs)

It is the responsibility of the investigator to maintain adequate and accurate CRFs (according to the technology used). All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.
Should a correction be made, the information to be modified must not be overwritten. The corrected information should be transcribed by the authorized person next to the previous value, initialed and dated.

11. DATA PROTECTION

The investigators ensure that all safeguards are in place to minimize any eventual risk of breaches and comply otherwise with requirements of GDPR as implemented in its policy on data protection. Patient data collected will be anonymized (a number will be assigned at each patient) and all documents will be stored in locked security cabinets in controlled areas.
The investigators regularly check all their procedures relevant to the processing of personal data, so that it ensures privacy by design and compliance with GDPR.

12. DATA PROPERTY AND PUBLICATION POLICY

Clinical study data are property of Department of Periodontology of San Raffaele Hospital.

The results of this study will be submitted for publication primarily in peer-reviewed journals, or as abstracts, posters, or other presentations at scientific meetings.

13. GLOSSARY

- AE/SAE - adverse event/serious adverse event
- BoP - Bleeding on probing
- CAF - coronally advanced flap
- CEJ - cement-enamel junction
- CRC - complete root coverage
- CRF – case report form
- CTG - connective tissue graft
- CM - collagen matrix
- EDTA - Ethylenediaminetetraacetic
- FMBS - full mouth bleeding score
- FMPS - full mouth plaque score
- GT - gingival thickness
- KTW - keratinized tissue width
- MCAF - modified coronally advanced flap
- MCAT - modified coronally advanced tunnel technique
- MGJ - muco-gingival junction
- RC % - percentage of root coverage
- REC - gingival recession depths
- PI - plaque index
- PP - post-surgical pain
- PPD - pocket probing depth

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