Adjunctive benefit of a Xenogenic Collagen Matrix associated with Coronally Advanced Flap for treating multiple gingival recessions.
A superiority, double blind, randomized clinical trial.

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INTRODUCTION

In patients with a sufficient amount (≥2mm) of keratinized tissue, the Coronally Advanced Flap (CAF) has been demonstrated to be very effective in treatment of single (Linee Guida) and multiple recessions with advantages also in terms of aesthetics and morbidity (Chambrone et al. 2018, Pini Prato et al. 2014). Although CAF is a safe and predictable approach for root coverage (Pini Prato et al. 2018a), the application of this surgical technique in conjunction with autologous material (connective tissue graft) was reported to enhance the probability to achieve complete root coverage (CRC) in gingival recessions without interproximal attachment loss and non carious cervical lesions, with a long term stability (Chambrone et al. 2015, 2018; Pini Prato et al. 2018b).

Free gingival graft (FGG) technique has been confirmed as a valuable method to obtain newly created keratinized tissue stability up to 27 years (Agudio et al. 2009). However, since this technique uses epithelialized grafts, it generally results in compromised aesthetics ("patch-like area"). Alternatively, free connective tissue grafts (CTG) are used providing higher predictability and resulting in better colour matching (Chambrone et al. 2015, 2018; Pini Prato et al. 2018b). Unfortunately, both techniques are associated with a variable patient morbidity due to the wound at the palatal donor site and with the limited available amount of soft tissue.

As a consequence, part of the research in Mucogingival Surgery is now focusing its attention on the validity assessment of potential soft tissue substitutes in order to permit a their easier and broader use in reconstructive technique and avoiding limitations in the size, shape and homogeneous thickness of the alternative material. Several companies are offering in the market different quality of substitutes with different characteristics. As a consequence, several studies (Tonetti et al. 2018, Ahmedbeyli et al. 2014, Rotundo et al. 2012, Thoma et al. 2010) have been conducted in order to test them and to assess their efficacy and biological capability comparing with the gold standard approach represented by the use of a soft tissue autograft. For instance, there is evidence that the use of CAF with acellular dermal matrix (ADM) leads to a higher possibility of CRC achievement and thicker periodontal biotype changes (Chambrone et al. 2015, Ahmedbeyli et al. 2014). However, since the allograft material is derived from human cadavers, it is associated with ethical concerns and the risk of disease transmission. A recent systematic review and meta-analysis was aimed to compare clinical outcomes and width of keratinized tissue (KT) around teeth, following a soft tissue alternative (living cultured

cells) and FGG procedures. Data analyses showed that soft tissue alternatives resulted in an increased width of KT, but inferior (1.39mm) when compared with FGG (Dragan et al. 2017).
An option to avoid patient morbidity (due to donor sites) as well as the use of allograft material (withspecific risk of transmission of human diseases) is the use of xenogenic collagen matrices (XCM). The suggested device is structured with a spongious portion (predominant) and a compact layer. The spongious part of the XCM is likely to allow for tissue ingrowth, which might improve blood vessel ingrowth, root attachment, gingival thickness and consequently improving predictability and the sustainment of recession coverage. Ghanaati et al. (2011) reported that the bilayered matrix elicits a favorable tissue reaction, demonstrates potential as a barrier for preferential tissue ingrowth, and achieves a desirable therapeutic result when applied in humans for soft tissue regeneration.

The use of XCM in the treatment of gingival recessions has shown promising results and considered to be a suitable substitute to the connective tissue graft (Sanz et al. 2009, Herford et al. 2010, Schmitt et al. 2013). A recent systematic review (Atieh et al. 2016) was aimed to evaluate the use of XCM in comparison with CTG, CAF and FFG for the treatment of gingival recessions and/or insufficient KT in terms of clinical parameters and patient- related outcomes. The conclusions based on the only 2 available studies at unclear risk of bias (Cardaropoli et al. 2014, Jepsen et al. 2013) showed that no evidence resulted to demonstrate the effectiveness of XCM in achieving greater root coverage, recession reduction and gain in KT compared to CTG plus CAF. Superior short-term results in treating root coverage compared with CAF alone were possible. In addition, there was limited evidence that XCM may improve aesthetic satisfaction, reduce postoperative morbidity and shorten the operating time.

Therefore, the aim of the present CONSORT-based randomized clinical trial is to test the adjunctive benefit of XCM to the CAF in terms of root coverage, KT augmentation and patient-reported outcomes.

MATERIALS AND METHODS

Trial design

This is a single-centre, superiority, double blind clinical trial, with balanced randomisation and parallel two groups design according to CONSORT statement (Schulz et al. 2010). Ethical approval was obtained by the competent local authority (Azienda USL 3 Pistoia, prot. 24/CESM 19.11.2012). All subjects will sign an informed consent and all study procedures will be performed according to the Declaration of Helsinki on experimentation involving human subjects.

Participants

Patients will be recruited in a private office in Pistoia, Italy. All the recruited patients had to satisfy the following inclusion and exclusion criteria:

Inclusion Criteria

1. The patient (male or female) must be 18 years or older
2. Presence of gingival recessions in the upper jaw, involving teeth from central incisor to first molar
3. Gingival recessions on at least 2 adjacent teeth with a minimal depth of 2mm and detectable cemento-enamel junction (CEJ) (abrasion step <1mm)
4. The patient is able to comply with the study-related procedures such as exercising good oral hygiene and attending all follow-up procedures
5. Full Mouth Plaque (FMPS) and Bleeding (FMBS) Score <20%
6. The patient is able to fully understand the nature of the proposed surgery and is able to provide a signed informed consent

Exclusion Criteria

1. Smoker patients
2. Pregnant patients
3. Patients affect by uncontrolled diabetes

4. General contraindications for dental and/or surgical treatment are present
5. History of malignancy, radiotherapy, or chemotherapy for malignancy within the past 5 years
6. The patient is taking medications or having treatments which have an effect on mucosal healing in general (e.g. steroids, large doses of anti-inflammatory drugs, anticoagulation drugs)
7. The patient has a disease, which affects connective tissue metabolism (e.g. collagenases)
8. The patient is allergic to collagen
9. The patient is an abuser of alcohol or drug
10. Patients have participated in a clinical trial within the last six months
11. Presence of untreated periodontitis
12. Gingival recessions on molar teeth (excluding the first) or on malpositioned teeth
13. Presence of abrasion ≥ 1 mm or cervical restoration, with non-detectable CEJ

Intervention

Pre-Surgical Phase

All subjects will receive a full periodontal examination, with probing of pocket depth (PD), Full Mouth Plaque Score (FMPS) and Full Mouth Bleeding Score (FMBS). Prior surgical therapy, all patients will receive instructions on correct (atraumatic) domiciliar oral hygiene procedures, in order to avoid the persistency of wrong tooth cleaning habit and a course of professional oral hygiene procedure.

Surgical Procedure

A single operator (RR) with more than 20 years of experience in mucogingival surgery will perform all surgical interventions. According to Zucchelli & De Sanctis (2000), an envelope split-full-split thickness flap without vertical incisions will be carried out. The horizontal incision will extend to include one tooth on each side of the teeth to be treated, in order to facilitate the planned coronal

repositioning of the flap tissue over the exposed root surfaces. The chronometer will start at the first incision. The oblique interdental incisions will be carried out keeping the blade parallel to the long axis of the teeth in order to dissect split-thickness the surgical papillae. Gingival tissue apical to the root exposures will be raised full-thickness in order to provide with more thickness that portion of the flap critical for root coverage. The most apical portion of the flap will be elevated split-thickness to facilitate its coronal displacement. Afterwards, the interdental papillae were de-epithelialized using a microscissor. The root surfaces will be mechanically treated with the use of curettes, avoiding the connective attachment area near the bone crest. A sharp dissection into the vestibular lining mucosa will be then carried out to eliminate muscle tension. Only at this point of the surgical procedure the envelope will be opened to allocate the patient to the treatment. In the test site the xenogenic collagen matrix (XCM)* will be applied to all teeth with recession defect. The surgical technique employed in the test group consisted of the following additional steps:

1. After the preparation of the flap, the XCM will be cut into the right dimensions, measured with the probe, and its measurements recorded.

2. XCM will be placed from the CEJ to the bone crest on the recipient bed using single sutures, 7/0 PGA sutures.

3. The matrix will be rehydrated with blood, in order to reconstitute and maintain the maximal thickness possible.

4. The flap will be closed slightly coronal to the CEJ with a sling suture using resorbable PGA 6/0 sutures and avoiding any compression of the matrix.

In the control group, sling sutures will be performed to accomplish a precise adaptation of the buccal flap on the exposed root surfaces and to stabilize every single surgical papilla over the de-epithelialized anatomic papillae.

Postoperative Care and Measurement

Following the surgery, patients will be instructed to rinse twice daily with chlorhexidine mouth rinse (0.12%) for 3 weeks. No toothbrushing will be allowed for 21 days, than they will be instructed to use an ultrasoft toothbrush. Anti-inflammatory therapy (Ibuprofen tablet, one before the surgery and one after 6 hours), antimicrobial therapy and additional analgesics will be prescribed according to the

* Geistlich Mucograft®, Geistlich Pharma AG, Wolhusen, Switzerland

individual needs and the patient will be instructed to record daily the intensity of pain and the dose of medication in the patient questionnaire. All the sutures will be removed after 14 days.

Outcomes

The objective of this RCT is to compare the coronally advanced flaps with a xenogeneic collagen matrix (test group) versus coronally advanced flaps alone (control group) in the treatment of multiple recession defects. In order to establish a superiority effect of the collagen matrix, the following endpoints will be considered:

Primary Endpoint: Mean recession reduction after 6 and 12 months post treatment

Secondary Endpoints:

1) Percentage of complete root coverage after 6 and 12 month

2) Thickness of soft tissue over the root after 6 and 12 month

3) Recession width after 6 and 12 month.

4) Keratinized Tissue (KT) width

5) Patients satisfaction

Clinical Measurements

For the assessment of the periodontal and marginal health status the following variables will be measured on mid buccal surface of the treated teeth by the calibrated blinded examiner, using a calibrated North Carolina University probe. The measures will be rounded to the nearest 0.5mm:

1. Distance between CEJ and the free gingival margin (*Rec depth*)

2. Distance between incisal margin to the free gingival margin (*IM-GM*)

3. *Recession width (Rec width)*, represented by the horizontal measurement of gingival recession at the CEJ level

4. *Bleeding on Probing (BOP),* recording the presence/absence of bleeding after probing (Ainamo & Bay 1975)

5. *Plaque Index (PI),* recording the presence/absence of plaque on tooth surface (Ainamo & Bay 1975)

6. *Probing Pocket Depth (PD)*, measured using a periodontal probe between GM and the end of the gingival sulcus

7. *Clinical Attachment Levels (CAL)*, calculated as PD+Rec depth

8. *Keratinized tissue (KTw) width*, assessed with the visual and functional method by means a probe as a distance between GM and mucogingival junction (MGJ)

9. *Keratinized tissue (KT thick) thickness*, measured by the use of a needle pierced through the center of a circular-shaped silicon marker of 3 mm in diameter. The edge of the marker (k-file nr. 10) will be positioned at the soft tissue margin providing a distance from the margin of 1.5 mm. The distance between the tip of the needle and the silicon marker will be assessed by the use of a magnifying glass and a Dentsply Maillefer silicon stops AO197 will be used. In addition, a digital calliper C041 0-150 mm (Kennon Instruments) with a sensibility of 0.01 mm will be used (da Silva et al. 2004; Santamaria et al. 2008)

10. Duration of the surgery (in minutes), where the chronometer started from the first incision and stopped at last suture.

The periodontal indexes will be measured before the surgery (baseline) and at the follow-up visits, 3, 6 and 12 month after the surgery.

Standardized photos will be taken at baseline, after flap elevation, after material application, after suturing, and at 7 and 14 days, 1, 3, 6 and 12 months post-op. All pictures will be taken always frontal and in profile.

Patient Reported Outcomes

A first questionnaire will be given to the patients to assess the baseline in problems with aesthetics, discomfort while brushing teeth, and hypersensitivity (whereas zero is no problem and 10 is major problems). Afterwards, patients will be instructed to use a diary for the first 7 days after the surgery to record patient reported experience measures (PREMs). In the diary patients had to record post-surgery sequelae, pain and discomfort, chewing function, interference with daily activities, use of medications more than the prescription. This questionnaire will be then collected at 7 days after surgery.

At 6 and 12 months, other two questionnaires will be administered in order to record data about discomfort, chewing function, tooth cleaning procedures, dental hypersensitivity and esthetic outcome.

Calibration session

Only 1 calibrated examiner (LG) took all the measurements. For *recession depth* and *incisal margin-gingival margin* measurements, an intra-rater agreement study was performed for the examiners. A set of 20 recessions were evaluated twice with a two-hour interval between the measurements. The examiner was considered reliable if the intraclass coefficient of correlation was greater than 0.70.

Sample Size

The following 2 hypothesis were considered: H0, where there is no difference in mean recession reduction between CAF+XCM and CAF alone; H1, where there is a difference in mean recession reduction between CAF+CM and CAF alone.

The following variables were used in order to calculate the sample size:

- Endpoint: Normal. Difference in reduction in gingival recession (root coverage) between baseline and 1 year
- Clinical important difference (Effect size d): set at 1 mm
- Assessing variability: From a previous study (Woodyard et al. 2004) in an envelope type of CAF for multiple recessions the standard deviation of recession reduction was 0.93 mm.
- Mean number of treated teeth per patient: from a previous study (Woodyard et al. 2004) it was 2.92
- Intraclass correlation coefficient (ICC) of the cluster sites (recessions nested into patient): from a previous study (Woodyard et al. 2004) it was 0.35
- Allocation ratio: 1:1
- Type I error: $\alpha = 0.05$
- Type II error: $\beta = 0.10$, corresponding to a Power of 90%
- Accounting for drop-out: Anticipation of 10% of patient drop-out.

Based on this consideration and applying a formula for cluster design to detect a difference between treatments of 1 mm in recession reduction (standard deviation of 0.93 mm - Woodyard et al. 2004) with a two- side 5% significance level, a power of 90%, a mean number of treated teeth per patient

of 2.92, an intraclass correlation coefficient of 0.35, a sample size of 12 patients per treatment will be necessary.

Randomization and Allocation Concealment

The recession sites will be randomized to one of the two groups: CAF + CM (test group) and CAF alone (control) at a ratio of 1:1. Randomization code will be computer generated by a researcher not involved in the clinical evaluation (MN). A blocked randomization will be used: the 24 patients will be divided in 12 patients per treatment. For designation of the treatment to each patient, the center will receive 24 sequentially numbered and sealed envelopes containing the information on the applicable surgery. The envelope will be opened by the investigator only after flap elevation.

Blinding

Whereas the surgeon will be aware of the allocation arm, patients and the outcome assessors will be kept blinded to the allocation.

Data analysis

Descriptive statistics will be performed using a mean and standard deviation for quantitative data and frequency and percentage for qualitative data. All unintentional side effects in each group will be reported. For quantitative variables mixed models will be performed with the treatment (CAF versus CAF+CM) as a fixed explicative variable and patient as a random variable. Baseline value will be used as a covariate. Interaction terms between treatment and the covariate will be used only if significant.

Complete root coverage will be analysed with a multilevel logistical model at two level (patient and tooth). For the patient-reported outcomes and experience measures t-tests will be applied. Estimates for the treatment effect, standard errors, p-values and 95% confidence intervals are provided. The statistical software will be MLwiN 2.21 Centre for Multilevel Modelling, University of Bristol.

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