12.9 Regenerative Procedures for Root Coverage

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12.9.1 Overview

Gingival recession (GR) is defined as the exposure of the root surface due to the displacement of the gingival margin apical to the cementoenamel 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 (REC) can often be associated with mechanical factors (trauma caused by excessive tooth brushing, orthodontic therapy or piercing), or inflammatory periodontal disease (Daprile et al., 2007; Susin et al., 2004). The exposed root surfaces are frequently associated with esthetic complaints, root hypersensitivity and difficulties to achieve optimal plaque control (Daprile et al., 2007; Susin et al., 2004).

Gingival recessions can be localized (e.g., single recessions) (Fig 12.9-1) or generalized (multiple recessions) (Figs 12.9-3a and 12.9-4a).

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 coronally advanced flap (CAF) technique, with and without soft tissue grafting and/or biologic agents, such as an enamel matrix derivative (Cairo et al., 2014; Chambrone et al., 2010). However, in cases where root coverage and gain in keratinized tissue are expected, the use of connective tissue grafts (CTG) appeared to yield the best outcomes (Chambrone et al., 2010).

On the other hand, the treatment of multiple gingival recessions appears to be more challenging for the clinician, since in these cases the management of soft tissues becomes more difficult and the wound healing may be compromised by various factors, such as width of the avascular surface, limited blood supply, differences in recession depth and position of the teeth (Aroca et al., 2009; Aroca et al., 2010; Aroca et al., 2013; Graziani et al., 2014; Hofmanner et al., 2012). Moreover, due to the longer surgical time and increase in patient morbidity, treatment of multiple gingival recessions is very demanding for both the clinician and the patient. Recent data indicate that the coronally advanced flap, with and without soft tissue grafting and the modified coronally advanced tunnel using soft tissue grafting are the most predictable techniques for obtaining complete root coverage in Miller Class I, II and III multiple gingival recessions.

Findings from a long-term study suggest that, in patients with a high standard of oral hygiene and 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 contralaterally 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 (Aguadío et al., 2009). These results are in line with those from a 5-year follow-up split mouth study comparing the clinical outcomes of the coronally advanced flap (CAF) alone, versus the coronally advanced flap plus connective tissue graft.
(CAF + CTG) in the treatment of multiple gingival recessions (Pini-Prato et al., 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.

Therefore, recession coverage procedures should not only aim to improve esthetics and root sensitivity along with the ability to perform adequate oral hygiene, but also to increase tissue thickness and enhance long-term stability of the outcomes (Agudio et al., 2009; Pini-Prato et al., 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 (Buff et al., 2009; Reiser et al., 1996). In order to minimize patient morbidity, new soft tissue grafts of human or animal origin have been developed aiming to replace the CTG. Data from randomized clinical studies indicate that treatment of single Miller Class I and II recessions with the coronally advanced flap and some of the available soft tissue grafts may result in comparable short-term (6 months to 1 year) results in terms of root coverage and tissue blending to those obtained with CTG (Cardaropoli et al., 2012; McGuire and Scheyer, 2010). On the other hand, treatment of multiple adjacent Miller Class I and II gingival recessions with a modified coronally advanced tunnel technique (MCAT) by means of a collagen matrix (CM) or CTG resulted in statistically significant improvements in terms of complete root coverage, mean root coverage (MRC), increase in keratinized tissue width (KTW) and increase in gingival thickness (GT) as compared to baseline (Aroca et al., 2013). However, the use of CTG yielded significantly higher CRC percentages, as compared to the use of CM. On the other hand, the use of CM resulted in significant reduction of the surgery duration and patient morbidity compared with the use of CTG.

Taken together, the available evidence appears to indicate that the use and further development of soft tissue replacement grafts bears clinical relevance since they may reduce surgical time and patient morbidity. On the other hand, it is obvious that, at present, the “gold standard” for soft tissue grafting is still the CTG, and thus the ultimate goal of any newly developed soft tissue graft is to yield comparable outcomes to those obtained with CTG.

12.9.2 Research Question
Since the main reason for using soft tissue replacement grafts is to have an alternative to CTG, it seems reasonable that any clinical study designed to test the clinical efficacy of a newly developed soft tissue graft should compare the new material with CTG. Furthermore, since the soft tissue replacement graft is intended to be used for both single and multiple recessions, studies should be designed to test the new material for these indications. From both the patient’s and the clinician’s point of view, the most pertinent question is to what extent the newly developed material yields comparable outcomes, in terms of complete root coverage and esthetic results to (those obtained with) CTG. Patient morbidity and satisfaction, along with the acceptance of the treatment procedure, are also of relevant clinical importance and should be evaluated. Thus, in the following, the most important aspects to be considered when designing a clinical study aiming to test the clinical efficacy of regenerative procedures for root coverage are presented. For procedures that can augment keratinized tissue, refer to Chapter 12.8.

12.9.3 Timeline of the Study
In most studies, a 6- or 12-months standard endpoint was selected to evaluate the outcomes. However, since long-term studies indicate that
changes in CRC may occur over time, it is desirable that clinical studies should follow-up with the patients over a period of at least 3 to 5 years to provide information on the long-term outcomes. Early wound healing should be also evaluated at weeks 1, 2, 3 and 4 postoperatively.

12.9.4 Inclusion and Exclusion Criteria

Before a study is initiated and first patients are screened and included, the protocol and the patient’s informed consent should be approved by the appropriate institutional review board (IRB). Signed informed consents from the study subjects should be obtained prior to study participation.

Subjects are evaluated for initial study eligibility during the screening visit. Those subjects who appear eligible according to the inclusion/exclusion criteria are asked to sign the informed consent form and are enrolled in the study. All of the following criteria must be met for inclusion in the study:

Inclusion Criteria

- Subjects must be in good general health.
- Subjects must have voluntarily signed the informed consent form before any study-related procedures.
- Subjects should exhibit one or multiple (i.e., at least 2) Miller Class I, II or III gingival recessions located in the maxillary or mandibular arch with an apico-coronal extension (i.e., recession depth >2 mm).
- Subjects must have healthy periodontal conditions (i.e., no presence of sites ≥ 4 mm and/or presence of intrabony defects at the selected sites).
- Subjects must be males and females of at least 18 years of age.
- Subjects must have adequate oral hygiene (full mouth plaque index (PI) of <25% at baseline (i.e., following initial oral hygiene instructions and prophylaxis).
- Subjects must have adequate control of inflammation (full mouth bleeding on probing (FMBP) of <25% at baseline (i.e., following initial oral hygiene instructions and prophylaxis).
- Subjects must be committed to the study and the required follow-up visits.

Exclusion Criteria

If any of the following criteria are met prior to surgery, the subject must be excluded from the study:

- Subjects with any contraindications for oral surgical procedures.
- Subjects with a history of neoplastic disease requiring the use of chemotherapy.
- Subjects who are on prolonged antibiotic treatment or anti-inflammatory treatment within 4 weeks prior to surgery.
- Subjects with mucosal diseases (e.g., oral lichen planus, mouth ulcer).
- Subjects with medical conditions requiring prolonged use of steroid therapy.
- Subjects who currently use intravenous or intramuscular bisphosphonates.
- Subjects with local inflammation or infection.
- Subjects with disorders or treatments that compromise wound healing.
- Subjects with the presence of oral lesions (such as ulceration, malignancy).
- Subjects with inadequate oral hygiene or unmotivated for adequate home care (see inclusion criteria).
- Subjects that have been treated with an investigational drug or device within the 30-day period immediately prior to surgery on study day 0.
- Subjects who currently smoke.
- Female subjects who are nursing, pregnant, or plan to become pregnant.
- Subjects with chronic or aggressive periodontitis requiring periodontal therapy (see also inclusion criteria).
- Hypersensitivity to the tested biomaterial(s).
- Simultaneous participation in other clinical trials.
- Increased tooth mobility (≥ Class II).
**Endpoints (Primary and Secondary)**

**Primary endpoint:**
- Percentage (%) of complete root coverage (CRC) compared with baseline (see Figs 12.9-1 and 12.9-2).

**Secondary endpoints:**
- Percentage (%) of mean root coverage (MRC) compared with baseline
- Keratinized tissue width (KTW)
- Tissue thickness (TT) measured 3 mm apically from the free gingival margin at the mid buccal aspect of the tooth (teeth)
- Width of the attached tissue (AT)
- Probing depth (PD)
- Clinical attachment level (CAL)
- Early wound healing (EWH)
- Postsurgical pain (PP)
- Root dentin hypersensitivity (RDH)
- Esthetic outcome
- Duration of surgery
- Full mouth plaque index (FMPI)
- Full mouth bleeding on probing (FMBP).

**12.9.6 Additional Observations and Measurements**

Adverse events that may occur due to the surgical procedure or may be related to the use of the new material should also be recorded. Examples of such events observed in clinical studies are listed below.

Local soft tissue reactions:
- Local redness
- Postoperative hemorrhage
- Infection
- Wound dehiscence
- Sloughing of tissue
- Paresthesia
- Inflammation soreness
- Gingival irritation
- Hematoma/ecchymosis
- Bleeding
- Loosening of sutures
- Oral candidiasis
- Tissue necrosis/cratering
- Herpes-like blisters
- Hypoesthesia (burning and itching reaction on the tongue)
- Oral mucosal reaction
- Fibrin layer
- Discoloration
- Increased tooth mobility
- Hypersensitive root surfaces (root sensitivity)
- Pain.

General reactions:
- Urticaria
- Itching skin reaction
- Gastrointestinal disturbances
- Urogenital disturbances.

**12.9.7 Preoperative Care**

Intraoperative photographs of the surgical area should be taken. Patients should rinse their mouth with a 0.1%, 0.12% or 0.2% chlorhexidine solution. Preoperative administration of systemic antibiotics may be considered according to the protocol or to the local regulations. Local or block anesthesia will be given.

**12.9.8 Test Groups (Test and Control)**

Each subject that is eligible should be randomized via a validated computer program to one of the two treatment groups at the time of surgery. The
randomization should be made by opening an envelope at the moment the surgeon decides to start the treatment procedure (immediately after flap preparation and root debridement). The surgeon should document on the envelope the data and time the envelope was opened and the subject identification.

The treatment group should preferably be assigned according to the randomization scheme generated by an independent external service provider. The randomization will be stratified according to the study center with blocks of variable size. No access to the randomization logic should be available to the study center, study subjects, or any other persons (e.g., employees of the company providing the test material).

To prevent examiner-related bias, the clinical evaluations should be performed by a masked examiner. The surgeon performing the surgeries should be provided with the treatment group information at the moment of surgery by opening the randomization envelope. The calibrated examiner should perform the clinical measurements at baseline and at the follow-up visits in a blinded way.

In most cases, recessions are either treated using a coronally advanced flap (CAF) (Cairo et al., 2014; Zucchelli and De Sanctis, 2000; Zucchelli et al., 2014) or by means of a modified coronally advanced tunnel (MCAT) (Aroca et al., 2010; Aroca et al., 2013; Molnar et al., 2013) using either the new soft tissue replacement graft (test) (Fig 12.9-2) or a CTG harvested from the palate (control) (Fig 12.9-3). In single-center studies, the surgeries (test and control site) should be preferably performed by the same experienced
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PPD: probing pocket depth; CAL: clinical attachment level; GR: gingival recession; TT: tissue thickness; AG: attached gingiva; KT: keratinized tissue.
surgeon. In multicenter studies, however, it is desirable that the surgeries are performed by one experienced surgeon per center. In such cases, a calibration meeting previous to the start of the study should be performed to standardize the surgical procedure. When testing new materials, the surgeons should train the handling of the new devices and the learning curve should be considered prior to the beginning of the study.

It is recommended that, in every single case, the surgery is photographically documented (Figs 12.9-2 and 12.9-3). The following steps are suggested to be recorded on intraoral photographs:

- preoperative view
- intraoperative view
- immediate postoperative view
- clinical outcome at 6 or 12 months.

Additionally, standardized photographs should be taken to document the early wound healing events and the healing of the palatal donor site at the postoperative follow-up visits according to the protocol.

Patient screening and inclusion along with the clinical measurements should not be performed by the same person who will perform the surgeries. Calibration and intra- and/or interexaminer reproducibility should be ensured before including the first patient in the study.

12.9.9 Postoperative Care

Post-surgically, patients will be given analgesics according to the individual needs and antibiotics according to the protocol or to the local regulations for implantable biological materials. Patients will be instructed to rinse their mouth with a 0.1%, 0.12% or 0.2% chlorhexidine solution, two times a day for 1 min for at least 3 to 4 weeks. Patients will be instructed to avoid brushing in the operated area until suture removal (usually at 2 weeks) and will undergo supragingival tooth cleaning during the follow-up visits according to the protocol (see Table 12.9-1). At suture removal (in most cases at 2 weeks after surgery), patients will be controlled and instructed in mechanical tooth cleaning of the operated areas using a soft toothbrush. Patients will be recalled according to the protocol and will also receive a session of prophylaxis, including reinforcement of oral hygiene, supragingival debridement, and tooth polishing.

12.9.10 Assessment of Adverse Events

Relationship to the Investigational Device

The investigator should assess the relationship of the adverse event to the investigational device. The relationship should be assessed using the following categories:

- Related: there is a reasonable causal and temporal relationship between the treatment with the investigational device and the adverse event.
- Probably related: the relationship between the treatment with the investigational device and the adverse event is highly likely but lacks a reasonable causal and temporal relationship.
- Possibly related: the relationship between the treatment with the investigational device and the adverse event is less likely and the determination that there is no relationship cannot be made.
- Unrelated: no relationship between treatment with the investigational device and the adverse event exists.
- Unknown: the relationship between treatment with the investigational device and the adverse event is not known.

Relationship to the Procedure

The investigator should assess the relationship of the adverse event to the surgical procedure (e.g., periodontal surgery). The relationship should be assessed using the categories described in section 12.9.6.

Severity

Each adverse event should be assessed for its severity, or the intensity of an event experienced by a subject, using the following:
Mild: discomfort noticed, but no disruption in daily activities.
Moderate: discomfort sufficient enough to reduce or affect normal daily activity.
Severe: inability to work or perform normal daily activity.

Power Calculation
Power calculation should always be performed prior to the initiation of the study. The study design (i.e., parallel or split-mouth) together with the primary study endpoint may significantly affect the statistical power and conversely, may affect the clinical relevance of the conclusions. Therefore, before the initiation of any controlled clinical trial, it is strongly recommended to consult a biostatistician.

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References


