Clinical evaluation of coronally advanced flap with acellular dermal matrix graft or connective tissue graft in the treatment of gingival recession with thin periodontal phenotype: study protocol for a split-mouth randomized controlled trial

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Study protocol

Keywords: Acellular dermal matrix, Connective tissue graft, Gingival recession, Root coverage

DOI: https://doi.org/10.21203/rs.3.rs-32870/v1

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Abstract

Background

Among all mucogingival deformities, gingival recession is one of the most prevalent conditions that demand surgical correction. Accordingly, root coverage procedures are essential parts of plastic periodontal surgeries. It is undeniable that autogenous tissue grafts remain the gold standard for root coverage procedures. Substantial evidences have identified that the connective tissue graft (CTG) combined with coronally advanced flap (CAF) achieves favorable root coverage of recession. Nevertheless, there are some noticeable disadvantages of harvesting autogenous tissue, such as postoperative bleeding, pain, or discomfort at the donor site, restricted tissue supply, increased morbidity, and longer operative duration. In order to overcome the drawbacks of autogenous tissue harvesting, several non-vital substitutes have been produced as alternative options for replacing connective tissue graft. Acellular dermal matrix (ADM) is an allograft derived from human skin, which has been used extensively in various areas of dental practice over the last two decades. ADM exhibits undamaged collagen and elastin matrices that has been used as a substitute for connective tissue for root coverage procedures. Although its clinical efficacy has been discussed in several reviews, conclusions about the application of this material are still unclear and controversial. Moreover, the level of evidence on the clinical outcomes and patient-reported outcomes relevant to ADM graft (ADMG) is low. Therefore, the objective of this split-mouth; randomized, controlled, clinical study is to compare the long-term clinical efficacy of ADMG combination with CAF on root coverage, aesthetics and patient satisfaction with CTG combination with CAF for gingival recession with thin periodontal phenotype, hoping to provide some reference to dentists.

Methods/design

Forty participants with bilateral Miller Class I/II gingival recession randomly received ADMG (test group) on one side and CTG (control group) on the contralateral side in conjunction with CAF. Gingival recession depth (GRD), gingival recession width (GRW), keratinized tissue width (KTW) are measured at baseline, 2, 4, 12, 24, 48 and 96 weeks. Mean root coverage (MRC), complete root coverage (CRC), root coverage aesthetic score (RES), color change ($\Delta E$), and patient satisfaction are assessed in postoperative follow-up.

Discussion

CAF combined with CTG has been shown as a predictable technique in root coverage. At present, there is limited long-term data evaluating ADM on root coverage, aesthetics and patient satisfaction for the treatment of gingival recession with thin periodontal phenotype. The result of this split-mouth randomized controlled clinical studies is performed to evaluate the long-time efficacy of ADM, particularly when compared to the “gold standard” (CTG), contributing to an advanced treatment strategy of gingival recession with ideal clinical outcome.
Trial registration

International Clinical Trials Registry Platform (ICTRP), ID: ChiCTR2000033230. Registered on 25 May 2020, http://www.chictr.org.cn/showproj.aspx?proj=54052

Background

Gingival recession is defined as the apical migration of gingival margin to the cemento-enamel junction (CEJ) with exposure of the root surface [1, 2]. This is a common feature in populations [3-6], reaching prevalence about 51% among subjects [7]. Mechanical factors, such as restoration invading the biological width, tooth brushing trauma, piercing trauma, muscle inserts, localized plaque induced inflammatory lesions, and gingival anatomic factors, are the common etiological factors leading to gingival recession [8, 9]. The coverage of exposed root surfaces has become an important therapeutic issue due to patients’ increasing demands, such as dentinal hypersensitivity, aesthetic problems, root erosion, root caries, or hampering plaque removal [10].

Different surgical techniques have been used for root coverage [11-21]. Evidence indicates coronally advanced flap (CAF) as an effective periodontal plastic surgical procedure for the treatment of Miller Class I/II gingival recessions [22-26]. CAF can be used alone [22-24, 27], or in combination with connective tissue grafts (CTG) [25, 28-31], enamel matrix derivatives (EMD) [32], platelet-rich fibrin (PRF) [33], or low intensity laser therapy [34] to improve the technique’s predictability. A systematic review [35] revealed that CAF either with or without CTG might lead to predictable complete root coverage (CRC) in the treatment of Miller Class I/II multiple recessions; while combination with CTG appeared to improve the long-term stability of CRC, which is accepted as the gold standard in the treatment of gingival recessions [27, 35, 36].

Although subepithelial connective tissue procedures provide excellent predictability. This technique, however need for the second surgical site, involves a certain degree of discomfort for the patient, increases the risk of pain and hemorrhage postoperatively. In addition, the amount of graft is limited by the palatal donor site and thickness. In order to overcome the drawbacks of autogenous tissue harvesting, PRF [33], platelet-rich plasma (PRP) [37], EMD [38], xenogeneic collagen matrix (XCM) [39-41], and acellular dermal matrix (ADM) [42, 43], and xenogeneic origin (XADM) [44, 45] have been used as alternative options to the CTG for plastic periodontal and implant surgery.

ADM is a derivative of human dermis, which is processed to remove the cellular and epidermal components, thereby removing the source of disease transmission and immunologic reaction, leaving a structurally intact connective tissue matrix composed of collagen fibrillar network, intact proteins, elastin filaments, proteoglycans and hyaluronan, and basement membrane allow ADM as a scaffold to allow ingrowth of host tissues, thereby giving it characteristics of a feasible soft tissue graft material [46]. It was initial use in the 20th century [47, 48]. Since that ADM has been used extensively in various areas of dental practice over the last two decades [49, 50]. The acellular dermal matrix graft (ADMG) has been recommended for the treatment of alveolar ridge deformities [51] to increase the width of keratinized
tissue around teeth and implants [52-54], for guided bone [55, 56] or tissue regeneration [57], for root coverage procedures [55, 58-60], avoiding the disadvantages of autogenous connective tissue. Although the clinical efficacy of ADMG has been discussed in several reviews (i.e., European Federation of Periodontology, American Academy of Periodontology, and Cochrane), the application of this material is still unclear and controversial. Moreover, the evidence level on the long-term clinical outcomes and patient reported outcomes relevant to ADMG are still low.

Periodontal phenotype has also been reported as an important parameter that could influence the clinical outcome of root coverage procedures and the predictability in root coverage [61-65]. In root coverage procedures, the gingival thickness less than 1 mm could harm the achievement of CRC [66] and might have a greater influence on the final outcome than the influence of keratinized tissue (KT) [62]. Due to ADM’s non-vital structure, which depends on cells and blood supply from the recipient site to achieve reorganization, the periodontal phenotype is very critical for the clinical outcome. To the best of our knowledge, no randomized controlled clinical trial has compared the outcomes of CTG versus ADM in treatment of gingival recessions with thin periodontal phenotype. Therefore, the aim of this study was to evaluate the clinical effectiveness of ADMG combination with CAF on root coverage, aesthetics and patient satisfaction compared to CTG combination with CAF for the treatment of Miller Class I and II gingival recessions with thin periodontal phenotype.

Objectives and hypotheses

The current single-centered, split-mouth, randomized, controlled clinical trial was planned to compare the clinical efficacy of ADMG and CTG in conjunction with CAF in the treatment of Miller class I and II gingival recessions with thin periodontal phenotype.

The primary hypotheses are ADMG and CTG with CAF provides similar amount of root coverage and aesthetic outcome in Miller class I and II gingival recessions. The second hypotheses are the incidence of postoperative complications was higher in CTG.

Methods/design

Overview

The study is a prospective single-center, split-mouth, randomized, controlled clinical trial. 40 patients who are with Miller class I and II gingival recessions in need of the coverage of exposed root surfaces. The assessments, interventions, and follow-ups will be performed at First Clinical Division, Peking University School and Hospital of Stomatlogy (Beijing, China). This study has been approved by the biomedical ethics committee of Peking University School and Hospital of Stomatlogy (PKUSSIRB-202054029) and registered in International Clinical Trials Registry Platform (ICTRP) under the ID: ChiCTR2000033230.

Inclusion criteria

The patients are selected according to the following inclusion criteria:
1. Age ≥ 18 years;
2. Patients willing to attend the study and provide an informed consent;
3. Systemically healthy and no contraindication for periodontal surgery;
4. Presence of localized bilateral Miller class I or II adjacent gingival recessions ≥ 3mm with thin periodontal phenotype in the maxillary or mandibular arches without any clinical sign of active/chronic periodontal disease;
5. Having full-mouth plaque score and full-mouth bleeding score ≤ 15%;
6. No history of surgical intervention in the relevant areas.

**Exclusion criteria**

1. Habitual tobacco smoking and/or chewing;
2. Habitual alcohol consumption;
3. Pregnancy or lactating women;
4. Participants having crowns or restorations involving the CEJ or those with nonidentifiable CEJ;
5. Individuals using medications that can interfere with healing and allergic to penicillin.

**Recruitment**

Subjects who are looking for the coverage of exposed root surfaces and are willing to join this trial will be recruited from First Clinical Division, Peking University School and Hospital of Stomatology. Subjects will receive the study information. Before subject is included in the present study, the consent form must be signed. Figure 1 shows the procedure of participants through this trial.

**Randomization, grouping, and blinding**

The randomization process is performed by a professor in the absence of the working investigators using a software program by a computer-generated randomly permuted block. Allocation is concealed in opaque envelopes until immediately before surgery to determine which sites of gingival recession will receive the test procedure and the contralateral teeth will receive the control procedure. All subjects will be treated by one experienced and calibrated periodontist who do not partake in the allocation, examination, and statistical analysis. The treatment plan and grouping will be confidential to the examiner and statistical analyst. Under postoperative adverse events, unblinding is permissible.

**Interventions**

All surgical procedures are performed at the First Clinical Division, Peking University School and Hospital of Stomatology by the same periodontist. Before the surgical procedures, the periodontal status is evaluated; the comprehensive clinical examination is performed; and the etiology of the recessions is determined for each eligible participant by a calibrated examiner. Identified etiological factors are eliminated; detailed oral hygiene instructions (OHI) are given; and full-mouth supragingival scaling and...
tooth polishing are performed. Surgical procedures are initiated at least 4 weeks after the final appointment in which the inclusion criteria are re-evaluated and the good oral hygiene is approved.

The surgeries are performed by an experienced periodontist who has been calibrated before the trial. Both test and control surgeries are performed at the same clinical appointment. The same surgical procedure is used for both groups, except that control sites received the ADMG (test group), while contralateral sites received the CTG (control group). Following local anesthesia, a coronally advanced flap design is performed in all cases as described by Zucchelli previously [67]. Briefly, an intracrevicular incision is made through the bottom of the crevice. Two mesial and distal vertical releasing incisions are made including both papillae adjacent to the area of gingival recession. The papillae in the surgical site are de-epithelialised by interdental incisions considering as anatomic papilla. The flap is elevated with a split-full-split approach in the apico-coronal direction and the soft tissue apical to the root exposures is elevated in a full-thickness manner to facilitate the highest possible thickness of the flap to cover the recession area. Finally, the apical part of the flap is raised in a split-thickness manner to release residual muscle tension and to facilitate the flap passively positioned over the CEJ without tension. Following flap elevation, the exposed root surface was gently planed with sharp curets (Gracey Curettes, Hu-Friedy, Chicago, Illinois).

The control group then received CTG obtained from the palate as previously described [28]. The connective tissue is trimmed to a shape and size designed to cover the root surface and the surrounding bone. The thickness of graft is 1mm.

The exposed root surface of the test group is treated with an ADM that is aseptically rehydrated in sterile saline, according to the manufacturer's instructions. The graft is trimmed to a shape and size designed to cover the root surface and the surrounding bone. The basement membrane side is placed adjacent to bone and tooth, and the connective tissue side is placed facing the flap, according to Harris [68]. The thickness of graft is 1mm.

Both the ADM and CT cover the recipient area at the level of CEJ on the coronal site and get over the vascular tissues 3 mm on the lateral and the apical borders of the recession defect. The grafts in both groups are secured on interdental areas and on lateral sites using 6-0 bioabsorbable sutures. The CAF is then positioned 1 mm coronally to the CEJ and covered the total graft surfaces in both groups. The CAF is sutured stress free at this position using 6-0 non-absorbable sutures, which are also used to secure the donor site. Microsurgical hand instruments (Hu-Friedy, Chicago, Illinois) and ×4.0 loupe (Q Optics, Texas) are used in all surgical procedures. No periodontal dressing is utilized.

All patients are instructed to discontinue tooth brushing and to avoid trauma or pressure at the surgical site. A 0.12% chlorhexidine digluconate gargle is prescribed 3 times daily for 14 days, and amoxicillin (500 mg, tid) was prescribed for 7 days.

The sutures are removed after 14 days, and the patients are instructed to clean the surgical sites with a 0.12% chlorhexidine digluconate gargle 3 times daily for 14 days. After this period, they will resume
mechanical tooth cleaning of the treated areas using a soft toothbrush and a careful roll technique. During the follow-up recalls, oral hygiene instructions are reinforced and professional tooth cleaning is performed if needed.

**Examination**

**Baseline examination**

Individual acrylic stents are prepared to use as the reference points to align the probe properly, and to ensure reproducibility during reevaluation examinations.

Clinical parameters including plaque index (PLI) [69], gingival index (GI) [70], probing depth (PD), clinical attachment level (CAL), gingival recession depth (GRD), gingival recession width (GRW), and keratinized tissue width (KTW) are measured using a periodontal probe (PCP-UNC 15; Hu-Friedy Manufacturing, Chicago, IL, USA) and rounded to the nearest 0.5 mm by a calibrated examiner (not the therapist), who has been trained to adequate levels of accuracy and reproducibility. Thin phenotype decision is given after gingival thickness (GT) measurement as described by Ahmedbeyli [71].

**Examination during the follow-ups**

**Follow-up**

All subjects will be recalled for follow-up at weeks 2, 4, 12, 24, 48 and 96 after the surgery. We will like to make a phone call to remind participants to promote complete follow-up. At weeks 4, 12, 24, 48 and 96 after the surgery, PLI, GI, PD, CAL, GRD, GRW, KTW, periodontal phenotype and the color measurements using an intraoral spectrophotometer (SpectroShade, Medical High Technologies) will be examined by a calibrated examiner. Aesthetic outcomes are evaluated using the Root Coverage Esthetic Score (RES) [72].

Patient satisfaction is assessed using a Visual Analogue Scale/Score (VAS) [73, 74]. Each patient is questioned about his/her satisfaction with regard to the following patient-centred criteria: root coverage; gingival colour, shape and contour; surgical procedure in terms of pain and discomfort related to the duration of the procedure; post-surgical phase in terms of the pain, swelling and post-operative complications.

**Primary parameters**

The primary parameters of this trial are mean root coverage (MRC), CRC, KTW, RES, and color change (ΔE). MRC percentage is calculated as \([(GRD \text{ baseline}-GRD \text{ 12, 24, 48, 96 weeks})/GRD \text{ baseline}] x 100\%.

CRC is evaluated at tooth level and is calculated as the percentage of teeth with gingival recession having complete coverage achieved as the gingival margin at or over CEJ \([(\text{Teeth with CRC})/(\text{All treated teeth})] x 100\%.

**Secondary parameters**
The secondary parameters of this trial are PD, CAL, and VAS scale to patient satisfaction.

**Sample size**

The sample size of this trial is calculated based on the formula:

\[ N = \left[ \frac{(s^2 + r^2)/(S^2)}{\alpha^2} \right] \cdot 2 \left( \frac{1}{\beta^2} + 1 \right). \]

According to the preliminary experiment results and data analysis from currently published articles, the mean difference of the reduction in gingival recession (δ) is around 0.1 mm and the standard deviation in groups (σ) is around 0.3 mm.

If the inspection level (α) is set at 0.05 and the power of test (β) is set at 90%, then 36 subjects will be required for each group. Given a loss to follow-up is around 10%, this study will require 40 subjects for each group.

**Timeline**

The recruitment began in June 2020, and the intervention period will be ending in June 2023. Figure 2 shows the schedule of enrollment, intervention, and assessments.

**Data collection and management**

The data of the patients will be documented both on spreadsheets and databases. The statistical analysis will be performed by two experimenters independently. The data monitoring committee is composited. There is not competing interests in the data monitoring committee.

**Statistical analysis**

The statistical analysis will be performed using a software program (SPSS version 22; SPSS, USA). The distribution of the variables was validated by D'Agostino-Pearson omnibus normality test and parametric tests are used for inter- and intra-group comparisons. Paired t test was used for inter-group comparisons of PI, GI, PD, CAL, GRD, GRW, KTW and the changes of these parameters. Intragroup comparisons for the same variables are done using repeated measures one-way ANOVA test and followed by Bonferroni correction for post hoc multiple comparisons. The number of teeth with MRC and CRC between groups were compared using Fisher's exact test. Multiple imputation will be used to handle missing data. Two-tailed p-values < 0.05 are considered statistically significant. Data analyses will be performed by SPSS software.

**Ethical considerations**

**Ethical approval**

The trial has been approved by the biomedical ethics committee of Peking University School and Hospital of Stomatology (PKUSSIRB-202054029). Before subjects are officially recruited into this study, they will
be given a study information and will be asked to sign the consent form. During the trial, any important protocol modifications will communicate to relevant parties.

**Withdrawal**

Subjects will be informed that they have the right to withdraw from this trial at any time without providing a reason. If the withdrawal occurs, treatment will also be provided to the subject. Under postoperative adverse events, discontinuing intervention for a given trial participant is permissible.

**Dissemination of results**

The results of this trial will be saved at International Clinical Trials Registry Platform (ICTRP) and published in an international peer-reviewed journal which will allow for anyone access to obtain the results.

**Discussion**

Several graft substitute materials for CTG and surgical techniques have been investigated for treating gingival recession [75-78]. Studies have shown that root coverage with ADM increased the coverage of exposed root and the thickness of the keratinized gingiva compared to when root coverage was attempted without ADM [79, 80]. Nevertheless, contradictory results were reported when ADM was compared to CTG [79, 81-83].

The long-term results of root coverage procedures have progressively gained interest among clinicians [84-86]. The 20-year outcomes of CAF alone for the treatment of localized gingival recession observed that gingival recession decreased from 68.59% (at 1 year) to 56.11% (at 20 years) and the stability of the gingival margin was maintained in 56% of the treated sites [85]. Similarly, the same authors also reported on the 20-year outcomes of patients treated with CAF + CTG for gingival recession, which found that the addition of a CTG seemed to provide benefits for maintaining the obtained results, as the minimal changes in MRC were noted over the 20 years’ timeframe (from 74.23% in the first year to 67.69% at the 20-year recall) [87]. A similar trend towards the recurrence of gingival recession following root coverage procedures has been reported in the literature [82, 84, 85, 88]. Evidence in the literatures is available when evaluating the efficacy of ADM in root coverage procedures in the short-term [89-91]. However, when observed in the long-term, clinical studies demonstrated a significant worsening in the outcomes of root coverage obtained with ADMG over time [79, 82].

This study thus intends to evaluate the long-term outcomes of ADM compare to CTG for treating gingival recessions with thin periodontal phenotype, to the best of our knowledge, have not been previously assessed. We hope that the results could lead to an advanced treatment strategy of gingival recession with ideal clinical outcome.

**Trial status**
The trial has been registered at International Clinical Trials Registry Platform (ICTRP), ID: ChiCTR2000033230, registered on 25 May 2020. The recruitment began in June 2020, and the recruitment will be completed in June 2021.

Abbreviations

ICTRP: International Clinical Trials Registry Platform; CEJ: cemento-enamel junction; CAF: coronally advanced flap; CTG: connective tissue grafts; EMD: enamel matrix derivatives; PRF: platelet-rich fibrin; CRC: complete root coverage; PRP: platelet-rich plasma; XCM: xenogeneic collagen matrix; ADM: acellular dermal matrix either from human; XADM: acellular dermal matrix either from xenogeneic origin; ADMG: acellular dermal matrix graft; MRC: mean root coverage; KT: keratinized tissue; OHI: oral hygiene instructions; PLI: plaque index; GI: gingival index; PD: probing depth; CAL: clinical attachment level; GRD: gingival recession depth; GRW: gingival recession width; KTW: keratinized tissue width; GT: gingival thickness; RES: Root Coverage Esthetic Score; VAS: Visual Analogue Scale/Score; ∆E: color change; SD: standard deviation.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

YZ, MZ, and FL conceive the study design and drafted the protocol. XC participates in the recruitment and allocation. YZ is the major contributor in writing the manuscript. All authors read and approved the final manuscript.

Funding

This trial was conducted with no funding.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The trial was approved by the biomedical ethics committee of Peking University School and Hospital of Stomatology (PKUSSIRB-202054029). The trial complies with the Standard Protocol Items: Recommendations for Interventions Trials (SPIRIT) Checklist. Informed consent will be obtained from all study participants. Before subjects participate in this trial, the consent form must be signed.

Consent for publication
Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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