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Two-stage method of free gingival graft prior to periodontal regenerative surgery for the treatment of intrabony defects with insufficient keratinised tissue width: a study protocol for an open-label randomised controlled trial

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ABSTRACT

Introduction Guided tissue regeneration (GTR) combined with bone grafting for periodontal regenerative surgery has ideal clinical results for intrabony defect. However, some sites of intrabony defects often suffer from insufficient keratinised gingival width, which affects the efficacy and long-term prognosis of periodontal tissue regeneration. Free gingival graft (FGG) is an effective surgical procedure to widen the keratinised gingiva, but there are few clinical studies on FGG prior to GTR combination with bone grafting to improve clinical outcomes.

Methods This study is an open-label randomised controlled trial. 68 patients with periodontitis with at least one intrabony defect depth with ≥3 mm are recruited and randomly grouped. In the test group, FGG is performed first, followed by GTR and bone grafting. After completion of all procedures, the patients will be recalled at 3 months, 6 months and 12 months and the relevant clinical and radiographic examinations will be carried out and statistical analysis of the data will also be performed. The present research has received approval from the Ethics Committee of Shanghai Stomatological Hospital (No.2022–007) on 4 August 2022.

Discussion Exploring the effectiveness of the two-stage approach of FGG prior to periodontal tissue regenerative surgery for the treatment of keratinised gingival width deficient intrabony defects can provide a high-level evidence-based basis for the formulation of relevant treatment strategies in clinical practice.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial is designed as an open-label randomised controlled clinical trial.
⇒ The trial will be the first clinical study to investigate and compare the periodontal regenerative effect of the two-stage method of free gingival graft prior to guided tissue regeneration combined with bone grafting for the treatment of intrabony defects.
⇒ The follow-up in the trial will last for 1 year.
⇒ The outcome of this study will not be applied to older patients with systemic diseases.

Trial registration Chinese Clinical Trial Registry, ID: ChiCTR-2200063180. Registered on 1 September 2022.

BACKGROUND

Periodontitis is a complex oral chronic disease characterised by the resorption of alveolar bone, which is a primary cause of tooth loss and masticatory difficulties, with a prevalence of above 90% in adults in China.1 Moderate and severe periodontitis, often accompanied by the presence of deep intrabony pockets, has been shown to significantly increase the progressive risk by more than 10-fold.2 3 Periodontal regenerative surgery has been proposed for the treatment of intrabony defects within deep pockets.4 Also, periodontal regeneration is one of the important periodontal treatment objectives, which is currently used as a standard option for the treatment of severe periodontitis.5 The procedures for periodontal regeneration include guided tissue regeneration (GTR) and bone grafting, which are often performed in combination. Increasing evidence suggests that periodontal regeneration surgery can achieve significant clinical outcomes in the
treatment of intrabony defects with long-term stability, and the outcomes are sustained over 10 years, allowing for preservation of teeth.6,7

Keratinised gingiva acts as a defensive barrier due to highly keratinised superficial epithelium, which is very resistant to local irritation.9 Adequate keratinised gingiva is an important factor in maintaining periodontal health, which facilitates oral hygiene and plaque control. Inadequate keratinised gingiva will weaken the resistance and worsen local inflammation. There is a common consensus that keratinised tissue width (KTW) of >2 mm and attached gingiva width of >1 mm is essential to maintain the periodontal health of natural teeth.9

Nevertheless, gingival recession, inadequate keratinised gingiva and insufficient vestibular groove are often present in some patients with moderate and severe periodontitis clinically, particularly in sites with intrabony defects where there may be a coexistence of inadequate keratinised gingiva present. Insufficient keratinised gingiva can limit the operative incision design and repositioning of the gingival flap during bone grafting surgery, leading to gingival necrosis, postoperative gingival flap tears, exposure of bone grafts, gingival recession and poor clinical prognosis of bone grafting.10 Since 1963, free gingival graft (FGG) is one of the most common periodontal plastic surgeries to increase the width of keratinised tissue around teeth.11 There are few clinical studies and reports on FGG for the preservation of natural teeth in cases of moderate and severe periodontitis, in which the preservation of natural teeth is particularly important.

The major hypothesis in this study is that two-stage method of FGG prior to periodontal regenerative surgery might be more effective than only periodontal regenerative surgery for the treatment of intrabony defects with insufficient KTW, which will be validated in the present open-label randomised controlled clinical trial.

METHODS/DESIGN
Overview
The present study is a randomised controlled clinical trial. Sixty-eight periodontitis patients having intrabony defects with insufficient KTW will be recruited. The recruitment, treatments and follow-ups will be accomplished in the Department of Periodontology, Shanghai Stomatological Hospital & School of Stomatology, Fudan University, China. A trial flowchart is shown in figure 1. The study protocol followed the Standard Protocol Items: Recommendations for Interventional Trials guidance for protocol reporting.

Inclusion criteria
b. Patients were diagnosed with stage III or IV grade C periodontitis according to the 2017 consensus classification of periodontal and peri-implant diseases and conditions.12

c. According to the radiographic examination, there is at least one intrabony defect depth 3mm.
d. The width of the keratinized gingiva at the defect site 2mm.
e. Periodontal pocket probing depth (PD) 5mm and gingival bleeding index (BI) 2 at the intrabony defect site.13
f. Vital pulp or complete root canal treatment of the affected tooth.
g. Good compliance and good oral hygiene habits.
h. Able to obtain informed consent.

Exclusion criteria
a. Smoking.
b. Women who are pregnant or breast feeding.
c. The patients with systemic diseases such as tumour, diabetes and cardiovascular disease.
d. Any situation in which periodontal surgery is not suitable.
e. The affected tooth has III° furcation involvement or III° loosening.
f. The affected tooth has undergone periodontal surgery before.

Recruitment
The subjects recruited for this study were all patients attending the Department of Periodontology, Shanghai Stomatological Hospital. Before recruitment, each patient will undergo initial periodontal therapy, which consists of oral hygiene instructions (OHI), full mouth scaling and root planing. Hand curettes (Hu-Friedy, USA) and an ultrasonic device (PIEZON MASTER 700, Switzerland) will be used in the therapy. Based on the results of the re-evaluation that will be performed 6–8 weeks after initial periodontal therapy, the need for periodontal surgery will be judged. If the need exists, the study information will be explained to the patients. Only the patients who would like to participate in the trial and agree to sign a written informed consent will be enrolled in the study.

Randomisation and blinding
In this study, subjects who met the criteria were randomly divided into test and control groups using a zone group randomisation method. Randomisation was masked by the opaque envelope method. The random sequence is produced through a random number table and the assignment is saved in a sealed envelope. All patients will be randomly assigned to two groups. Test group: FGG 3 months prior to GTR and bone grafting. Control group: GTR and bone grafting. The trial is an open-label study because neither the patients nor the researchers can be blinded.

Interventions
All patients will be subjected to periodontal surgeries, which will be carried out by an experienced operator (MC). Periodontal surgery will be performed under local anaesthesia by 4% articaine containing 1:100,000 epinephrine. FGG consists of a two-step procedure: obtaining
keratinised epithelium-covered connective tissue from donor palatal mucosa and transplanting the graft into the recipient area (figure 2). Making incisions is to remove a piece of free gingival tissue from the palate, and the tissue may be trimmed to fit the size of the recipient area. Once the recipient site is prepared, the graft is placed onto the area and carefully positioned to cover it. The sutures are placed around the edges of the graft to secure the graft. Periodontal regenerative surgery includes open flap debridement, guided tissue regeneration and bone grafting (figure 3). Sulcular incisions will be followed by elevation of mucoperiosteal flaps. After thorough debridement and careful rinsing with saline solution, Bio-Oss (Geistlich, Switzerland) will be filled into the intrabony defects. A resorbable collagen membrane (B type, ZH-Bio, China) will be used to cover the defects. Finally, a vertical mattress suture will be performed to close the wound. The details of the step that bone graft is filled into each intrabony defect will be recorded respectively. The patients will be required to rinse with a 0.2% chlorhexidine solution twice a day, and the suture will be removed 2 weeks after surgery. All patients will be recalled for follow-up visits every 3–6 months after the surgery. At each time point during the follow-up personalised OHI and supportive periodontal therapy will be carried out. OHI should include instruction on proper toothbrushing technique and interdental cleaning. The patients should be encouraged to brush twice daily using a soft-bristled toothbrush and the modified Bass technique are recommended for patients. Also, the patients should be instructed on the use of interdental brushes, floss or other interdental aids. The difference of the procedures in the control group will be that only GTR and bone grafting was performed without prior FGG.

**Examination**

At baseline, all the enrolled patients will receive a clinical periodontal examination by using an automated probe (Florida Probe, USA) by a calibrated examiner (MG). The patient’s PD, clinical attachment level (CAL), KTW and BI at the intrabony defect sites will be recorded. At each intrabony defect site, the buccal and lingual clinical parameters (PD, CAL and BI) will be recorded respectively. In addition, the intrabony defects will be examined using cone beam CT (CBCT) radiographs. All patients will be reevaluated 3, 6 and 12 months after surgery. At

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**Figure 1** Consolidated Standards of Reporting Trials diagram.
each re-evaluation, the same clinical examination will be performed. At 6 and 12 months after surgery, CBCT radiographs will also be carried out.

**Outcome measures**
The primary outcome is CAL. The secondary outcomes include (1) PD, (2) BI, (3) KTW, (4) depth of intrabony defect and (5) vertical alveolar bone loss. Both depth of intrabony defect and vertical bone loss are radiographic parameters by CBCT.

**Sample size**
The sample size will be calculated according to the following formula:

![Clinical photos of free gingival graft procedures.](image1)

(A) Initial visit; (B) donor palatal area; (C) harvesting the tissue; (D–E) suture.

![Clinical photos of periodontal regenerative surgery procedures.](image2)

(A) Initial visit; (B) open flap debridement; (C) bone grafting; (D) covering resorbable collagen membrane; (E–F) suture.
Based on a previous retrospective study by our team,14 the change in CAL for periodontal regenerative surgery due to insufficient keratinised gingival width was compared with a difference ($\delta$) of 1.04 mm, with an SD ($\sigma$) of 1.45 mm, a test level ($\alpha$) of 0.05 and a test efficacy (1-$\beta$) set at 0.8. Thus, the sample size was calculated to be 31 in each group. Considering a 10% loss to follow-up rate, the final sample size for this study is, therefore, ultimately set at 34 per group, with a total of 68 patients recruited.

Data collection
For the reliability of measurement, all the data collections will be accomplished by the same researcher (XC). All data collected will be stored both in paper and digital formats. Besides, the data will also be uploaded in the Chinese Clinical Trials Registry (http://www.chictr.org.cn/).

Statistical analysis
Before analysis, normality will be tested using the Shapiro-Wilk test, and variance equality will be tested using the Levene variance homogeneity test. Normally distributed data will be shown as the mean±SD, otherwise as median (lower to upper quartile). The paired samples t-test will be applied to detect any difference between baseline and 1-year follow-ups. Statistical analyses will be accomplished using SPSS V.25.0 (IBM, USA). The level of statistically significant difference will be set at 0.05.

Withdrawal
Participants will be informed that they can quit the research at any time and no reason is needed. The withdrawal will not influence their follow-up treatment in the future.

Dissemination of data
Data from the present research will be available at the Clinical Trials Registry Platform once the study is completed. Additionally, we will disseminate the results through scientific dental journals.

Ethics and dissemination
The present research has received approval from the Ethics Committee of Shanghai Stomatological Hospital (No.2022–007) on 4 August 2022. The patients will be incorporated into this trial only after their written informed consent has been obtained. The study will be performed according to the 2013 revision of the Helsinki Declaration of 1975. Personal information of all subjects will be stored in the Department of Periodontology of Shanghai Stomatological Hospital. Data of the present research will be registered with the Clinical Trials Registry Platform. Additionally, we will disseminate the results through scientific journals.

Patient and public involvement
Neither patients nor the public was involved in the design, conduct, report or dissemination of this trial. Once the trial has been published, participants will be informed of the results by telephone or email.

DISCUSSION
Inadequate KTW in patients with intrabony bone defects is one of the most challenging challenges faced by periodontal clinicians nowadays. When keratinised gingiva is excessively narrow, it is likely to be stretched by the nearby alveolar mucosa and muscle causing the gingiva to separate from the tooth surface. In cases with poor oral hygiene, lack of keratinised tissue is also a contributory factor to periodontitis susceptibility. Not only is inadequate KTW lacking keratinised tissues around the teeth to protect the periodontal tissue against surrounding inflammation, but also makes it more difficult for the clinician to perform periodontal regeneration procedures and has a negative impact on the prognosis. In our retrospective study of previous cases,14 we found that periodontal regeneration with inadequate KTW is likely to be associated with postoperative wound dehiscence, graft exposure and postoperative gingival recession. Recently, a staged procedure for periodontal regeneration has been proposed for cases with root furcation with KTW <1 mm and shallow vestibular groove, in which FGG is recommended to increase keratinised gingival width and vestibular groove depth 3 months prior to periodontal regenerative procedure.16 However, there have been no relevant clinical studies validating this. There was also a case report of combining mucogingival surgery with periodontal bone grafting for the treatment of root furcation sites of intrabony defects with inadequate keratinised gingiva with good clinical results.17 Due to the paucity of such clinical studies, further studies are needed to determine whether the two-stage treatment of FGG prior to periodontal regeneration for intrabony defects with insufficient KTW results in better clinical outcomes and long-term stability, compared with the direct periodontal regeneration.

Trial status
The trial protocol received ethics approval in 4 August 2022 and was registered at the International Clinical Trials Registry Platform on 1 September 2022. The trial is recruiting patients; it is scheduled to be completed in June 2025.

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Contributors
HL, JL and MC proposed the concept of this work and designed the trial. HL and JL drafted the manuscript and documents. XC and MG participated in the recruitment and allocation of the study participants. MC reviewed and finalised the manuscript. All authors agreed with the final version.
REFERENCES


