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The impact of autologous concentrated growth factors on the alveolar ridge preservation after posterior tooth extraction: A prospective, randomized controlled clinical trial

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Abstract

Background: Alveolar ridge preservation can effectively decrease alveolar ridge resorption following tooth extraction, but it can be limited by reducing new bone formation and residual bone graft material. Efforts to develop more efficacious approaches are thus an area of active research.

Purpose: To assess the impact of autologous concentrated growth factors (CGF) on alveolar ridge absorption and osteogenesis following posterior tooth extraction.

Materials and methods: Fifty patients were randomly assigned to have extraction sockets treated with CGF or no treatment. At 10 days, 1 month, and 3 months postextraction, soft tissue color and texture were examined and evaluated with healing score. Cone-beam computed tomography (CBCT) scans were performed before and 3 months after extraction, while radiographic analyses were used to assess vertical and horizontal bone changes. Bone samples were collected from the extraction sockets during implant placement, and micro-computed tomography (micro-CT) scans and histological analysis were performed to evaluate new bone formation. *t*-Test or Mann–Whitney *U* test was used to compare data and the level of statistical significance was set at 0.05 for all analyses.

Results: Forty-six patients completed the trial. Sockets in the experimental group exhibited significantly better healing score on Day 10 postextraction relative to the control group, whereas comparable healing was observed in both groups at 1 and 3 months postextraction. Experimental group exhibited reduced vertical bone changes relative to the control ($p < 0.05$). Significant reductions were observed in ridge width changes at 1 and 2 mm apical to the crest ($p < 0.05$), although differences at 3 and 5 mm apical to the crest were not significant. Significant differences of bone mineral density (BMD) and microarchitecture of trabecular bone were observed via micro-CT analyses, and the experimental group had better results.

Conclusion: CGF application following posterior tooth extraction may reduce vertical and horizontal bone resorption and promote new bone formation.

KEYWORDS
alveolar ridge reconstruction, bone regeneration, CBCT imaging, coagulation

What is known

- Alveolar ridge preservation has been proved to be effective in reducing resorption and remodeling of alveolar bone. However, current bone graft materials have some problems in inhibiting the formation of new bone and residual materials.
- Concentrated growth factors (CGF) is a next-generation form of autologous platelet-rich plasma preparations, which has distinct clinical and biological properties in tissue regeneration. But the well-conducted RCT studies about the use of CGF in isolation in the field of alveolar ridge preservation are still lacking.

What this study adds

- The prospective, randomized controlled clinical trial assessed the relative impact of CGF on alveolar ridge absorption and osteogenesis following posterior tooth extraction.
- CGF application following posterior tooth extraction could suppress vertical and horizontal bone resorption, promoting new bone development and improving the overall quality of new bone.

1 | INTRODUCTION

Alveolar ridge reduction is a common consequence of tooth extraction,[1,2] with Tan and colleagues having reported 11%–22% changes in the vertical dimension at 3 months postextraction, whereas the horizontal dimension was altered by 32% and 29%–63% at 3 and 6–7 months postextraction, respectively.[3] Such bone resorption can impact the positioning of implants, potentially resulting in bone defects that can adversely impact long-term implant stability or aesthetics, necessitating additional reconstructive surgery.[3–5]

Alveolar ridge preservation efforts seek to overcome the challenges inherent in tooth extraction using a range of approaches including growth factors, barrier membranes, and bone grafts. Relative to natural healing, alveolar ridge preservation has been shown to be an effective approach to suppressing bone resorption and preserving the shape of the alveolar fossa.[6,7] Few randomized controlled trials (RCTs) of alveolar ridge preservation techniques capable of promoting new bone formation have been conducted to date. The majority of studies of bone grafts also encounter certain problems, such as residual graft material, an inability to enhance new bone formation, reduced new bone formation, and long healing time.[6,8]

Autologous platelet-rich plasma preparations have been studied for many years in the context of alveolar ridge preservation. Some studies have identified the use of autologous platelet-rich plasma preparations, also known as platelet-rich fibrin (PRF), as being effective treatments capable of facilitating alveolar ridge preservation.[9,10] However, some studies also suggest that using PRF alone as an approach to alveolar ridge preservation has no significant effect on reducing bone absorption.[11] Hauser and colleagues found that the filling of the extraction socket with PRF following extraction significantly altered bone tissue quality.[12] Stumbras and colleagues proved plasma rich in growth factors (PRGF) had been effective in bone regeneration by histomorphometrical analysis.[13] But Areewong and colleagues determined that the new bone formation ratio was higher in a PRF group than in a control group with no statistically significant difference between the two.[14] CGF is a next-generation form of PRP with distinct clinical and biological properties. CGF is prepared using a special centrifuge (Medifuge, Silfradentsrl, Italy) and a series of controlled speeds to concentrate factors from patient blood samples. There is evidence[15–17] that CGF contains almost all of the growth factors present within centrifuged blood samples. The release of these growth factors is closer to the natural process of tissue healing, such that CGF can readily promote soft and hard tissue healing.

Some studies[18–21] have found that the use of CGF alone or mixed with bone graft material in the context of maxillary sinus augmentation surgery or periodontal surgery was associated with good clinical results, increased new bone formation, and reduced bone absorption. There has been only one report[22] regarding the effects of CGF mixed with bone graft materials on alveolar ridge preservation to date, and so far, no studies of the use of CGF in isolation in such a context have been published to our knowledge.

The present study was designed to assess the impact of autologous CGF on alveolar ridge absorption and osteogenesis following posterior tooth extraction.

2 | MATERIAL AND METHODS

2.1 | Patient selection

This was a prospective RCT conducted in a manner consistent with the Declaration of Helsinki of 1975 and its amendments from 2000. This study was approved by the Institutional Review Boards of the Peking University School and Hospital of Stomatology (Approval Number: PKUSSIRB-201943029; Chinese Clinical Trial Registry Identifier: ChiCTR1900023243). In total, the study enrolled 50 patients who visited the First Clinical Department of Peking University School and Hospital of Stomatology from May 2019 to January 2020. Patients need to take cone-beam computed tomography (CBCT) twice

TABLE 1 Inclusion and exclusion criteria

Inclusion	Exclusion
Age >20 years	Minors or cognitive impairment, unable to understand the content of the experiment
Need of molar or premolar extraction	Severe systemic diseases, unable to tolerate routine outpatient extraction and implantation
The presence of one adjacent tooth at the extraction site	History of radiotherapy for head and neck tumors
Adequate oral hygiene (bleeding on probing <20%; plaque index <20%)	Long-term administration of corticosteroids, bisphosphate, and other drugs affecting bone regeneration
Systemically healthy with no contraindication for oral surgical procedures	Severe periodontitis or poor oral hygiene
Intention to implant-retained prostheses after extraction	Smokers (>10 cigarettes/day)
Signed informed consent form	Teeth with acute infection

and be collected two 9 mL samples of blood. All the enrolled patients signed an informed consent form before participating in the trial.

Eligible patients included those scheduled to undergo premolar or molar extraction for whom implant-retained prostheses were to be implemented following extraction. Detailed study inclusion and exclusion criteria are shown in Table 1.

2.2 | Randomization

Patient randomization was achieved using a computer-generated list (http://www.randomized.org). Allocation concealment and storage was performed by someone unfamiliar with the study protocol. Patients were randomized into the control and experimental groups by drawing lots.

2.3 | Preparation for treatment

Clinical photographs, clinical examinations, and periapical radiographs were used to confirm that a given tooth could not be retained. Patients meeting study inclusion criteria underwent CBCT (Crestream 9300, Crestream Health, France; 60–90 kV; 2–15 mA; field of vision: 10*10 cm; slice thickness: 180 μm) one week prior to surgery. Oral hygiene instructions, scaling, and routine blood tests for patient coagulatory, renal, and hepatic function were conducted.

2.4 | CGF preparation

Two 9 mL samples of blood were collected from each patient without any anticoagulant into sterile vacuum tubes (Greiner Bio-One, GmbH, Kremsmunster, Austria), which were then immediately spun in a centrifuge (Medifuge, Silfradentsrl, Italy) using the following settings: acceleration for 30 s, 2700 rpm for 2 min, 2400 rpm for 4 min, 2700 rpm for 4 min, 3000 rpm for 3 min, deceleration to a stop for 36 s. After this centrifugation process, three fractions of blood were evident—an upper layer containing serum free of fibrinogen or coagulation factors (platelet-poor plasma [PPP]), a lower layer containing the red blood cells (RBCs), and a middle layer containing the CGF composed of three sections including an upper white part (WP), lower red part (RP), and a buffy coat (BC) in the middle.[23,24]

Solid CGF was extracted from each tube after centrifugation with sterile tweezers, after which it was immersed in sterile saline. The lower RP was cut away and discarded. Two pieces of CGF were thus prepared per patient, with one being used as a gel to fill the extraction socket and the other being compressed into a membrane (Figure 1).

2.5 | Surgical procedures

Before tooth extraction, patients were instructed to rinse for 1 min with a 0.2% chlorhexidine solution. An experienced oral surgeon conducted all procedures including atraumatic extraction and alveolar ridge preservation, with the same approach being used for all patients under local anesthesia. Gingival separation without flap elevation was achieved using periotomes, which were used together with elevators to carefully extract the tooth while preserving the surrounding soft and hard tissue. Diamond fissure bur was used to section roots when necessary. Following extraction, debridement of the socket was performed with surgical curettes to remove any remaining soft tissue, after which a solution of 0.3% hydrogen peroxide was used to irrigate the socket, which was subsequently rinsed with sterile saline. If present, the interseptal bone was removed such that the inter-radicular septum was at least 6 mm from the highest point of the crest to prevent native bone collection during bone core harvesting.[25,26] Sockets were then finished and treated based upon random group assignments as follows (Figure 2):

- Control group: Sockets were filled without any graft materials and were sutured closed with 4–0 absorbable sutures.
- Experimental group: Sockets were filled with CGF gel and covered with a CGF membrane that had been shaped so as to overlap with the extraction socket margins by 2–3 mm. The membrane was positioned slightly under the marginal mucosa and was fixed in

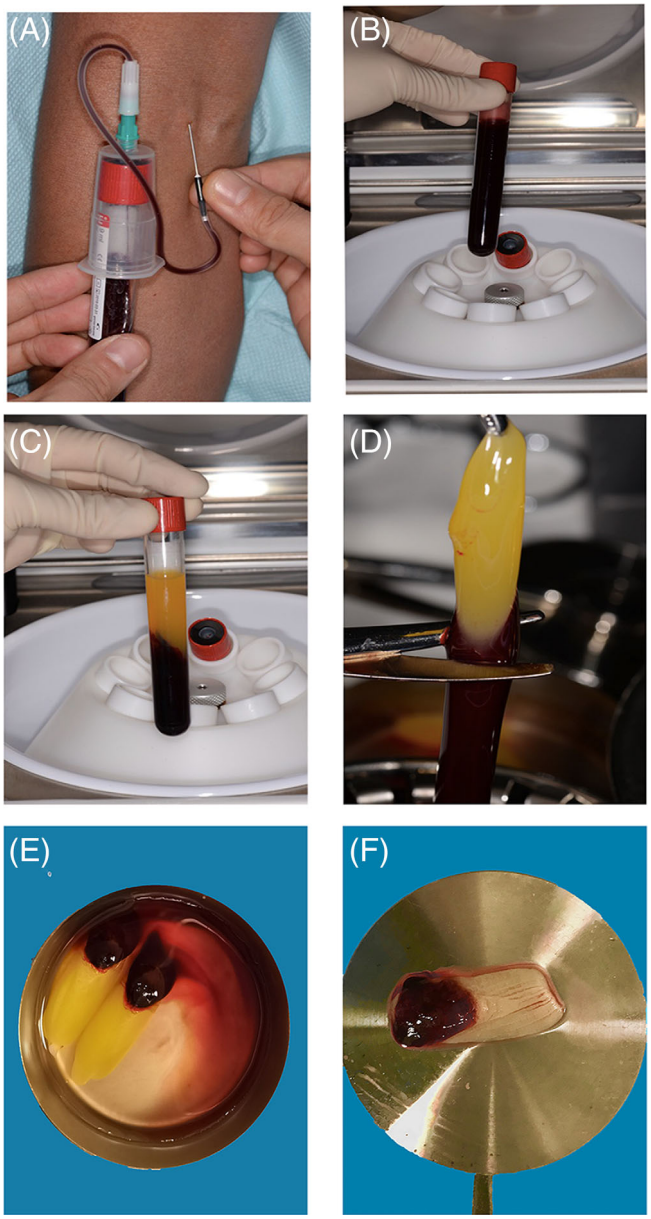

FIGURE 1 Preparation of autologous concentrated growth factors (CGF). (A) Draw blood from the patients. (B) Two tubes in the centrifuge. (C) Tube after centrifugation. Three parts are clearly visible (red blood cells, the solid CGF, and platelet poor plasma). (D) CGF clots are removed from the tubes using tweezers. A scissor is used to separate the red blood cells from the CGF clot. (E) CGF clots are immersed in sterile saline. (F) One clot is pressed into membrane

place with a horizontal mattress suture with 4–0 absorbable sutures. The membrane was exposed to the oral cavity.

Patients were not prescribed any pharmacological treatments, and sutures were removed on Day 10 postextraction. Follow-up analyses of these patients were performed at 10 days, 30 days, and 3 months postextraction. CBCT scans were performed at 3 months postextraction, while dental implants were inserted via a standard approach at 3.5 months postextraction.

Implant placement was conducted under local anesthesia, with surgeons forming a mucosal flap and conducting a 6 mm-long bone biopsy with a core drill that had a 2 mm internal diameter (Hager & Meisinger GmbH, Neuss, Germany) (Figure 3). After collection, bone biopsy samples were immediately transferred to 10% formalin. Treatment did not interfere with implant bed preparation protocols.

2.6 | Outcome measures

Outcomes were measured in a blinded manner by someone who did not know the grouping, and included soft tissue healing scores, CBCT analyses, micro-computed tomography (micro-CT) scans, and histological assessments.

2.6.1 | Soft tissue healing

Soft tissue regeneration, maturation, and quality were assessed with a modified version of the Masse healing index (HI),[27,28] which was initially developed for evaluating healing with primary closure following periodontal surgery. Three scoring levels for each of four parameters were used to assess socket healing without primary closure in the modified HI as follows: tissue color (1 = the gingival tissue was entirely pink; 2 = less than half of the gingival tissue was red, movable, and hyperemic; 3 = more than half of the gingival tissue was red, movable, and hyperemic), healing tissue consistency and color (1 = pink, close-grained; 2 = red, soft; 3 = gray-green, fragile), bleeding (1 = none; 2 = only upon palpation; 3 = spontaneous), and suppuration (1 = none; 2 = none, but significant amounts of plaque around the walls of the socket; 3 = suppuration). Scores ranged from 4 to 12, corresponding to excellent and severely impaired healing, respectively.[27]

2.6.2 | Cone-beam computed tomography

CBCT was conducted at baseline prior to extraction and at 3 months postextraction under identical conditions (Crestream 9300, Crestream Health, France; 60–90 kV; 2–15 mA; field of vision: 10*10 cm; slice thickness: 180 μm). Two DICOM (Digital Imaging and Communications in Medicine) data sets were generated and analyzed with a volumetric imaging software (Mimics 17.0, Materialise, Leuven, Belgium) that was used for 3-dimensional reconstruction. Teeth were readily removed from images, and distinctive anatomical markers including the anterior nasal spine and mental foramen were used to guide the superimposition of selected areas of the virtual models. Following superimposition, these two sets of data were manually evaluated to determine whether perfect matching had been achieved[29,30] (Figure 4). Image J (version 1.47, National Institutes of Health, Bethesda, MD) was then used to measure data at identical reference points at these two time points. For these analyses, we selected the transverse section at the level of the enamelo-cemental junction of

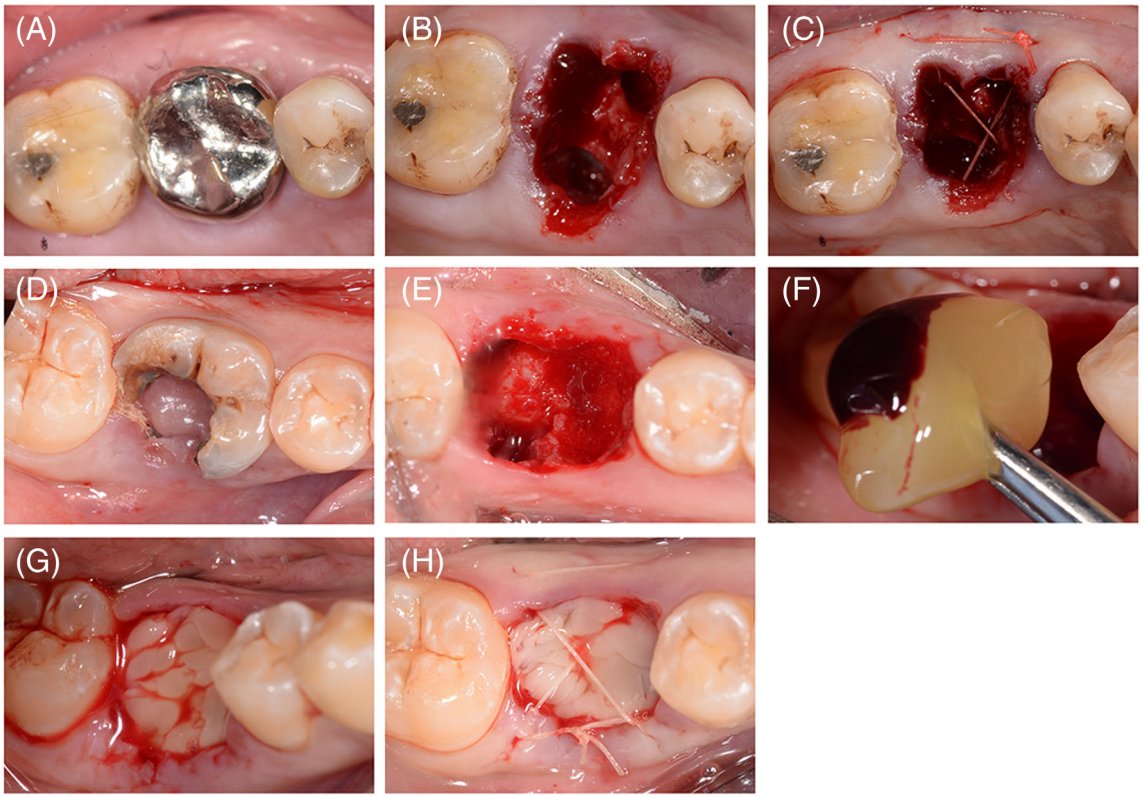

FIGURE 2 Surgical procedures. (A–C) The control group: extraction, debridement, and suture. (D–H) The experimental group: extraction, debridement, filled with autologous concentrated growth factors (CGF) gel, covered with CGF membrane and suture

FIGURE 3 The core drill for taking bone biopsy

the adjacent teeth, with the socket being separated into quarters at that section (Figure 5). Measurements of the following three sagittal sections were then made: (1) the center, (2) the mesial quarter, and (3) the distal quarter of the mesial-distal distance of the alveolar socket. Final values were determined by averaging values for three adjacent sections (Figure 5). A single trained investigator made all measurements, with a calculated measurement accuracy of 0.01 mm.

1. Horizontal ridge width was assessed at four levels (crest −1 mm [HW-1mm], crest −2 mm [HW-2mm], crest −3 mm [HW-3mm], and crest −5 mm [HW-5mm]) below the aspect of the buccal crest.
2. Vertical resorption on both the buccal and palatal/lingual sides. We identified the most coronal points of the extraction plate on the buccal side and the palatal/lingual side as A and P, respectively, while the most coronal extensions of the healed ridge in these two sections were A′ and P′, respectively. Vertical resorption included both the buccal side (AA′) and the palatal/lingual side (PP′).

2.6.3 | Micro-CT analysis

Sample bone mass and architecture was evaluated using a high-resolution micro-CT scanner (GANTRY-STD CT 3121, Siemens) prior to histological assessment.[31] Round regions of interest (ROIs; 2 mm diameter) were selected in 2-dimensional reconstructed cross-sectional slices, after which scanning was conducted with the following settings: isometric resolution = 8.89 μm, voltage = 80 kV, current = 500 μA, and exposure time = 1000 ms. ROIs were then combined to yield a 4 mm-tall cylinder as a defined volume of interest (VOI) that was subjected to quantitative analyses. Newly formed trabecular bone was then subjected to

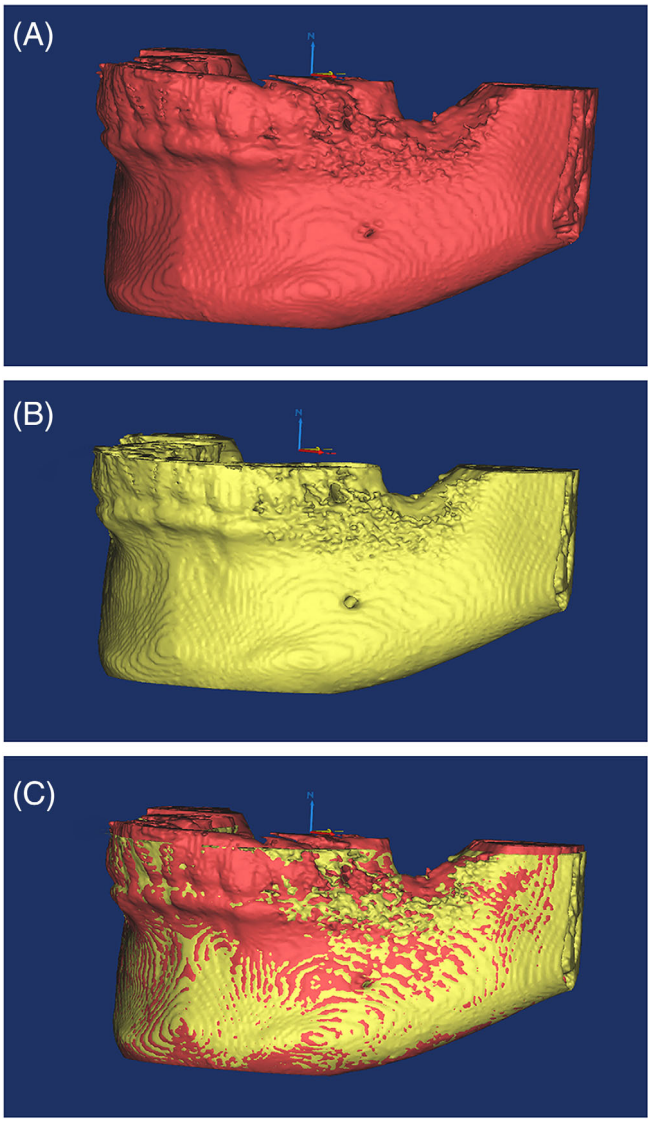

FIGURE 4 Superimposed images of the two 3-dimensional virtual mandible. (A) Before tooth extraction. (B) 3 months after healing. (C) Matching two images

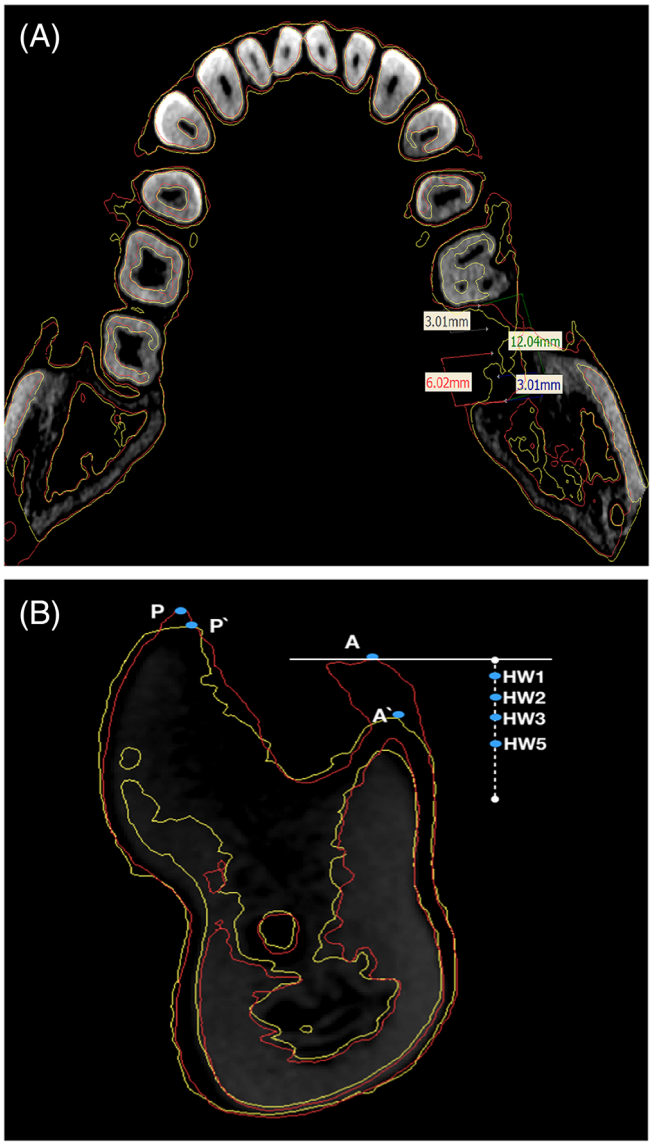

FIGURE 5 Cone-beam computed tomography (CBCT) analyses. (A) The socket being separated into quarters at that section. (B) Schematic drawing of the landmarks for measurements. Red, before tooth extraction; yellow, 3 months after healing

morphological analyses of factors such as bone mineral density (BMD), bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N), and trabecular separation (Tb.Sp).[12]

2.6.4 | Histological analyses

Paraffin-embedded decalcified samples were sliced to prepared 3 μm sections that were subsequently dehydrated with an ethanol gradient and stained using hematoxylin and eosin (H&E) (Zhongshan Goldenbridge, Beijing, China). A light microscope was used to assess new bone formation, with panoramic scans being conducted with 3DHISTECH (Pannoramic MIDI, Hungary). Additional histological analyses will be reported in a follow-up study.

2.7 | Statistical analysis

Based on a previous study reporting mean and standard deviation (SD) values pertaining to horizontal alveolar ridge changes,[10] at $\alpha = 0.05$ we determined that we would require 23 patients per group to achieve 80% statistical power, whereas 25 per group would be necessary to study vertical changes.[25] A sample size of 25 was therefore chosen for this study.

Measurements were recorded in a spreadsheet in Excel 2013 (Microsoft Corporation, WA) and were then analyzed using SPSS 20.0 (SPSS Inc., IL). Data are given as mean ± SD and were evaluated via a Shapiro–Wilk test to assess distribution normality. Normally distributed data were compared via *t*-test or analysis of variance (ANOVA),

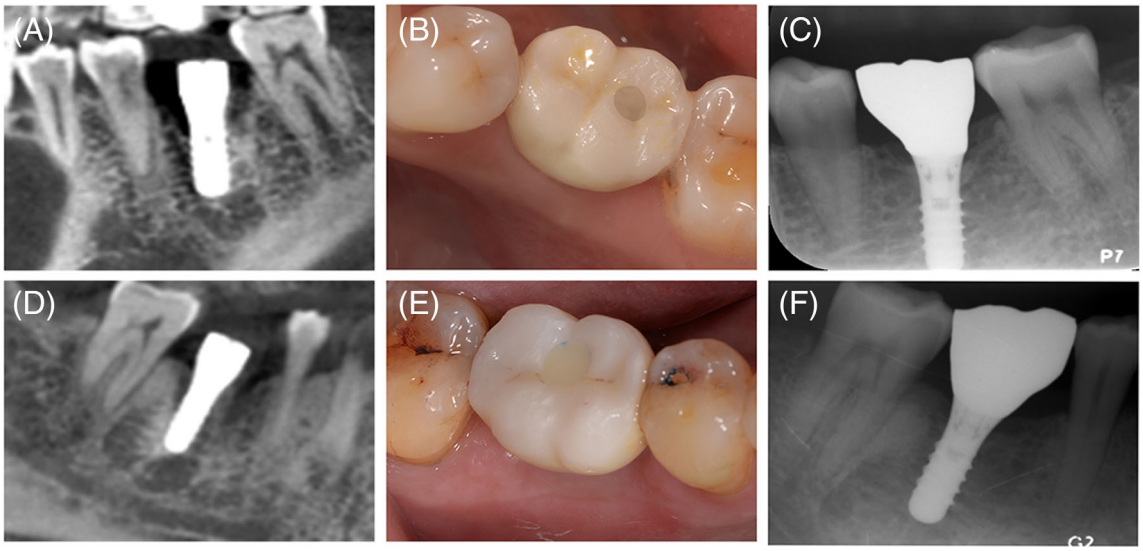

FIGURE 6 One year follow-up. (A) Immediately cone-beam computed tomography (CBCT) after implantation in control group. (B, C) One year after restoration in control group. (D) Immediately CBCT after implantation in experimental group. (E, F) One year after restoration in experimental group

TABLE 2 Demographic characteristics and clinical indices for control and experimental groups

	Control	Experimental	*p*-value
Age			
Median (range)	37 (29–72)	45 (23–67)	
Mean ± SD	42.65 ± 13.39	45.3 ± 14.38	0.502
Gender			
Male	13	15	
Female	10	8	
Total number of teeth	23	23	
Tooth position			
Maxillary tooth	5	13	
First premolar	0	1	
Second premolar	2	4	
First molar	3	6	
Second molar	0	2	
Mandible tooth	18	10	
First premolar	0	1	
Second premolar	0	1	
First molar	10	6	
Second molar	8	2	
Condition of buccal plate			
Number of intact	20	18	
Number of incomplete	3	5	
Distance from apex to maxillary sinus	4.27 ± 0.72	4.16 ± 1.17	0.566
Width of keratinized tissue	>2 mm	>2 mm	

Note: No significant differences were observed ($p > 0.05$).

TABLE 3 Healing index of soft tissue

		Healing index score (4–12)		
		Control	Experimental	*p*-value
10 days	Mean ± SD	6 ± 1.23	5.30 ± 0.70	0.026
	Median (range)	6 (4–9)	5 (4–7)	
1 month	Mean ± SD	4.48 ± 0.51	4.22 ± 0.42	0.066
	Median (range)	4 (4–5)	4 (4–5)	
3 months		4	4	

Note: No significant differences were observed ($p > 0.05$).

while non-normally distributed data were compared via Mann–Whitney *U* test. A significance level of $\alpha = 0.05$ was used for all analyses.

3 | RESULTS

In total, we identified 50 patients meeting study enrollment criteria, of whom 46 (23 in each group; 18 females and 28 males; mean age: 43.98 ± 13.8 years) completed all trial protocols and subsequent implant restoration. One patient in the control group was lost to follow-up, while the remaining three patients failed to complete return visits within the proscribed time frame. Patients of both two groups reported no severe pain and discomfort after extraction. Surgical wound healing was uneventful in all patients, with no significant complications. One year after loading, the survival rate of implant restoration was 100% with no mechanical and biological complications. The success rate of implantation was 100% in both groups (Figure 6).

Patient demographics and information pertaining to extraction sites are shown in Table 2. There were no significant differences in average patient age between the control (42.65 ± 13.39, 29–72 years) and experimental groups (45.3 ± 14.38, 23–72 years) ($p = 0.758$).

3.1 | Soft tissue healing

Implantation was successful in all patients, with no instances of infection. Details regarding patient healing are shown in Table 3. Average healing scores in the control and experimental groups at 10 days postextraction were 6 ± 1.23 and 5.30 ± 0.70, respectively ($p = 0.026$), while at 1-month postextraction these respective scores were no significant difference between groups ($p = 0.066$). At 3 months postextraction, scores in both groups were 4, which was the minimum possible HI score (Figure 7).

3.2 | CBCT analysis

Baseline measurements of the sockets were comparable between both groups (Table 4). At 3 months postextraction, resorption in the control group on the buccal and palatal/lingual sides were shown in

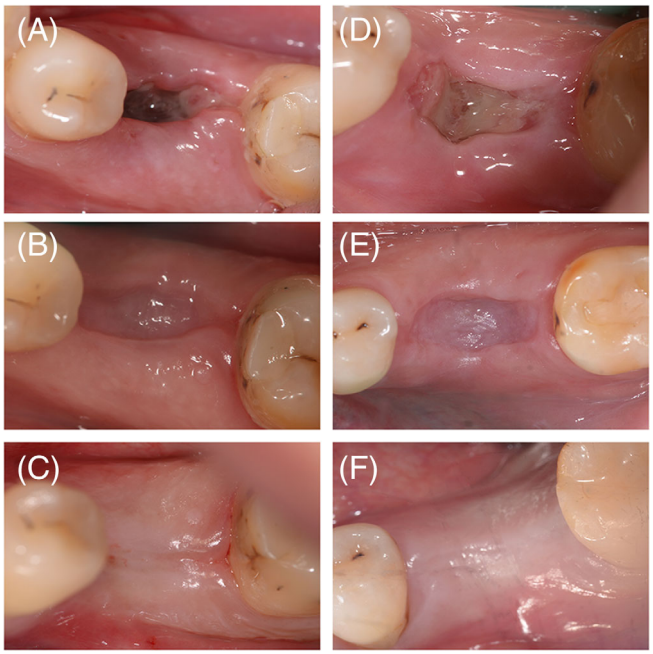

FIGURE 7 Soft tissue healing. (A–C) 10 days, 1 month, and 3 months postextraction in control group. (D–F) 10 days, 1 month, and 3 months postextraction in experimental group

TABLE 4 Baseline measurements of the sockets in control and experimental groups (mm; mean ± SD)

	Control	Experimental	*p*-value
HW1b	6.65 ± 3.9	5.73 ± 2.90	0.684
HW2b	9.95 ± 3.57	9.38 ± 3.43	0.588
HW3b	12.38 ± 2.55	11.55 ± 2.98	0.312
HW5b	15.52 ± 2.42	14.2 ± 2.87	0.100
SH	8.95 ± 1.2	8.39 ± 1.27	0.095
BT1	1.67 ± 0.51	1.35 ± 0.75	0.214
BT2	2.16 ± 0.55	1.97 ± 0.81	0.277
BT3	2.5 ± 0.74	2.29 ± 1.06	0.282
BT5	3.18 ± 0.85	2.69 ± 1.17	0.059

Note: No significant differences were observed ($p > 0.05$).
Abbreviations: b, before the extraction; BT, thickness of buccal bone plate; HW, horizontal ridge width; SH, socket height.

Table 5. As such, there were significant differences between these two groups with respect to buccal and palatal/lingual vertical bone resorption ($p < 0.05$).

Changes in ridge width and reduction rate at the four assessed vertical levels were showed in Table 6. Differences between these groups were significant at the HW1 and HW2 levels ($p < 0.05$) (Figure 8).

3.3 | Micro-CT analysis

Of the 46 collected samples, 5 (2 in the control group, 3 in the experimental group) were damaged during sampling and were omitted from our analyses. Micro-CT analyses of the remaining 41 samples were performed in a blinded fashion at the time of biopsy, revealing significant differences in BMD between the control and experimental groups ($p < 0.05$). Similarly, BV/TV was higher in the experimental group, as was Tb.N. In contrast, Tb.Sp was lower in the experimental group relative to the control group, and Tb.Th in the experimental group was larger relative to the control group, although this difference was not significant ($p > 0.05$) (Figure 9 and Table 7).

TABLE 5 Vertical resorption of both buccal and palatal/lingual sides in control and experimental groups (mm; mean ± SD)

	Control	Experimental	*p*-value
The buccal side (AA′)	1.49 ± 1.31	0.63 ± 0.67	0.011*
The palatal or lingual side (PP′)	0.69 ± 0.77	0.23 ± 0.50	0.008*

*Statistically significant difference ($p < 0.05$).

3.4 | Histological analyses

We did not observe inflammation in any samples, and all exhibited active bony regeneration. Many osteoblasts were evident at the border of the newly formed bone, with osteocytes present in the bone lacunae. When magnified 10 times, more new bone tissue, larger area of bone tissue and more lamellar bone could be seen in experimental group. At 40× magnification, the new trabeculae of experimental group were denser and the number of bone lacunae was much more (Figure 10). Additional histological analyses will be reported in a follow-up study.

4 | DISCUSSION

Herein, we evaluated the impact of CGF application on alveolar ridge preservation following posterior tooth extraction via histological, radiographic, and clinical evaluations. This approach confirmed that CGF application is safe and more effective than natural healing as a

TABLE 6 Ridge width changes in control and experimental groups

	Ridge width changes (mm; mean ± SD)			Ridge width reduction rate (%; mean ± SD)		
	Control	Experimental	*p*-value	Control	Experimental	*p*-value
HW1	3.13 ± 2.28	1.38 ± 2.46	0.016*	50.18 ± 32.15	14.93 ± 42.67	0.003*
HW2	4.02 ± 2.28	2.40 ± 2.72	0.033*	44.40 ± 25.27	21.43 ± 27.66	0.005*
HW3	2.10 ± 2.38	1.11 ± 3.38	0.121	17.44 ± 20.07	3.58 ± 19.64	0.067
HW5	0.47 ± 0.89	0.36 ± 1.03	0.709	3.39 ± 6.34	3.41 ± 5.58	0.921

Abbreviation: HW, horizontal ridge width.
*Statistically significant difference ($p < 0.05$).

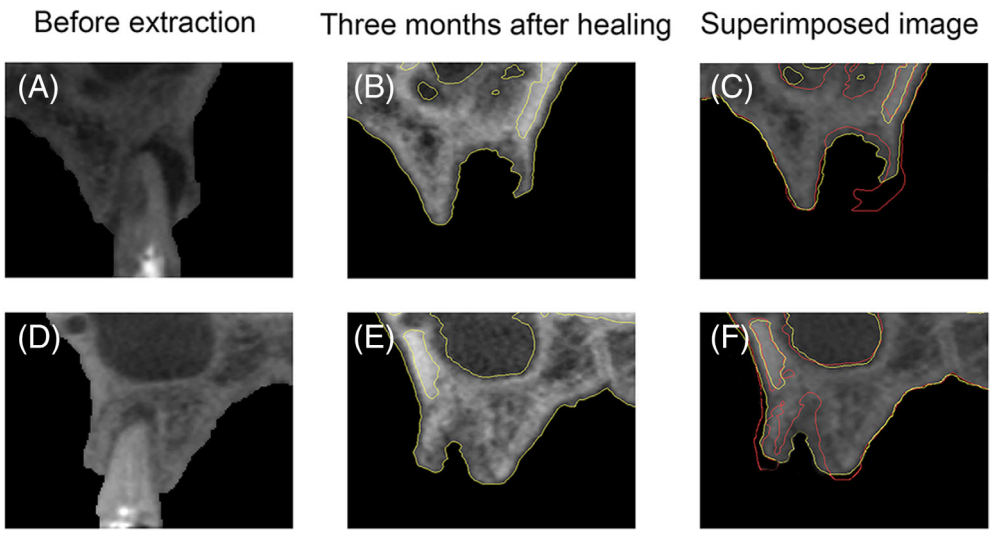

FIGURE 8 Sagittal sections of the virtual models (red line indicates the bony outline before extraction, and yellow line indicates the bony outline after healing). (A–C) Before extraction, after healing, and superimposed images of control group. (D–F) Before extraction, after healing, and superimposed images of experimental group

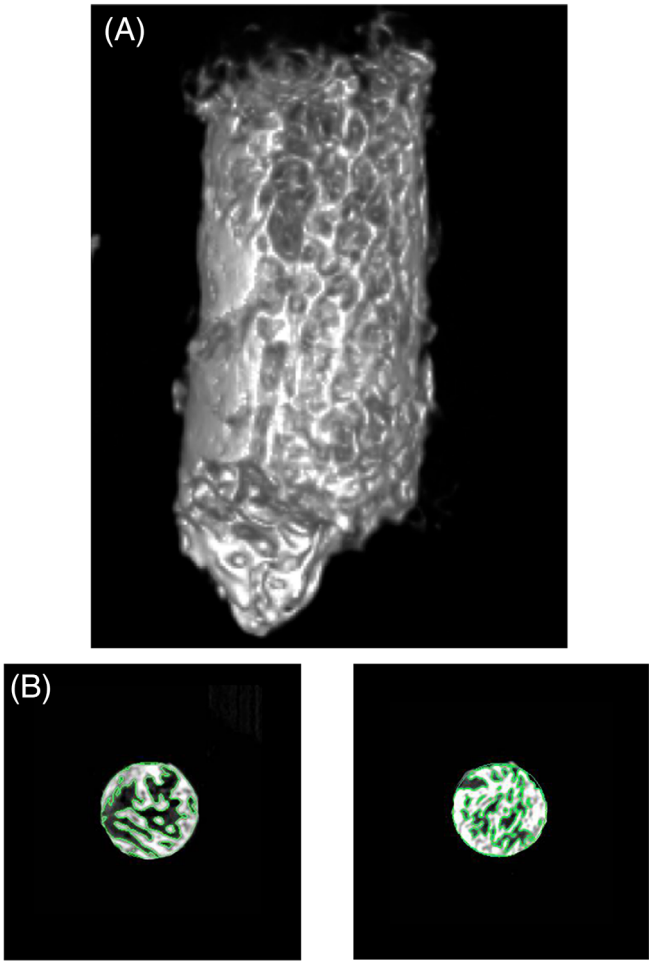

FIGURE 9 Micro-computed tomography (micro-CT) analysis of bone sample. (A) 3-dimensional virtual bone sample. (B) The cross-section of one sample in control group. (C) The cross-section of one sample in experimental group

TABLE 7 Microarchitecture of the new trabecular bone analyzed by micro-CT

	Control	Experimental	*p*-value
BMD mg/cm^3	936.42 ± 225.86	1121.19 ± 291.35	0.03*
BV/TV	0.48 ± 0.13	0.58 ± 0.13	0.02*
Tb.Th	0.14 ± 0.03	0.15 ± 0.04	0.557
Tb.N	3.48 ± 0.79	4.00 ± 0.85	0.038*
Tb.Sp	0.16 ± 0.07	0.12 ± 0.07	0.013*

Abbreviations: BMD, bone mineral density; BV/TV, bone volume fraction; micro-CT, micro-computed tomography; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness.
*Statistically significant difference ($p < 0.05$).

means of reducing reductions in ridge dimensions and new bone regeneration following tooth extraction.

CGF is a form of autologous platelet-rich plasma preparation prepared using a special centrifuge and a series of controlled spins to concentrate factors from patient blood samples without any graft residue. Three key factors are necessary to facilitate optimal regenerative medicine: growth factors, autologous cells, and scaffolding,[32,33] all of which are all present in CGF.[23] CGF preparations are semitransparent gelatinous, smooth, soft, and elastic when viewed by eye. Histological observations of these preparations revealed a fibrin lattice structure containing leukocytes and platelets.[34] Under a scanning electron microscope, a network structure composed of random discrete fibers was observed. The fibrin network and architecture differed between the buffy coat and white sections of these preparations, with the network being strictly compact nearer to the buffy coat, whereas it formed a larger mesh at greater distances.[15] There are different views on the study of the role of leukocytes in platelet preparations. Including leukocytes in platelet concentrates is beneficial. Some reports propose eliminating leukocytes,[35] while others consider the anti-infectious, growth factor secreting, and anti-inflammatory benefits of leukocytes.[36,37] Puidokas and colleagues[38]conducted a systematic review which found that in the presence of WBCs, platelet concentrates promote cell migration, proliferation, and differentiation less effectively and are responsible for a potentially prolonged inflammation phase due to cytokine release. In our study, CGF promoted the healing of soft tissue. The distribution and function of leukocytes in CGF need to be further studied. CGF promoted soft and hard tissue regeneration and wound healing mediated by internal growth factors and the fibrin matrix.[24,39] During the process of CGF preparation, the release of platelet alpha granules was most effectively stimulated. At least 16 types of growth factors were present in CGF preparations, functioning both individually and in a synergistic manner. These factors have been reported to induce the osteogenic differentiation of mesenchymal stem cells, promote the proliferation and migration of osteoblasts and osteocytes, inhibit bone resorption, and accelerate the regeneration of bone tissue by regulating gene expression.[40] Prior work has shown CGF to have a denser network structure than PRF, thereby better protecting growth factors and delaying their release kinetics.[23,24]

Walker and colleagues[25] assessed socket bone changes via CBCT following molar tooth extraction, revealing horizontal and vertical reduction values of 3.11 ± 3.83 mm and 2.6 ± 2.06 mm, respectively. Similarly, Barone and colleagues[41] detected a horizontal reduction of 3.6 ± 0.72 mm and vertical reductions on the buccal and lingual/palatal side of 2.1 ± 0.66 mm and 2.31 ± 0.63 mm, respectively. Changes in ridge width in the control group in our study were in line with these prior findings, although we observed significantly reduced amounts of vertical reduction. This may be attributable to the buccal bone wall thickness, residual alveolar ridge height following tooth extraction, or specific study inclusion criteria. Walker and colleagues[25] also found that avoiding ridge preservation did not affect the ability of clinicians to successfully conduct implantation while meeting specific inclusion criteria, although it did increase bone graft rates in the context of implantation. As such, minimizing posterior socket bone resorption following extraction is important to facilitate optimal implantation.

The most common technique involved raising a primary flap into which biomaterials are placed prior to primary flap closure,[6] but such flap elevation can disrupt blood flow to the underlying bone and can

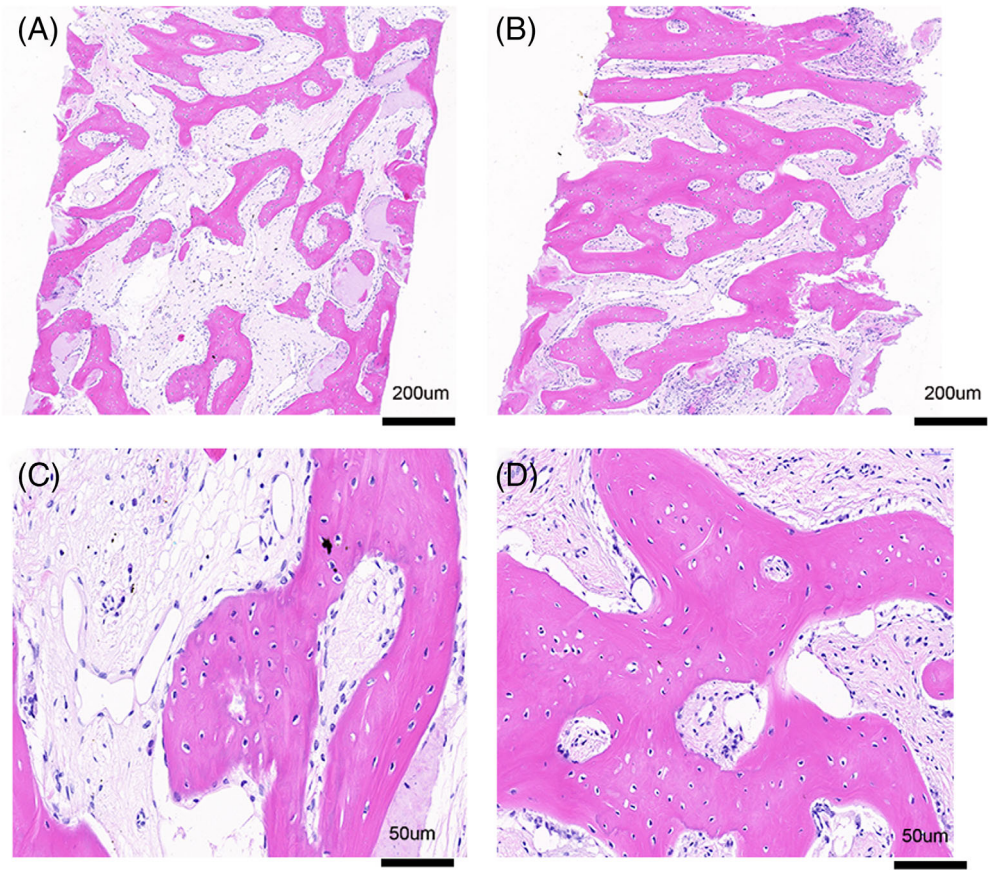

FIGURE 10 Hematoxylin and eosin (H&E) staining. (A) Sample of control group*10 (bar = 200 μm). (B) Sample of experimental group*10 (bar = 200 μm). (C) Sample of control group*40 (bar = 50 μm). (D) Sample of experimental group*40 (bar = 50 μm)

thus adversely impact horizontal bone remodeling and keratinized tissue width.[42,43] It is thus important to minimize the invasiveness of all surgical approaches wherever possible. As CGF is primarily composed of a fibrin network,[23] it can be safely exposed in the mouth without strict suturing, thus allowing for minimally invasive extraction. In the present study, we utilized a modified HI to assess socket soft tissue healing in an objective and straightforward manner. This analysis revealed that mean healing in the experimental group was significantly better than that in the control group at 10 days postextraction, although this difference was no longer significant at 1 and 3 months postextraction. This suggests that CGF promotes soft tissue healing early after extraction, while complete recovery (HI = 4) was achieved in both groups within 1–3 months postextraction. Mozzati and colleagues[27] previously used PRGF for alveolar ridge preservation and observed significant improvements in healing at 3 and 7 days postextraction, with borderline differences at 14 days postextraction. As such, CGF may be able to accelerate soft tissue healing during these early time points prior to Day 10, although further research will be needed to confirm this possibility.

There are different methods that can be used to measure the alveolar ridge resorption. Herein, we used matched data for CBCT analyses to achieve greater precision.[44] Jambhekar and colleagues[45] conducted a systematic review of 32 RCTs assessing 1354 sockets in order to explore dimensional parameters following a 3-month healing period. In so doing, they detected that xenografts exhibited the lowest mean loss of buccolingual width at the ridge crest (1.3 mm), followed by allografts (1.63 mm), alloplasts (2.13 mm), and sockets without any grafting (2.79 mm). The loss at 1 mm below the crest in the control group in the present study (3.13 mm) was thus in line with these prior studies,[25,43] while in the experimental group this value was 1.56 mm. In the prior systematic analysis, mean loss of buccal wall height from the ridge crest was lowest for xenografts (0.57 mm) and allografts (0.58 mm), followed by alloplasts (0.77 mm) and sockets without grafting (1.74 mm). Our results were in line with these findings, with a value of 1.49 mm in the control group and 0.63 mm in the experimental group. The similar results were showed in the RCT of PRGF compared with bone graft materials.[46] The low value in our study may be attributable to differences in study inclusion criteria, although further work is required to fully understand any potential differences between these analyses. Several studies have reported ridge width changes at 1, 3, and 5 mm below the crest,[30,44,47] with diminishing changes and reduction rates. However, few studies have assessed these parameters at 2 mm below the crest. We observed maximal changes at this 2 mm position, although further research is essential to understand the basis for this finding. Overall, our data suggest that CGF yields efficacy comparable to that offered by previously tested osseous substitutes.

In other reports of alveolar ridge preservation, the meta-analysis about new bone formation and graft remains is rare. Cancellas and colleagues[8] conducted a systematic review which found that no tested bone graft materials were able to improve rates of new bone formation, but that eight tested materials including Bio-collagen and Bio-oss were able to significantly reduce these rates.[8] Both of these

materials significantly decreased new bone formation following the initial period of alveolar healing (3–6 months postextraction). Large amounts of residual graft were typically observed after this same period,[48–52] indicating that these materials are resorbed at a slow rate.[8] Such biomaterials may thus be ideal tools for maintaining socket dimensions following tooth extraction.[53] However, residual graft material has the potential to adversely impact primary implant stability and the success of osseointegration.[8] One histological study[54] assessed new bone formation with 16- and 32-week alveolar ridge preservation, healing protocols using deproteinized bovine bone mineral covered with a collagen matrix, and determined that new bone formation was significantly improved at the 32-week time point without any difference in graft residual rate. CGF is a next-generation platelet concentrate preparation with no residual graft material that exhibits excellent safety and that does not prolong healing time compared with nature healing.[55,56]

Hauser and colleagues first demonstrated the ability of second-generation PRF to facilitate the formation of new bone in sockets via micro-CT.[12] Herein, we obtained bone samples without causing any additional damage to patient tissues, as all patients underwent scheduled implant surgery at 3.5 months postextraction. Micro-CT analysis of the collected samples revealed that CGF application led to better outcomes in treated patients relative to controls with respect to BMD, BV/TV, Tb.N, and Tb.Sp. BMD is reflective of bone quality, while BV/TV reflects bone mass and is related to Tb.Th and Tb.N, which are trabecular thickness and number, respectively. Trabecular separation (Tb.Sp) was used as a measure of the average distance between bone trabecular, with greater degrees of separation corresponding to poorer bone structure. We found that BMD and BV/TV values in the CGF group were significantly increased relative to the control group, whereas this treatment was associated with a significant reduction in Tb.Sp. As such, we concluded that the application of CGF gel and a CGF membrane was sufficient to promote new bone formation and improved bone structure following posterior tooth extraction.

This RCT confirmed that CGF application is an effective approach to alveolar ridge preservation through soft tissue, imaging analyses via CBCT, micro-CT, and histological analyses, respectively. While our results are objective and accurate, there are nonetheless certain limitations to the present study including the relatively small sample size, the short follow-up duration. Because the supportive abilities of CGF are relatively weak,[20] further research regarding the optimal means of applying CGF in patients with large extraction socket bone defects is necessary. The large sample and long follow-up further study is also necessary.

CGF can be safely used in a single-step procedure under clinical conditions. The use of CGF to achieve alveolar ridge preservation will save time, facilitating a simple, effective, minimally invasive approach that leaves no residual graft.

5 | CONCLUSIONS

The results of the present RCT suggest that CGF can be used as a socket filling material following posterior tooth extraction in order to achieve ridge preservation over a 3–3.5 months observation period. Compared with the natural healing, CGF treatment promoted soft tissue healing, decreased bone resorption, and accelerated the formation of new bone.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Feifei Ma: Design; data collection; drafting article; approval of article. **Ye Lin**: Design, critical revision of article; approval of article; funding secured by. **Feng Sun**: Design; data collection; critical revision of article; approval of article. **Xi Jiang**: Data analysis; critical revision of article; approval of article. **Tai Wei**: Data analysis; statistics analysis; critical revision of article; approval of article.

DATA AVAILABILITY STATEMENT

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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