Concentrated growth factor application in alveolar ridge preservation on anterior teeth. A split-mouth, randomized, controlled clinical trial

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ABSTRACT

Aim This clinical trial aimed to evaluate the effects of concentrated growth factors (CGF) on ridge socket and soft tissue preservation, as well as pain management, following the extraction of anterior teeth in a split-mouth setting.

Materials and methods Forty-five candidates of anterior teeth implant therapy were selected for this clinical, split-mouth trial and 39 patients completed the study. CGF was prepared from the patients venous blood using specialized equipment. Teeth were extracted atraumatically, and then one of the extraction sockets randomly received CGF, and the other was left to heal naturally. Postoperatively, pain according to the visual analog scale (VAS), soft tissue healing based on a modified healing index (HI) and overall well-being were evaluated in a 7-days follow up. Cone beam computed tomography (CBCT) was used to assess alveolar bone changes immediately after extraction and at two months post-extraction.

Results The application of CGF resulted in significantly reduced bone resorption in horizontal widths of 1, 3 and 5 mm under the crest($P < 0.01$) as well as buccolingual and mesiodistal widths of the ridge($P < 0.001$) compared to natural healing. Additionally, CGF showed better pain management, with significantly lower pain levels on days 2, 3 and 4 ($p < 0.05$). Soft tissue healing was also significantly improved in the CGF group on day 7 ($p < 0.001$).

Conclusion The application of CGF in alveolar sockets following tooth extraction showed promising results in maintaining alveolar bone, facilitating soft tissue healing and enhancing pain management. These findings provide support for the potential role of CGF in the success of implant therapy. Nevertheless, further investigation is necessary to understand the underlying mechanisms and optimize its clinical usage.

KEYWORDS: Alveolar bone preservation, Concentrated growth factors, Soft tissue healing, Dental implant

INTRODUCTION

After tooth extraction, the alveolar bone undergoes varying degrees of absorption within a year, with the most significant dimensional changes occurring within the first 2-4 weeks. The process of wound healing after tooth extraction involves a complex cascade of anatomical and physiological changes in both the soft tissue and alveolar bone architecture (1). Unfortunately, this can lead to the loss of 29-63% (2.46-4.56 mm) of the original width and 11-22% (0.8-1.5 mm) of the original height of the alveolar ridge, resulting in a deficiency of bone that can affect the long-term functionality and aesthetic outcomes of dental implants. Preserving both the bone and soft tissue contour is crucial for achieving optimal esthetic results. Thus, preserving alveolar bone mass poses a challenge in implant therapy (2). To address this, alveolar ridge preservation (ARP) is considered an effective method for reducing bone resorption and maintaining the morphology of the alveolar bone after extraction. ARP involves filling the socket with various biomaterials and sealing it with closure materials to prevent early loss of the underlying biomaterial (3). By reducing bone loss in the extraction socket and promoting bone regeneration, ARP aims to preserve the morphology of both the soft and hard tissues. There are several ARP techniques and types of materials available, including autogenous bone, allografts, xenografts, and platelet concentrates (4). Platelets are a valuable source of autogenous growth factors. Platelet substitutes can be categorized into three generations based on their properties and preparation techniques. The first generation is platelet-rich plasma (PRP), which was established in the 1970s. The second generation

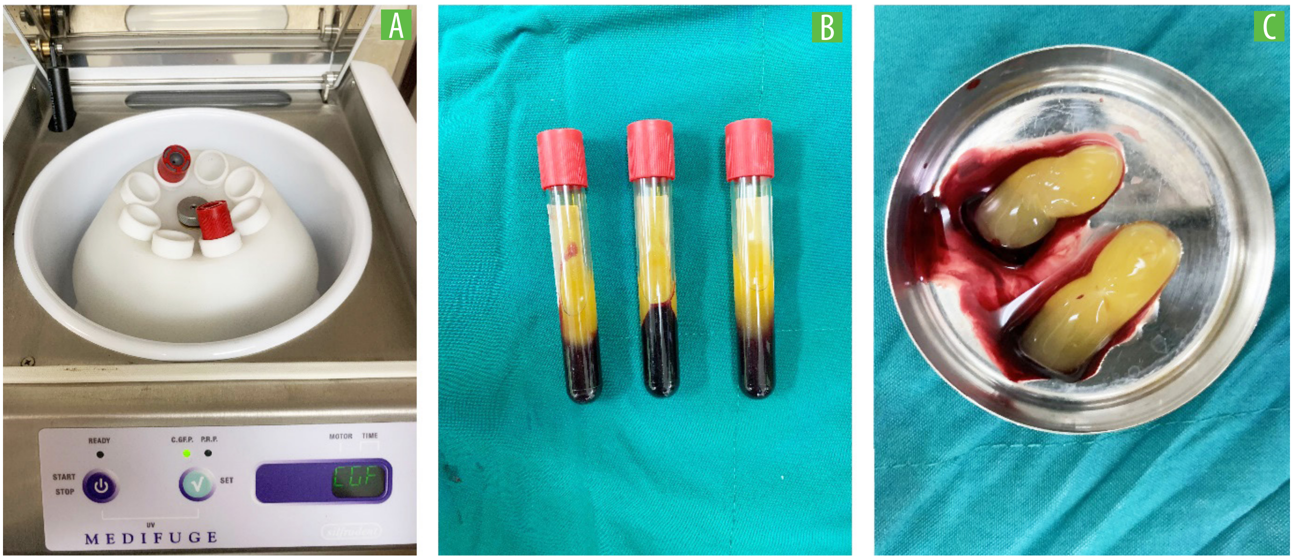

FIG 1 A) Special centrifuge with fixed setting for preparing CGF (Medifuge), B) Clot tubes after centrifuge, C) Isolated CGFs from the clot tubes

is platelet-rich fibrin (PRF), introduced in 2001. The third and most recent generation is concentrated growth factors (CGF), developed by Sacco in 2006. CGF is a novel concentrated platelet substance used for repairing bony defects and enhancing the success of bone grafting techniques. It is obtained from the individual's fresh venous blood, without anticoagulants, through centrifugation using specialized equipment (5). CGF has shown a significant impact on postoperative complications such as delayed wound healing, swelling, and pain after surgical extraction (6). A number of studies have already investigated the effect of CGF on alveolar bone preservation in different settings and reported a wide range of outcomes, some of which are contradictory. Almost all of the studies were not able to completely prevent the ridge resorption and had only reduced the amount of bone loss after applying their ARP procedures (2, 7, 8); Elayah et al. , on the other hand and surprisingly, reported an increase in the buccal and lingual wall heights along with alveolar bone width after 3 months (5). To the best of our knowledge the majority of studies have focused on the effect of CGF on the alveolar bone and the number of studies evaluating its effect on the quality of soft tissue and pain management is limited (2). Thus, this study aimed to investigate the ridge socket and soft tissue preservation effects and pain management of CGF after the extraction of anterior teeth in a clinical trial, split-mouth setting.

MATERIAL AND METHODS

Study design, population and ethics

This study was a prospective, split-mouth, randomized, controlled, clinical trial that was conducted on 45 patients who referred to university clinic of dentistry faculty, Tabriz, Iran from December 2022 to June 2023. All the patients required extraction of at least two symmetric and bilateral anterior teeth (central incisors, lateral incisors or canines) in maxilla and were candidates for implant. The procedures and setting of this study were approved by Research Ethics Committees of Tabriz University of Medical Sciences (IR.TBZMED.REC.1401.732) and registered in the Iranian registry of clinical trials (IRCT20221216056831N1). All patients were fully informed about the potential benefits and risks of applying CGF after surgery, and the ones who agreed with the conditions, all signed a written consent in this regard. Inclusion criteria were:

1) minimum age of 18 years;
2) need for extraction of at least two anterior teeth, both of them in maxilla;
3) absence of any systemic disease;
4) no inflammation or infection in the surgery site.

Exclusion criteria were:

1) pregnancy;
2) more than 5 cigarette use per day;
3) allergic reaction to any of materials;
4) any post-extraction complication;
5) patients who were not cooperative and did not follow the instructions.

Both tooth extractions of each patient were carried out by one surgeon in one visit.

Preparation of CGF

On surgery day and before the operation, 9 ml fresh venous blood was drawn from each patient and was collected in non-additive clot tubes. Immediately after collection, the tubes were centrifuged using Medifuge (MF200; Silfradent®Srl, Italy) with fixed setting for isolating CGF (9) (Fig 1.A). Briefly, acceleration for 30 s, 2700 rpm for 2 min, 2400 rpm for 4 min, 2700 rpm for 4 min, 3000 rpm for 3 min and deceleration to a stop for

36 s. After the centrifuge, CGF (the white buffy coat) was carefully separated from the red blood cell clots(Fig 1.C).

Surgical procedure and randomization

All the patients were instructed to rinse their mouths with 0.2% chlorhexidine twice a day 2 days before the surgery, and just before the operation, their mouths were rinsed with 0.2% chlorhexidine 3 times as well. Local anesthesia was used and teeth were extracted atraumatically. A flapless approach was taken for extraction and no intraligament or intrapapillary infiltration was performed so as to prevent interference with post-extraction treatments. After removing the teeth, the extraction sockets were completely debrided and after curettage, the sockets were rinsed with physiological saline (Fig 2.A). Following, the sockets of each patient were randomly assigned as either control or test sites in a split-mouth design according to a randomization table. The treatment codes (CGF-test / no CGF-control) were contained in sealed envelopes. An assistant who was not part of the study opened these envelopes after the curettage process. For CGF Group, the CGF was cut into smaller shape so that can completely fit into the extraction socket and was then stabilized with tight non-resorbable sutures. Meanwhile, the control extraction socket was sutured and left to heal naturally(Fig 2.B). Buccolingual and mesiodistal dimensions of alveolar bone at crestal level were measured using a calibrated periodontal probe immediately after extraction and 2 months post-extraction. All the patients were asked to visit the clinic for 7 days in row after the surgery to monitor infection, pain (on 7 days), soft tissue healing (on days 1, 3 and 7) and their overall well-being including smoking, any trauma to the extraction sites, fever, allergic reaction or any sickness. Sutures were removed on day 7.

Pain assessment and soft tissue healing.

After the surgery, the amount of pain in each extraction site for each patient was evaluated via visual analog scale (VAS) in a 7-days follow up (Pain on day 1 was assessed 2 hours after the surgery). VAS is a line with anchor points at each end. The left end is labeled as 0 (no pain) indicating the absence of pain, while the right end is labeled as 10 (worst pain imaginable) representing the highest level of pain (10). Patients were asked to mark a point on the line that corresponds to the intensity of their pain for each of their extraction sites.
The quality of gingiva and soft tissue was evaluated on days 1, 3 and 7 after the surgery. To assess the healing progress, a modified healing index (HI) protocol was employed. HI involves four specific criteria: bleeding, suppuration, tissue color, and consistency. The scores assigned to each criterion range from 1 to 3, reflecting the level of healing. For bleeding, the scores represent the absence of bleeding, bleeding upon touch, or spontaneous bleeding. Suppuration scores indicate the absence of pus, the presence of plaque, or the presence of pus. Tissue color scores correspond to 100% pink, less than 50% red, and more than 50% red. Consistency scores were based on descriptors: pink and grainy; red and smooth; and grey and friable (11).

CBCT analysis

Radiographic features and changes of alveolar bone were assessed using cone beam computed tomography (CBCT) immediately after extraction and 2 months afterward. CBCT scans were taken with a resolution of 0.3 mm, scanning time of 8.5 seconds and exposure time of 4 seconds, 120 kV and 5 mA with volume dimensions of 6 × 17 cm. Horizontal width 1 mm below the crest (HW-1), horizontal width 3 mm below the crest (HW-3) and horizontal width 5 mm below the crest (HW-5) were recorded in both timepoints.

Statistical analysis

Analysis of data was carried out using Statical Package for Social Sciences (SPSS). Quantitative variables were described as mean ± SD, while qualitative variables were presented as frequency (n) and percentage (%). In order to compare the means between two groups, Independent T-test (Parametric data) or Mann-Whitney U test (Non-parametric data) was used. P value less than 0.05 was considered statistically significant. GraphPad Prism was used to illustrate charts.

RESULTS

Patients and demographic variables

Forty-five cases were invited to participate in the study. Three patients did not agree with the conditions and were

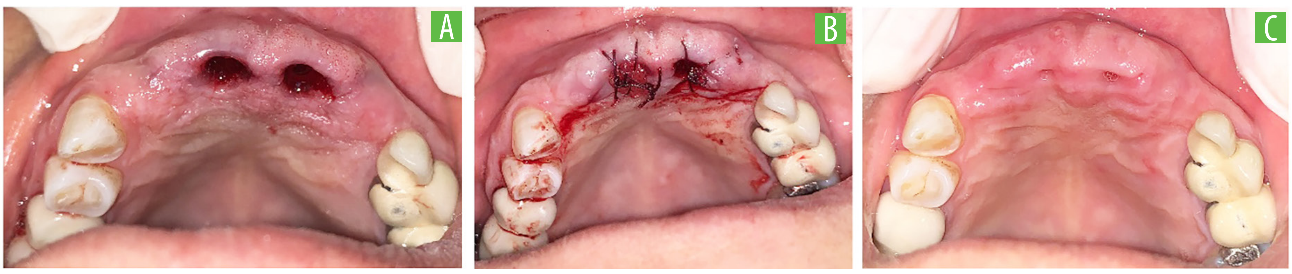

FIG 2 A) Teeth sockets after extraction, B) Sockets after suture: CGF on the left and natural healing on the right, C) Clinical view of the sockets after two months healing

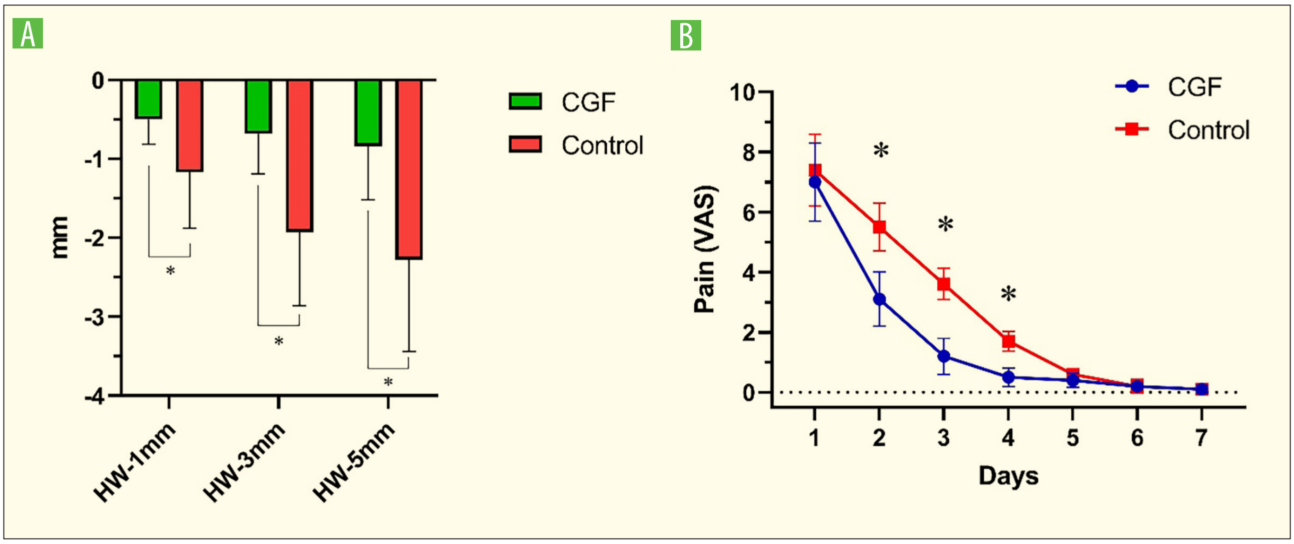

FIG 3 A) Horizontal bone resorption at 1, 3 and 5 mm under the crest 2 months after extraction, B) Pain assessment according to visual analog scale on 7 days in row after the extraction, starting from the operation day and 2 hours after surgery. Data are presented as mean ± SD. HW: Horizontal Width, mm: millimeter, CGF: Concentrated Growth Factor, VAS: Visual Analog Scale, *: Mean difference is statistically significant (two-tailed T-test).

not included. Two patients experienced severe pain and 1 patient presented fever after the surgery; therefore all of them were prescribed antibiotics and analgesics and were excluded from the study. Overall, 39 patients (18 men and 21 women) with the mean age of 41.79 ± 13.12 (Range: 19 - 64) were enrolled in the study. Total of 78 sockets were intervened (26 central incisors, 36 lateral incisors and 16 canines). Demographic differences between CGF and control groups were not significant according to the spilt-mouth study design. During the 7-days follow-up after the surgery, no infection, fever, sickness or allergic reaction was observed in any patient.

Pain management and soft tissue healing

Both CGF and control groups roughly experienced the same amount of pain on the first day, and by day 6, both groups almost had no pain. Nevertheless, pain in CGF group decreased more rapidly and its mean difference with control group on days 2, 3 and 4 was statistically significant(Fig 3.B) ($P < 0.05$).

Soft tissue healing index did not show any significant difference between CGF and control groups on days 1 and 3 after the extraction, but a better soft tissue healing was observed in CGF group on day 7, and its mean difference with control group was statistically significant ($P < 0.001$). Healing indexes of CGF and control groups are shown in Table 1.

Day	Groups		P value*
	CGF	Control	
1	6.73 ± 1.62	6.8 ± 1.79	0.857
3	5.13 ± 1.55	5.51 ± 1.2	0.23
7	4.62 ± 0.32	4.97 ± 0.46	<0.001

*CGF: Concentrated growth factor, *: two-tailed T-test.*
Data are presented as Mean ± SD

TABLE 1 Comparison of post-extraction soft tissue healing between CGF and Control groups

CBCT analysis

Horizontal width changes (from buccal to lingual) 1, 3 and 5 mm under the crest after two months healing are shown in Fig 3.A . Bone resorption in CGF group was statistically lower than that of control group in all three levels under the crest (HW-1mm and HW-3mm, $P < 0.01$; HW-5mm, $P < 0.001$).

Extraction socket changes

Immediately after extraction (baseline), no statistically significant differences were observed in buccolingual and mesiodistal horizontal widths between CGF and control groups ($P > 0.05$), while two months after the extraction, both buccolingual and mesiodistal horizontal widths were significantly higher in CGF group compared to control ($P < 0.001$). Buccolingual and mesiodistal horizontal widths at crestal level at baseline and two months after extraction are represented in Table 2.

DISCUSSION

The morphology and physiology of alveolar bones are highly linked to the presence of teeth, and significant changes occur upon tooth loss. Managing the changes in the alveolar socket following tooth extraction remains a challenge in dentistry. This issue has drawn special attention to researchers during the last decade because it has a direct negative impact on implant

Width (mm)	Timepoints	CGF (Mean ± SD)	Control (Mean ± SD)	P value
Buccolingual	T1	5.67 ± 0.76	5.82 ± 0.91	0.432*
	T2	5.47 ± 0.71	4.2 ± 0.68	< 0.001*
P value		0.233*	< 0.001*	-
Mesiodistal	T1	6.25 ± 1.72	6.35 ± 1.67	0.795*
	T2	5.9 ± 1.35	4.35 ± 1.21	< 0.001*
P value		0.321*	< 0.001*	-

*T1: immediately after extraction, T2: two months post-extraction, CGF: concentrated growth factor, *: two tailed T test.*

TABLE 2 Socket widths immediately after extraction and after two months healing

treatment (12, 13). One of the promising methods for retaining alveolar bone after tooth extraction is the use of autologous materials such as Platelet-rich plasma (PRP) (14), Leukocyte and Platelet-Rich Fibrin (L-PRF) (15), advanced platelet-rich fibrin, (A-PRF) (16) and Bone Morphogenetic Proteins (BMPs) (17). In this study, we investigated the effect of concentrated growth factors (CGF) on the preservation of anterior dental sockets two months post-extraction in a randomized, controlled, and split-mouth intervention.

The results of this study demonstrated that using CGF, as one type of autologous material, in alveolar sockets after tooth extraction can result in significantly better pain management, improved soft tissue healing and reduced bone loss compared to natural healing. These findings are consistent with previous studies investigating the effect of autologous materials on alveolar bone preservation and regeneration (18-21).

The results of this study showed that the application of CGF has a significant impact on reducing bone loss in various dimensions of the alveolar crest including horizontal buccolingual and mesiodistal widths as well as the horizontal width 1, 3 and 5 mm below the crest, all compared to natural healing. Liu evaluated the efficacy of CGF membrane for the sealing of alveolar socket in ARP and found that it can help to reduce postoperative pain at the early stage of healing, promote formation of sufficient keratinized gingival tissue, and effectively maintain the height and width of alveolar bone in the three-dimensional direction (22). Similar findings were reported by Keranmu in their study on anterior teeth (23). In a surprising discovery, Elayah et al. reported an increase in the height of buccal and lingual bone, along with the width of alveolar bone, three months post-operation with CGF applied in sockets (5). A number of other studies also support the positive effect of CGF regarding bone healing (24, 25).

CGF is a novel platelet concentrate that has been developed after PRP and PRF. CGF has been found to be more effective than PRF due to its higher concentration of growth factors. The production of CGF involves the use of variable rotation speeds to separate blood cells from the fibrin-rich layer, resulting in a denser layer with a higher concentration of growth factors compared to PRF. Srinivas did not observe a significant difference between PRF and control group in terms of alveolar ridge preservation (26). The same results were reported by Girish (27). CGF potential in maintaining the ridge after tooth extraction is due to its nature and content. CGF is prepared from the patient's own blood and contains a combination of platelets, leukocytes, growth factors, and fibrin matrix (28). Our hypothesis is that when CGF is placed in the tooth socket, several beneficial mechanisms occur in order to maintain the cavity:

1) various growth factors present in CGF, including PDGF, TGF-B, IGF and VEGF, are exposed to the cells of the cavity tissue, promoting repair, angiogenesis and bone formation (29); thus, it leads to cell division, differentiation and finally bone regeneration.

2) CGF also contains different leukocytes that release anti-inflammatory cytokines such as IL-10, IL-4 and IL-13 in tooth enamel (30), which reduce inflammation and create suitable environmental conditions for repair. 3) The fibrin matrix in CGF acts as a scaffold, creating a three-dimensional structure that facilitates cell junctions and proliferation, which leads to bone regeneration in tooth sockets (31). However, all these statements are hypotheses, and more studies must specifically examine those paths.

In present study, the application of CGF showed lower pain on days 2, 3 and 4 along with better soft tissue healing on day 7 post-extraction. This finding was in line with Liu (22)and Kernamu (25) results. Additionally, Mozzati (32) compared the use of CGF and leukocyte-and-platelet-rich fibrin (L-PRF) for enhancing post-extraction socket healing and found no significant difference in outcomes between CGF and L-PRF, but pain was Significantly lower in CGF group compared to L-PRF. CGF contains various growth factors including nerve growth factor (NGF) (33). The pain experienced after tooth extraction is due to the damage to the nerves in the area resulting from the surgery. NGF promotes the growth, regeneration, and improvement of nerve function by binding to specific receptors on nerve cells and causing their growth and differentiation (34). Therefore, CGF is an effective factor in reducing pain after tooth extraction.

Soft tissue healing showed better progress in CGF group. This finding is consistent with other studies investigating CGF application on soft tissue healing post-extraction (2, 7, 35, 36). In addition, a clinical study conducted by Kamal (37) evaluated the efficacy of CGF in the healing of alveolar osteitis following tooth extraction. The study found that CGF insertion into the socket significantly reduced pain and improved granulation tissue formation compared to conventional treatment.

CONCLUSION

In conclusion, the application of CGF in alveolar sockets after tooth extraction is a promising method for retaining alveolar bone and improving pain management and soft tissue healing, which promote the success of implant therapy. However, further research is needed to fully understand the mechanisms behind the positive effects of CGF and to optimize its use in clinical practice.

Conflict of interest

Authors declare no conflict of interest.

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