MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 4384-4389
DOI: 10.12659/MSM.917025

Received: 2019.04.17
Accepted: 2019.05.23
Published: 2019.06.12

One-Year Results Evaluating the Effects of Concentrated Growth Factors on the Healing of Intrabony Defects Treated with or without Bone Substitute in Chronic Periodontitis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BDE 1,2 Yan Xu
AF 3 Jiling Qiu
CF 3 Qinfeng Sun
AE 3 Shiguo Yan
BC 3 Wenxia Wang
BEG 1,3 Pishan Yang
ADG 1,3 Aimei Song

1 Shandong Provincial Key Laboratory of Oral Tissue Regeneration, School of Stomatology, Shandong University, Jinan, Shandong, P.R. China
2 Jinan Stomatological Hospital, Jinan, Shandong, P.R. China
3 Department of Periodontology, School of Stomatology, Shandong University, Jinan, Shandong, P.R. China

Corresponding Authors: Pishan Yang, e-mail: yangps@sdu.edu.cn, Aimei Song, e-mail: sam1972@sdu.edu.cn
Source of support: This work was supported by the National Natural Science Foundation of China (grant no. 81771076) and the New Medical Technology Start-Up Fund of the School of Stomatology, Shandong University (grant no. 20140201), Jinan, China

Background: The restoration of damaged periodontium, especially one-wall intrabony defects, is a major challenge for clinicians. Concentrated growth factors (CGF) are a 100% autologous fibrin with multiple concentrated growth factors. The rigid fibrin structure of CGF makes it possible to preserve or reconstruct the initial bone volume. The aim of this study was to evaluate the clinical healing patterns after surgical application of CGF with and without a Bio-Oss graft in one-wall infrabony defects.

Material/Methods: We randomly divided 120 one-wall intrabony defects in 54 patients into 4 groups: flap surgery alone (Group 1), flap surgery with autologous CGF (Group 2), flap surgery with Bio-Oss (Group 3), and flap surgery with CGF+Bio-Oss (Group 4). Clinical parameters such as probing depth (PD) and clinical attachment level (CAL) change were recorded at baseline and at 6 and 12 months postoperatively.

Results: At 12 months postoperatively, Group 2 showed significant improvement in clinical parameters over Group 1 ($P<0.05$) and the results were significantly greater in Groups 3 and 4 compared to the other groups ($P<0.05$). Although no significant difference was noted between Groups 3 and 4 in clinical parameters ($P>0.05$) compared to Group 3, the mean change of CAL at 6–12 months in Group 4 was not significant ($P>0.05$).

Conclusions: CGF reduced periodontal intrabony defects depth and, when mixed with Bio-Oss, CGF showed better results in the early period and the effect was more stable.

MeSH Keywords: Chronic Periodontitis • Receptors, Growth Factor • Therapeutics

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/917025

2145 4 — 38

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Periodontal diseases comprise a wide range of inflammatory conditions that affect the tooth-supporting tissues and can lead to tooth loss and contribute to systemic inflammation [1]. The restoration of damaged periodontium or periodontal tissue regeneration is the ultimate goal of periodontitis treatment [2]. Periodontal regenerative therapy by applying bone grafts, guided tissue regeneration (GTR), and growth factors is a clinically available entity to solve this problem.

Bone autograft has been identified as the criterion standard for bone grafts, mainly because of its osteoinduction activity. The use of autografts is, however, hindered by the morbidity from procurement and difficulty in harvesting sufficient bone. Correspondingly, deproteinated bovine-derived xenograft products such as Bio-Oss® are widely used in clinical practice [3–5]. However, bovine-derived xenografts lack osteoinduction activity, and clinical effectiveness depends on the anatomic characteristics of the intrabony defects and the regenerative potential of residual periodontal tissues [6–8].

Polypeptide growth factors play an important role in the growth and osteogenic differentiation of periodontal regeneration-associated cells. rhBMP-2 [9], PDGF-BB [10], and enamel matrix derivative (EMD) [11] have been used clinically in periodontal/bone regeneration alone or in combination with bone grafts or GTR, with variable results.

More and more studies have begun to focus on platelet-rich preparations in the fields of tissue engineering, wound healing, and bone grafting [12–14]. Platelet-rich plasma (PRP), the first generation of platelet gel, has been suggested as a modality to enhance the outcome of periodontal regenerative surgery since 1998 [15]. However, the effect of PRP as hard tissue regeneration is controversial [16]. Unlike PRP, concentrated growth factors (CGF) are well known to accelerate new bone formation [17].

CGF, a new generation of platelet concentrate biomaterial, contains a much larger amount of growth factors and more rigid fibrin matrix from autologous platelets than those of previous preparations [18,19]. In contrast to PRP, the production of CGF does not require adding other reagents, and formation of the fiber network is nearly natural [20,21]. CGF is a 100% autologous fibrin and is free from transmissible disease agents. In combination with many biological materials or used alone, CGF is widely applied in repair or regeneration of gingiva [22] and alveolar bone [23–25], as well as in implant/periodontal surgery [24,26–28].

However, inconsistent results exist regarding enhancement of periodontal/bone regeneration. Studies showed that concentrated platelet products exerted no additive effect on periodontal regeneration [29–31]. Therefore, the present clinical trial evaluated the outcome after periodontal regenerative surgery in intrabony defects, using CGF with or without bone substitute materials, in order to evaluate the potential ability of CGF in the enhancement of periodontal tissue regeneration.

Material and Methods

Study design

The study followed instructions based on the Helsinki Principles (2008). The study protocol was reviewed and approved by the Ethics Committees of the School of Stomatology, Shandong University (No. 20131201, dated 2013 Oct 16). All participants provided written informed consent. The study was performed from November 2013 to August 2016 and was completed at the end of 2017, with a 1-year follow-up. A total of 58 patients (26 females and 32 males, mean age=55.2±8.3 years) who had moderate-to-severe chronic periodontitis were included in this study. Patient enrollment was conducted by a single therapist. From these 58 patients, we randomly assigned 120 sites to Group 1 (flap surgery alone), Group 2 (flap surgery with autologous CGF), Group 3 (flap surgery with Bio-Oss [Geistlich AG, Wolhusen, Switzerland]), or Group 4 (flap surgery with CGF+Bio-Oss).

The patients were diagnosed with moderate-to-severe chronic periodontitis, according to the 1999 classification of periodontal diseases. The inclusion criteria were: presence of one-wall intrabony defects without furcation involvement and intrabony defects with probing depth ≥6 mm and clinical attachment level ≥6 mm when evaluated 6 weeks after initial therapy. The exclusion criteria were: (1) having systemic or blood-borne diseases, (2) taking any medication within the past 6 months, (3) smokers, (4) lactating or pregnant females, (5) previously treated for periodontal reasons, (6) 2- or 3-wall defects, (7) aggressive periodontitis, and (8) age <18 years.

Intra-examiner calibration

Clinical measurements were obtained by the same trained periodontist who was blinded to the groups. To ensure acceptable intra-examiner reproducibility, the examiner was calibrated by examination of 30 defects in 10 patients 2 times between baseline (BL) and 48 h. Calibration was accepted if measurements were similar to 1 mm at the 95% level.

Initial therapy

Initial periodontal therapy consisted of detailed oral hygiene instructions, as well as full-mouth supra- and subgingival

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

scaling and root planing under local anesthesia both by hand (Hu-Friedy, Chicago, IL, USA) and with ultrasonic instruments (Cavitron, Dentsply, York, PA, USA) in order to minimize the bacterial insult. If occlusive trauma was observed, occlusal adjustment was done. Periodontal evaluation was done 6 weeks after initial therapy as baseline (BL).

The clinical parameters measured included probing depth (PD), measured from the gingival margin to the bottom of the pocket, and clinical attachment level (CAL), measured from the cementoenamel junction (CEJ) to the bottom of the pocket, using the University of North Carolina no. 15 (UNC-15, Hu-Friedy, Chicago, IL, USA) periodontal probe. All clinical parameters of the same treated sites were re-evaluated at 6 and 12 months after surgery.

CGF preparation

We collected 9 mL intravenous blood sample from each patient in sterile glass vacuum tubes without anticoagulant solutions. These tubes were then immediately centrifuged with a matching centrifuge device (Medifuge, Silfradentsr, Sofia, Italy) using a program as following: 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 for 36 s, and stop. At the end of the centrifugation, 3 layers were observed in the tube: (1) the superior serum layer, (2) the interim fibrin gel with CGF layer, and (3) the lower red blood cell (RBC) layer. The CGF clot was removed carefully from the tube and separated from the RBC using microsurgical scissors.

Surgical procedure

The same expert periodontist performed all operations. After local anesthesia, buccal and lingual intracrevicular incisions were made, then the full thickness mucoperiosteal flaps were elevated. Thorough defect debridement and root planing were achieved with the use of hand instruments and an ultrasonic device. While flap surgery alone was the treatment in Group 1 patients, autologous CGF was transplanted in intrabony defect sites in Group 2 patients. Intrabony defect sites were filled with Bio-Oss in Group 3 patients. CGF mixed with Bio-Oss was placed into the defects in Group 4 patients. Tension-free flaps were repositioned and sutured with 3-0 non-absorbable black silk surgical suture with single interrupted sutures. Periodontal dressing was placed over the surgical area.

All patients were prescribed 500 mg amoxicillin 3 times daily for 7 days and told to rinse with 0.12% chlorhexidine digluconate (CHX) twice daily for 2 weeks. Suture removal was performed 14 days postoperatively. To make plaque control record less than 20% and gingival index score equal to 0, each patient was reinstructed for proper oral hygiene measures and plaque removal at 6 weeks postoperatively and examined at 3, 6, 9, and 12 months after surgery.

Statistical analysis

Before initiating the study, power analysis for sample size calculation was performed. To achieve 80% statistical power and detect a mean difference of 1 mm in clinical parameters among groups, a sample size of 76 sites was deemed sufficient. To allow for possible dropouts, 58 patients were finally recruited and 120 sites obtained. Each parameter from baseline to 12 months was expressed as the means ± standard deviation (SD). Shapiro-Wilk's W test was used to test normality assumption of the data, and the results showed that data were not normally distributed. For statistical evaluation of the changes, inter-group comparison was made by Kruskal-Wallis test and Mann-Whitney test. Wilcoxon signed rank test for intra-group comparison was used. P values <0.05 were considered statistically significant. Statistical Product and Service Solutions (SPSS) statistical software, version 20.0 (IBM, Armonk, NY, USA), was used to analyze the data.

Results

The study was completed by 54 of 58 patients; 4 patients (10 sites) were not able to attend follow-up. All treated cases' wounds healed well. Throughout the study, the level of oral hygiene and the number of bleeding sites remained stable. Inter-group comparison of the 4 groups showed that the mean values for clinical parameters (PD, CAL) were not significantly different (P>0.05) at baseline, but the parameters were significantly different at 6 and 12 months (P<0.05) (Table 1). All groups showed a significantly larger PD decrease and CAL gain in all periodontal outcome variables from BL to 12 months (P<0.01) (Table 2).

Compared with Group 1, PD and CAL depth reductions were significantly greater in Groups 2, 3, and 4 (P<0.05), but there was no significant difference between Group 3 and Group 4 (P>0.05) for any of the clinical parameters from BL to 12 months (Table 3).

Intra-group comparison of mean change in clinical parameters between 6 months and 12 months showed that the change in PD was not significant (P>0.05) in each group. There was a significant change in CAL in Group 1 and Group 3 (P<0.05), but the change in CAL was not obvious (P>0.05) in Group 2 and Group 4 (Table 4).

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Mean ±SD values of PD, CAL at different visits for all groups.

Parameter	Visits	Group 1	Group 2	Group 3	Group 4	*p*-Value
PD (mm)	BL	7.72±1.01	7.57±1.27	7.91±1.14	7.81±1.40	0.833
	6 months	6.64±1.12	5.71±1.11	4.64±0.81	4.04±1.34	<0.001*
	12 months	6.18±0.98	5.29±1.49	4.18±0.75	3.55±1.13	<0.001*
CAL (mm)	BL	8.91±1.45	8.72±1.49	8.82±2.18	8.64±1.69	0.960
	6 months	7.09±1.30	6.36±1.21	5.18±1.54	4.73±1.19	0.001*
	12 months	6.54±1.29	5.63±1.12	4.64±1.57	4.19±1.72	0.009*

**P*-value <0.05, statistically significant.

Table 2. Intra-group comparison of mean change of clinical parameters from BL to 12 months.

Parameter	Group	BL – 12months	*P*-value
ΔPD (mm)	1	1.55±0.93	0.004*
	2	2.45±0.76	0.003*
	3	3.72±0.90	0.003*
	4	4.36±1.03	0.003*
ΔCAL (mm)	1	2.36±0.92	0.003*
	2	3.09±1.14	0.003*
	3	4.18±1.08	0.003*
	4	4.45±1.13	0.003*

**P*-value <0.05, statistically significant.

Table 3. Inter-group comparison of mean change of clinical parameters from BL to 12 months.

Parameter	*P*-value					
	Group 1 *vs.* 2	Group 1 *vs.* 3	Group 1 *vs.* 4	Group 2 *vs.* 3	Group 2 *vs.* 4	Group 3 *vs.* 4
PD (mm)	0.040*	<0.001*	<0.001*	0.005*	<0.001*	0.064
CAL (mm)	0.032*	<0.001*	<0.001*	0.030*	0.013*	0.553

**P*-value <0.05, statistically significant.

Table 4. Intra-group comparison of mean change of clinical parameters between 6 months and 12 months.

Parameter	Group	6 month	12 month	*P*-value
ΔPD (mm)	1	1.09±0.95	1.55±0.93	0.096
	2	2.10±0.94	2.45±0.76	0.366
	3	3.27±0.79	3.72±0.90	0.157
	4	3.81±0.98	4.36±1.03	0.344
ΔCAL (mm)	1	1.82±0.98	2.36±0.92	0.011*
	2	2.63±1.20	3.09±1.14	0.059
	3	3.63±1.03	4.18±1.08	0.014*
	4	4.10±1.05	4.45±1.13	0.763

**P*-value <0.05, statistically significant.

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Discussion

Periodontal regeneration in non-contained one-wall infrabony periodontal defects usually has a low degree of predictability because of flap collapse, making it unsuitable for some regenerative management, such as guided tissue regeneration (GTR) and enamel matrix derivative application [11,32]. The rigid fibrin structure of CGF makes it possible to preserve or reconstruct the initial bone volume and supply a scaffold to allow cells to migrate, proliferate, and differentiate. Therefore, the CGF could theoretically be used in one-wall intrabony periodontal defect and promote wound healing. Thus, we chose to use the one-wall periodontal defect to study the effect of CGF on healing with or without bone grafts, hoping to find a new method for treatment of one-wall intrabony defects.

Our randomized controlled trial demonstrated favorable outcomes after 12 months. CGF used alone, bone graft, and bone graft combined with CGF significantly enhanced the mean PD reduction and mean CAL gain when compared to flap surgery. Although CGF alone reduced PD and enhanced the CAL gain, there was no additional effect when combined with bone graft. The improvement in clinical parameters shows that use of CGF or biological bone material is more effective than flap surgery alone in improving attachment levels in intrabony defects.

Usually, flap surgery alone can only result in limited new attachment formation because of the long epithelium migration and flap collapse after surgery [15,33] The unique fibrin network micro-structure of CGF is a complex tridimensional architecture constituted by thin and thick fibrillar elements. CGF can also provide a supportive matrix surrounded by multiple platelet cell elements and various cytokines and growth factors [18]. The significant improvement resulting from transplantation of CGF alone may be due to its biologic constituents and its scaffold structure [19,34]. Many studies have demonstrated that grafting materials are needed as a filler for predictable bone formation in one-wall infrabony defects with limited space-creating capacity [32,35,36]. In our study, the bone graft groups had significantly more CAL gain than in the open access flap group and CGF alone group.

Because of the fibrin matrix of platelets, leukocytes, and high concentrations of many growth factors (e.g., TGF-β1, PDGF-BB, VEGF, IL-1β, and IL-6) in CGF preparations [19], CGF can promote the proliferation and osteoblast differentiation of bone marrow cells and then promote wound healing processes and new bone formation [37]. Li et al. recently reported that CGF not only has an osteogenic effect on human periodontal ligament cells (hPDLCs) in a normal culture, but also promotes hPDLCs osteogenesis in a TNF-α-induced inflammatory microenvironment [38].

When CGF was mixed with Bio-Oss and transplanted into the bone defects, there was no additive effect regarding the PD reduction and CAL gain. This result is inconsistent with that of Qiao, who demonstrated that the addition of CGF significantly improved the clinical effectiveness of bone graft alone [27]. This discrepancy in results may be due to the defect characteristics. The 2- or 3-wall defects in Qiao's study allows more opportunity for CGF to promote the cell proliferation and differentiation needed in wound healing.

We also compared the mean change at 6 months and 12 months in parameters between the visits within Groups 1, 2, 3, and 4. When CGF was used, the change in CAL gain from baseline to 6 months and to 12 months was not significant, suggesting that CGF promotes the relative early wound healing and maintains the long-term effect in one-wall defects.

Conclusions

This preliminary study suggests that CGF can enhance wound healing and reduce the depth of periodontal intrabony defects. When combined with Bio-Oss, CGF might be a superior scaffolding material. However, additional studies with larger sample sizes and more rigorous experimental design are necessary to better understand the clinical effect of CGF on periodontal regeneration.

Conflict of interest

None.

References:

1. Kinane DF, Stathopoulou PG, Papapanou PN: Periodontal diseases. Nat Rev Dis Primers, 2017; 3: 17038
2. Stavropoulos A, Wikesjo UM: Growth and differentiation factors for periodontal regeneration: A review on factors with clinical testing. J Periodontal Res, 2012; 47: 545–53
3. Barone A, Todisco M, Ludovichetti M et al: A prospective, randomized, controlled, multicenter evaluation of extraction socket preservation comparing two bovine xenografts: Clinical and histologic outcomes. Int J Periodontics Restorative Dent, 2013; 33: 795–802
4. Schneider OD, Weber F, Brunner TJ et al: *In vivo* and *in vitro* evaluation of flexible, cottonwool- like nanocomposites as bone substitute material for complex defects. Acta Biomater, 2009; 5: 1775–84
5. Schwartz Z, Weesner T, van Dijk S et al: Ability of deproteinized cancellous bovine bone to induce new bone formation. J Periodontol, 2000; 71: 1258–69
6. Tonetti MS, Cortellini P, Lang NP et al: Clinical outcomes following treatment of human intrabony defects with GTR/bone replacement material or access flap alone. A multicenter randomized controlled clinical trial. J Clin Periodontol, 2004; 31: 770–76

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

7. Sculean A, Windisch P, Keglevich T et al: Clinical and histologic evaluation of human intrabony defects treated with an enamel matrix protein-derivative combined with a bovine derived xenograft. Int J Periodontics Restorative Dent, 2003; 23: 47–55
8. Susin C, Fiorini T, Lee J et al: Wound healing following surgical and regenerative periodontal therapy. Periodontol 2000, 2015; 68: 83–98
9. Jung RE, Glauser R, Schärer P et al: Effect of rhBMP-2 on guided bone regeneration in humans. Clin Oral Implants Res, 2003; 14: 556–68
10. Li F, Yu F, Xu X et al: Evaluation of Recombinant Human FGF-2 and PDGF-BB in periodontal regeneration: A systematic review and meta-analysis. Sci Rep, 2017; 7: 65
11. Aimetti M, Ferrarotti F, Mariani GM et al: A novel flapless approach versus minimally invasive surgery in periodontal regeneration with enamel matrix derivative proteins: A 24-month randomized controlled clinical trial. Clin Oral Investig, 2017; 21: 327–37
12. Alser OH, Goutos I: The evidence behind the use of platelet-rich plasma (PRP) in scar management: A literature review. Scars Burn Heal, 2018; 4: 1009034555
13. Arora NS, Ramanayake T, Ren YF et al: Platelet-rich plasma: A literature review. Implant Dent, 2009; 18: 303–10
14. Bielecki T, Dohan ED: Platelet-rich plasma (PRP) and Platelet-Rich Fibrin (PRF): Surgical adjuvants, preparations for *in situ* regenerative medicine and tools for tissue engineering. Curr Pharm Biotechnol, 2012; 13: 1121–30
15. Marx RE, Carlson ER, Eichstaedt RM et al: Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 1998; 85: 638–46
16. Plachokova AS, Nikolidakis D, Mulder J et al: Effect of platelet-rich plasma on bone regeneration in dentistry: A systematic review. Clin Oral Implants Res, 2008; 19: 539–45
17. Choukroun J, Diss A, Simonpieri A et al: Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part IV: Clinical effects on tissue healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2006; 101: e56–60
18. Rodella LF, Favero G, Boninsegna R et al: Growth factors, CD34 positive cells, and fibrin network analysis in concentrated growth factors fraction. Microsc Res Tech, 2011; 74: 772–77
19. Masuki H, Okudera T, Watanebe T et al: Growth factor and pro-inflammatory cytokine contents in platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), advanced platelet-rich fibrin (A-PRF), and concentrated growth factors (CGF). Int J Implant Dent, 2016; 2: 19
20. Honda H, Tamai N, Naka N et al: Bone tissue engineering with bone marrow-derived stromal cells integrated with concentrated growth factor in *Rattus norvegicus* calvaria defect model. J Artif Organs, 2013; 16: 305–15
21. Kobayashi M, Kawase T, Horimizu M et al: A proposed protocol for the standardized preparation of PRF membranes for clinical use. Biologicals, 2012; 40: 323–29
22. Bozkurt DS, Ongoz DF, Balli U et al: Concentrated growth factor in the treatment of adjacent multiple gingival recessions: A split-mouth randomized clinical trial. J Clin Periodontol, 2015; 42: 868–75
23. Mirkovic S, Djurdjevic-Mirkovic T, Pugkar T: Application of concentrated growth factors in reconstruction of bone defects after removal of large jaw cysts – the two cases report. Vojnosanit Pregl, 2015; 72: 368–71
24. Durmuslar MC, Balli U, Dede FO et al: Histological evaluation of the effect of concentrated growth factor on bone healing. J Craniofac Surg, 2016; 27: 1494–97
25. Pirpir C, Yilmaz O, Candirli C et al: Evaluation of effectiveness of concentrated growth factor on osseointegration. Int J Implant Dent, 2017; 3: 7
26. Sohn DS, Heo JU, Kwak DH et al: Bone regeneration in the maxillary sinus using an autologous fibrin-rich block with concentrated growth factors alone. Implant Dent, 2011; 20: 389–95
27. Qiao J, Duan J, Zhang Y et al: The effect of concentrated growth factors in the treatment of periodontal intrabony defects. Future Sci OA, 2016; 2: FS136
28. Ravi S, Malaiappan S, Varghese S et al: Additive effect of plasma rich in growth factors with guided tissue regeneration in treatment of intrabony defects in patients with chronic periodontitis: A split-mouth randomized controlled clinical trial. J Periodontol, 2017; 88: 839–45
29. Döri F, Nikolidakis D, Húszár T et al: Effect of platelet-rich plasma on the healing of intrabony defects treated with an enamel matrix protein derivative and a natural bone mineral. J Clin Periodontol, 2008; 3: 44–50
30. Döri F, Arweiler N, Huszar T et al: Five-year results evaluating the effects of platelet-rich plasma on the healing of intrabony defects treated with enamel matrix derivative and natural bone mineral. J Periodontol, 2013; 84: 1546–55
31. Döri F, Huszár T, Nikolidakis D et al: Effect of platelet-rich plasma on the healing of intra-bony defects treated with a natural bone mineral and a collagen membrane. J Clin Periodontol, 2007; 34: 254–61
32. Cochran DL, Jones A, Heiji L et al: Periodontal regeneration with a combination of enamel matrix proteins and autogenous bone grafting. J Periodontol, 2003; 74: 1269–81
33. Zucchelli G, Bernardi F, Montebugnoli L et al: Enamel matrix proteins and guided tissue regeneration with titanium-reinforced expanded polytetra fluoroethylene membranes in the treatment of infrabony defects: A comparative controlled clinical trial. J Periodontol, 2002; 73: 3–12
34. Kang YH, Jeon SH, Park JY et al: Platelet-rich fibrin is a Bioscaffold and reservoir of growth factors for tissue regeneration. Tissue Eng Part A, 2011; 17: 349–59
35. Shirakata Y, Yoshimoto T, Goto H et al: Favorable periodontal healing of 1-wall infrabony defects after application of calcium phosphate cement wall alone or in combination with enamel matrix derivative: A pilot study with canine mandibles. J Periodontol, 2007; 78: 889–98
36. Döri F, Arweiler N, Gera I et al: Clinical evaluation of an enamel matrix protein derivative combined with either a natural bone mineral or beta-Tricalcium phosphate. J Periodontol, 2005; 76: 2236–43
37. Takeda Y, Katsutoshi K, Matsuzaka K et al: The effect of concentrated growth factor on rat bone marrow cells *in vitro* and on calvarial bone healing *in vivo*. Int J Oral Maxillofac Implants, 2015; 30: 1187–96
38. Li X, Yang H, Zhang Z et al: Concentrated growth factor exudate enhances the proliferation of human periodontal ligament cells in the presence of TNF-α. Mol Med Rep, 2019; 19: 943–50

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]