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Evaluation of the Addition of Injectable Platelet Rich Fibrin to Xenograft in Management of Periodontal Intraosseous Defects. "Randomized Controlled Trial"

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ABSTRACT

Purpose: Platelet rich fibrin (PRF) has been widely and successfully used in periodontal regeneration. Injectable PRF (i-PRF) is a liquid form of PRF containing more leucocyte and growth factors. I-PRF was used with great success in management of gingival recession and implant therapy. So the aim of the study was to evaluate the benefit of adding i-PRF to xenograft in management of periodontal intraosseous defects. **Subjects and Methods:** Twenty four patients (age range 36 - 59 years), with stage III periodontitis with at least one intrabony defect, probing pocket depth **>** 5 mm and radiographic evidence of vertical bone loss, were enrolled in the present study. The patients were equally divided into two groups, the test group (i-PRF and xenograft) and the control group (xenograft only). Probing depth (PD), clinical attachment level (CAL.), bone defect depth and bone density were recorded at baseline and after 6 months. **Results:** The results showed a statistical significant reduction in PD, gain in CAL, bone fill and change in bone density from preoperative to 6 months in each group separately. There was a statistical significant difference between test and control groups with mean and standard deviation (SD) of PD reduction (4.2±0.4; 3.3±0.7) and CAL gain (3.8±0.4 ; 2.9±0.8) respectively in favor of the test group. Regarding bone fill, there was no statistical significant difference between both groups with mean and SD (2.6±0.7; 2±0.8) respectively. As for the increase in bone density, there was a statistical significant difference between both groups with mean and SD (17.5±4.9 ;10.9±6.8) respectively. **Conclusion:** We can conclude that adding i-PRF to bone grafting material might have a beneficial impact in treatment of periodontal intraosseous defects.

KEYWORDS

Injectable,
Platelet Rich Fibrin,
Intraosseous Defects,
Xenograft, Regeneration

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INTRODUCTION

Among the main goals of periodontal therapy is to regenerate the lost periodontal tissues after arresting the progress of the disease [1]. Surgical management of periodontally affected sites includes the conventional and regenerative procedures. The conventional modality as surgical debridement allows for reliable access to root surfaces leading only to healing by repair [2]. While the regenerative treatment options allow for regeneration of destroyed periodontal ligament and bone. Guided tissue regeneration (GTR), placement of bone grafting materials, addition of biologic mediators and combination of such techniques are the different forms of periodontal regenerative techniques [3].

Bone grafts are classified into autogenic, allogenic, xenogenic and synthetic bone grafts [4]. Xenografts are inorganic inert bone obtained from species other than the human being. They are thermally and chemically treated to extract all cellular and organic components keeping only the micro and macrostructure of the inorganic portion. It has an osteoconductive action, acting as a scaffold facilitating osteoblastic migration and three dimensional bone deposition. Its efficacy as bone substitutes has been well proven in both periodontal and implant therapy. Xenografts, when used in managing intrabony defects, have showed positive outcomes in terms of reduction in probing depth, gain in clinical attachment level and bone fill [5-7].

Platelet concentrates (PCs) are biological products obtained from the patient's own blood. Its main action is derived through its high content of platelets that release many growth factors and cytokines. The platelets granules release high amounts of growth factors which have a pivotal action in cells chemotaxis, proliferation and differentiation, with upregulation of extra-cellular matrix deposition and modulation of angiogenesis. Therefore, PCs were found to be having a great impact on soft tissue healing and bone regeneration [8,9].

The first generation of PC is the platelet-rich plasma (PRP), while the second one is platelet rich fibrin (PRF). There are many forms of PRF such as leucocytes rich PRF (L-PRF), advanced PRF (a-PRF) [10] and injectable PRF (i-PRF) [11]. I-PRF is the liquid form that is easily injected into the surgical site. It is prepared by centrifugation of patient's blood at slower rpm and less time than those used with the other forms of PRF. I-PRF is capable of releasing higher amounts of growth factors inducing significant deposition of collagen type 1, osteocalcin release and fibroblast chemotaxis [12]. Moreover, i-prf has the ability to increase alkaline phosphatase and osteonectin expression which in turn increases human osteoblastic activity [13].

I-PRF, when added to bone grafting material, renders the graft more sticky with more stability in any defect and easier for handling with sustained release of growth factors [14,15]. I-PRF has been successfully used in conjunction with bone graft in ridge augmentation prior to implant placement [16], in sinus floor augmentation [17,18]. It was also used with microneedling for gingival augmentation of thin gingival biotype [19], and in management of gingival recession whether combined with connective tissue graft [20] or free gingival graft [21].

A previous study showed that i-PRF had higher bactericidal effect when compared to the standard PRF and PRP. Its main bactericidal action is against 2 main periodontal pathogens which are Porphyromonas Gingivalis and Aggregatibacter Actinomycetemcomitans. Hence, they assumed that i-PRF might be highly efficient as an adjunct to the initial periodontal therapy [22]. Consequently, i-PRF has been injected in periodontal pockets in non surgical treatment of periodontitis patients and showed significant improvement in clinical parameters in terms of decrease in probing depth and gain in clinical attachment level [23,24]. This present study was conducted since, to the best of our knowledge, no studies were performed to report the effect of i-PRF in periodontal regenerative therapy when added to bone graft in management of periodontal intraosseous defects.

SUBJECTS AND METHODS

This randomized controlled, single blinded study followed the guidelines of the declaration of Helsinki (1975) revised in 2013 and all the steps were fully described to each participant included in the study and an informed consent was obtained from each patient.

Patient selection

Twenty four patients (age ranged between 36 - 59 years) were selected from the clinic of Oral Medicine, Diagnosis and Periodontology department, Faculty of dentistry, Cairo University. All patients were diagnosed as having stage III periodontitis [25] with at least one intrabony defect, probing pocket depth > 5mm (Fig. 1a) and radiographic evidence of vertical bone loss, after completion of phase I periodontal therapy. Only compliant patients were included in this study. Any patients with any systemic condition that might contraindicate any surgical intervention or affect healing were excluded from the study. Pregnant females arnd smokers were also excluded.

Sample size estimation was done based on the article[26], putting into consideration the effect size between groups using power 80% and 5% significance level, 10 patients were required in each group. This number was to be increased to a sample size of 12 patients in each group to compensate for any possible losses during the study follow up.

Preoperative phase

All patients received initial periodontal therapy including full mouth ultrasonic and manual supra- and subgingival scaling and root planing on 2 visits, with instructions for strict plaque control including brushing with soft toothbrush, use of interdental cleaning device. Re-evaluation was performed 6 weeks later to assess oral hygiene, and to record the probing depth (PD), and clinical attachment level (CAL). Standardized periapical radiographs were taken using long- cone parallel technique with customized bite block for each participant.

Allocation concealment, randomization and blinding

The allocation sequence was obtained from a computer software creating a randomization list. The patients were randomly classified into two groups, the first group was the test group (A) and the second one was the control group (B). The numbers randomly generated from the software were written on papers inserted inside opaque envelopes. These envelopes were opened immediately before the surgical procedures. This study was a single-blinded clinical trial. The outcome assessor and the statistician were blinded but it was not possible for the operator and the patients to be blinded due to the different nature of the interventions.

Surgical phase

For both groups, anesthesia of the operative area using either infiltration or nerve block technique was done. Open flap debridement (OFD) was performed starting with an intrasulcular incision, down to the alveolar crest followed by raising a full thickness mucoperiosteal flap to have full accessibility to the intrabony defect (Fig.1b). Removal of granulation tissue and root instrumentation were performed. For the test group, intrabony defects received xenograft (Gen-Os, Osteobiol by Technoss) mixed with i-PRF. I-PRF was prepared from the patient's own blood, venous blood was drawn into 2 (10 ml) plastic tubes and centrifuged in 700 rpm for 3 minutes. This led to the separation of the red blood cells at bottom of tube and i-prf appears as a yellow color fluid in the top of the tube [27]. The liquid (i-prf) was drawn then from the tube using plastic syringe (Fig. 2a) and then injected onto the xenograft, giving the graft a sticky form (Fig. 2b) which was packed inside the defect (Fig. 1c). While in the control group, intrabony defects received only xenograft. After packing the graft into the defect, the flaps were repositioned to their original position and secured using resorbable sutures (Fig.1d).

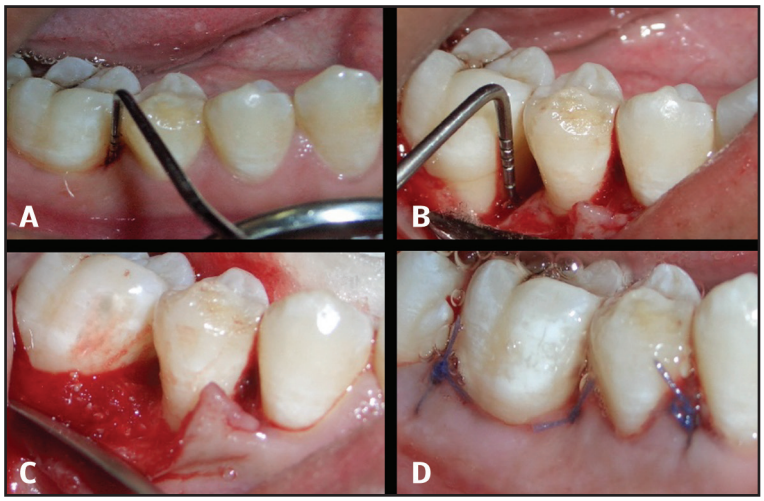

Figure (1) a) Pocket mesial to lower right first molar with PD 8 mm. b) Mucoperiosteal flap elevated revealing the intraosseus defect. c) After packing of (i-PRF and graft) inside the defect. d) Flap closure using interrupted sutures.

Postoperative phase

All patients were placed on antibiotics Amoxicillin 500 mg (E-mox , E.I.P.I.C.O., Egypt) 3 times daily for 5 days after surgery [28]. The patients were instructed to avoid hard food and brushing at the surgical site during the first week postoperatively. The patients were informed to use 0.12% chlorhexidine mouth wash (Hexitol, The Arab Drug Company for pharmaceutical & Chemical industry. Co. Egypt) twice daily for a period of 2 weeks. Sutures removal was done after two weeks and then the patients started to gently brush the operated area with a soft brush. All patients were recalled every month to check for the oral hygiene and to remove any deposits if present.

Postsurgical evaluation and outcomes recording:

6 months postsurgically, probing depth (distance from the gingival margin to the base of the pocket) and clinical attachment level (distance from the cementoenamel junction (C.E.J.) to the base of the pocket) were measured for all patients. Standardized periapical radiographs were taken six months postsurgically to record both bone defect depth and density measurements.

Using Digora software (Digora for windows 2.5™ , SOREDEX Inc., Finland.), linear measurements were done to calculate the depth of alveolar bone defect. A line was drawn connecting the C.E.J. of two neighboring teeth related to the defect. Then a second line parallel to the first line tangential to the base of the defect was drawn. The bone defect depth was measured from a third line perpendicular to the first 2 lines. Bone density of intrabony defect was assessed radiodensitometrically by measuring the mean values of grey levels in the determined region of interest (ROI). ROI is represented by a rectangle, whose borders were extending from crest of alveolar bone to the base of bony defect (Fig. 3).

Statistical analysis

Data were explored for normality using Kolmogorov-Smirnov test of normality. All Data were parametric and presented as mean and standard deviation (SD) values. Independant t-test was used to compare between the two groups. Paired t-test was used to study the changes by time within each group. The significance level was set at $P \leq 0.05$. Statistical analysis was performed with IBM® SPSS® Statistics Version 23.

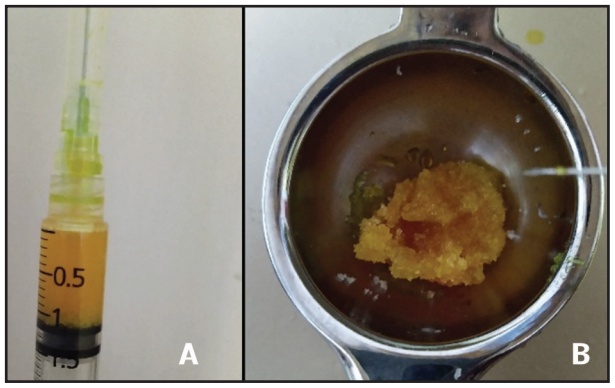

Figure (2) a) I-PRF in a plastic syringe. b) Graft in a sticky form after injection of i-PRF

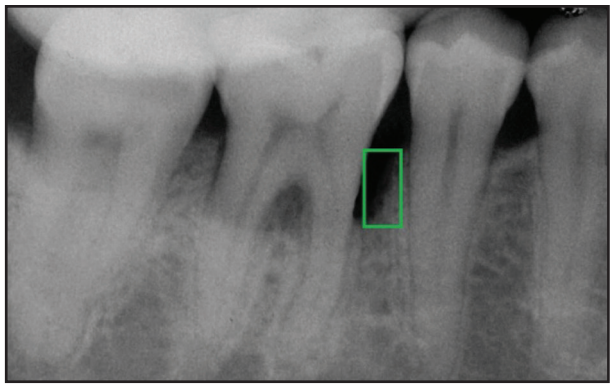
Figure (3) ROS for bone density measurement.

RESULTS

All 24 patients continued the 6 months follow up period without any signs of infection or any reported complications and there was no dropout since all patients continued the 6 months follow up period of the study.

Demographic data:

As presented in table (1), regarding the age, there was no statistical significant difference between test and control groups with mean and SD (47.64±11.39; 46.34±10.33) respectively (P=0.938)

Regarding the gender distribution, there was no statistical significant difference between test and control groups with 5 males (41.67%) in test group and 6 males (50%) in control group (P=1) as presented in table (2).

Table (1): *Mean and SD of subjects age in test and control groups*

	Group	Mean	SD	P-Value
Age	Test	47.64	11.39	0.938
	Control	46.34	10.33	

Statistical significance P ≤ 0.05

Table (2): *Gender distribution (numbers and percentage in both groups*

	Group	Number (males)	Percentage	P-value
Gender	Test	5	41.67 %	1
	Control	6	50 %	

Statistical significance *P ≤ 0.05*

Clinical Parameters:

Concerning PD, as presented in table (3), there was a statistical significant decrease from preoperative to 6 months in each group separately, with mean and SD for test group (6.6 ±1.1 ; 2.4 ±0.9) (P <0.001) and control group (7.8±1.8 ; 4.5±1.4) (P <0.001) respectively. The difference between preoperative mean values in both groups was not statistically significant (P=0.609) and it was statistically significant between the postoperative mean values of reduction in PD between both groups (P <0.001).

Regarding reduction in PD, there was a statistical significant difference between both groups with mean and SD (4.2±0.4 ; 3.3±0.7) (P=0.002) in favor of the test group as shown in table (4).

Concerning CAL, there was a statistical significant gain from preoperative to 6 months in each group separately, with mean and SD for test group (6.8±1.1 ; 3.0±0.8) (P <0.001) and control group (8±2 ; 5.1±1.9) (P <0.001) respectively. The difference between preoperative mean values

in both groups was not statistically significant (P=0.052) and it was statistically significant between the postoperative mean values of reduction in CAL between both groups with mean and SD (P=0.002) as presented in table (3).

Regarding CAL gain, there was a statistical significant difference between both groups with mean and SD (3.8±0.4 ; 2.9±0.8) (P=0.002) in favor of the test group as shown in table (4).

Radiographic Parameters:

Concerning bone defect depth, there was a statistical significant decrease from preoperative to 6 months in each group separately, with mean and SD for test group (8.5 ± 0.9 ; 5.9±1.2) (P <0.001) and control group (9±0.7 ; 7±1.4) (P <0.001) respectively. The difference between preoperative mean values in both groups was not statistically significant (P=0.143)**.** The same was found between the postoperative mean values between both groups with mean and SD (P=0.051) as presented in table (3)

Regarding bone fill, there was no statistical significant difference between both groups with mean and SD (2.6±0.7 ; 2±0.8) (P=0.063) as shown in table (4).

As for the bone density, there was a statistical significant increase from preoperative to 6 months in each group separately, with mean and SD for test group (52.5±10.4; 70±13.8) (P =0.002) and control group (50.7±15.7; 61.6±17.4) (P=0.012) respectively. The difference between preoperative mean values in both groups was not statistically significant (P=0.744). The same was found between the postoperative mean values between both groups with mean and SD (P=0.203) as presented in table (3).

Regarding change in bone density, there was a statistical significant difference between both groups with mean and SD (17.5±4.9; 10.9±6.8 (P=0.01) in favor of the test group as shown in table (4).

Table (3): *Mean and SD preoperative and postoperative values regarding PD, CAL, defect depth and bone density.*

Group / Period	Test		Control		*P*-value
	Mean	SD	Mean	SD	
1- PD					
Pre-op	6.6	1.1	7.8	1.8	**0.609**
Post-op	2.4	0.9	4.5	1.4	**<0.001***
***P*-value**	**<0.001***		**<0.001***		
2- CAL					
Pre-op	6.8	1.1	8	2	**0.052**
Post-op	3.0	0.8	5.1	1.9	**0.002***
***P*-value**	**<0.001***		**0.001***		
3- Bone defect depth					
Pre-op	8.5	0.9	9	0.7	**0.143**
Post-op	5.9	1.2	7	1.4	**0.051**
P-value	**<0.001***		**<0.001***		
4- Bone density					
Pre-op	52.5	10.4	50.7	15.7	**0.744**
Post-op	70	13.8	61.6	17.4	**0.203**
***P*-value**	**0.002***		**0.012***		

Statistical significance P ≤ 0.05 ;
** means statistically significant*

Table (4): *Mean and SD values regarding change in PD, CAL, defect depth and bone density.*

Group / Period	Test		Control		*P*-value
	Mean	SD	Mean	SD	
PD Reduction	4.2	0.4	3.3	0.7	**0.002***
CAL Gain	3.8	0.4	2.9	0.8	**0.002***
Bone Fill	2.6	0.7	2	0.8	**0.063**
B.D. Change	17.5	4.9	10.9	6.8	**0.01***

Statistical significance P ≤ 0.05;
** means statistically significant*

DISCUSSION

Autologous PCs have been widely used in the dental and medical fields, specifically PRF which has become an essential part of the treatment protocols in plastic surgeries, oral and maxillofacial field and implant therapy. PRF has shown enormous benefits in soft tissue healing and enhancing bone regeneration. PRF is usually obtained in the form of a gel or membrane, but can never be injected. Therefore, a simple modification in patient's own blood spinning protocol with less rpm and shorter duration led to the development of a liquid form of PRF called injectable PRF (i-PRF) [29].

This form which has more leucocytic content and more growth factors release, has been successfully applied in conjunction with soft tissue grafts in management of gingival recession[20] and in conjunction with bone grafts in implant therapy[17,18]. PRF has been widely used in management of deep periodontal pockets with great success, however, to the best of our knowledge, few studies evaluated i-PRF in non surgical treatment of periodontal pockets and no studies investigated its effect in periodontal regeneration. Hence, this study was conducted to investigate whether i-PRF would offer any beneficial impact on periodontal regenerative techniques as the grafting procedure.

The results of the present study showed a statistical significant decrease in PD and gain in CAL from baseline to 6 months in each group separately. Regarding reduction in PD after 6 months, there was a statistical significant difference between both groups with mean and SD (4.2±0.4 ; 3.3±0.7) in favor of the test group. Similarly, there was a statistical significant difference in CAL gain between both groups with mean and SD (3.8±0.4; 2.9±0.8) in favor of the test group.

These findings are consistent to what Patel et al. reported when they compared OFD with and without PRF placement in intrabony defects. They reported PD reduction mean values (3.0±1.70; 1.11±0.45) and CAL gain mean values (3.20±1.14; 0.90±0.32) in test and control groups respectively[30]. In addition, Vuckovic et al. investigated the additive effect of i-PRF in non surgical treatment of periodontitis patients. They found a statistical significant difference in mean CAL gain between both groups (i-PRF group 0.9 mm versus without i-PRF group 0.33 mm) in favor of the test group. The same was noticed in PD reduction with mean values 1.95 mm versus 1.37 mm in test and control groups respectively [24].

Furthermore, Liu et al., showed a statistical significant difference in PD reduction and CAL gain between both groups in favor of the test group 12 months after placement of bovine porous bone mineral , GTR with and without PRF in intrabony defects. The range difference in PD between the two groups was 0.6 to 0.7 mm and in CAL gain 0.9 to 1.1 mm [31] . This was also confirmed by *Vu and Pham* when they compared management of intrabony defects with OFD alone versus the addition of PRF. After 6 months, they noticed a statistical significant difference between both groups in favor of the test group in mean PD reduction (3.30±0.84; 2.57±1.36) and CAL gain (3.33±0.71; 2.23±1.22) in test and control groups respectively [32].

This enhancement in clinical parameters might be attributed to the impact of i-PRF on soft tissue healing which was confirmed by Zheng et al. when they investigated the impact of i-PRF on human periodontal ligament cells (PDLC). They found that i-PRF significantly enhanced human PDLC activity, differentiation and diminished notably the inflammation triggered by lipopolysaccharides [33]. Furthermore, Liu et al noticed an accelerated angiogenesis with an increased number of microvessels in the gingival tissue via upregulation of vascular endothelial growth factor after application of PRF [34].

Concerning bone defect depth, there was a statistical significant decrease from baseline to 6

months postoperatively in each group separately. Regarding bone fill, there was no statistical significant difference between both groups with mean and SD (2.6±0.7; 2±0.8). This is in accordance with what Melek and Taalab recorded when they compared the bone gain 6 months after applying β tricalcium phosphate graft and absorbable membrane with and without i-PRF. The mean bone gain was (4.6±0.4 4; 3±0.4) in test and control groups respectively with no statistical significant difference between both groups [16]. This goes along with the findings recorded by Liu et al., who found a non statistical significant difference (0.5%) between both groups in change in bony defect depth after 12 months [31].

In contrast, in the study conducted by Patel et al., PRF group showed a statistically significant higher percentage of bone fill in test group 45.18% versus 21.6% in the control group at the end of the study period. This disparity might be explained by the longer follow up period in their study which was 12 months[30]. Moreover, Vu and Pham showed a statistical significant difference between both groups in favor of the test group in mean bone defect fill (2.37±1.40 ; 1.0±0.64) in test and control groups respectively. This inconsistency might be justified by the addition of only PRF without the use of any grafting material in both groups of their study [32].

As for the bone density in the current study, there was a statistical significant increase from preoperative to 6 months in each group separately, in both groups. Regarding increase in bone density, there was a statistical significant difference between both groups with mean and SD (17.5±4.9; 10.9±6.8). This in accordance with the results reported by Melek and Taalab who found a statistically significantly higher mean of 347.7±9.6 in test group versus 129.7±0.8 in control group. The higher values recorded in their study compared to ours might be attributed to the use of a different type of bone graft (alloplast) in conjunction with G.T.R. in the regeneration of a different type of bony defects (well contained ridge defects) [16].

Similarly, Reda et al., evaluated the benefit of adding i-PRF to xenograft around immediate implants. 6 months postoperatively, they recorded mean change in bone density in the group which received i-PRF and xenograft 154.16±42.44 versus 74.83±19.31 in the group which received only xenograft with a statistical significant difference in favor of the test group [35]. The increase in bone density in the present study and the previously mentioned ones may be justified by the conclusion stated by Wang et al., who observed that i-PRF has a noticeable effect on osteoblasts migration, differentiation, activation, proliferation and survival rate. This effect was found to be more pronounced with i-PRF than with any of the other forms platelet concentrates. They attributed this to the greater content of leukocytes and fibrin proteins occurring in i-PRF [36].

CONCLUSION

Considering the limitations of this study, we can mention that i-PRF had offered an added benefit to xenograft in managing periodontal intraosseous defects in terms of significant reduction in probing depth, gain in clinical attachment with increase in bone density. However, i-PRF did not add a significant valuable benefit to xenograft in bone fill.

RECOMMENDATIONS

Studies with longer follow up period up to 12 months are needed to further investigate the impact of i-PRF on alveolar bone regeneration. It is also recommended to perform more clinical studies comparing i-PRF to other forms of PRF in management of periodontal intrabony defects and periodontal regeneration.

DECLARATIONS STATEMENT

This study is self-funded and there was no conflict of interest

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