Comparative assessment of periodontal regeneration in periodontal intraosseous defects treated with PepGen P-15 unaided or in blend with platelet-rich fibrin: A clinical and high-resolution computed tomography scan-assisted volumetric analysis

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Abstract:
Background: PepGen P-15, a xenograft, has proven its periodontal regenerative potential. Platelet-rich fibrin (PRF) is an autologous platelet concentrate which too contributes to periodontal redevelopment through the release of different polypeptide progression factors. The present study intended to evaluate the regenerative potential of PepGen P-15 xenograft when used unaccompanied or in blend with PRF in periodontal intraosseous defects in humans through clinical and a novel computed tomography (CT) scan analysis technique.

Materials and Methods: Twelve chronic periodontitis individuals with paired periodontal intraosseous defects were randomly treated either with PepGen P-15 exclusively (Control/Group A) or in concoction with PRF (Test/Group B) utilizing split-mouth study design. Pocket probing depth (PPD), relative attachment level (RAL), and relative position of gingival margin were assessed at 3- and 6-month interval, whereas the linear and volumetric bone defect regeneration were assessed at 6 months postoperatively using CT scan.

Results: Both the groups validated statistically significant PPD reduction, RAL gain at 3 and 6 months, but on intergroup comparison, test group CT images revealed significantly greater linear bone gain and volumetric bone gain, with mean difference of 0.73 ± 0.28 (P = 0.018) and 2.70 ± 1.36 (P = 0.06) at 6 months in comparison to the baseline data.

Conclusions: PepGen P-15 and PRF blend had better regeneration potential for the management of intrabony defects. Further long-term investigations on large sample size are recommended to authenticate the same.

Key words: Computed tomography scan, intrabony defects, PepGen P-15, periodontal regeneration, platelet-rich fibrin

INTRODUCTION

Harmonized refurbishment of all the supporting, investing, and surrounding structure of periodontium with coronal migration of junctional epithelium attachment on the cured periodontal disease cemental root surface remains a challenge for the periodontist. In spite of different periodontal regenerative attempts till date, we have not been able to regenerate the optimum inherent periodontal apparatus lost in the course of disease progression.

Among different regenerative materials only patients own bone grafts, demineralized freeze-dried bone allograft (DFDBA) and an organic bovine-derived matrix with P-15...
PepGen P-15 is a platelet-rich fibrin (PRF) act as an autogenous fibrin network with leukocytes to propagate the osteoblasts by exciting the production of osteoprotegerin to promote periodontal regeneration by liberating growth factors and show neo-angiogenic properties. Ample evidences are reported in the literature in favor of PRF associated periodontal regeneration when used unaided or in amalgamation with grafts in different periodontal hard-tissue defects and soft-tissue defects (marginal gingival tissue recession), etc. Hence, it was hypothesized that PRF as an adjunct to PepGen P-15 might yield a better result than PepGen P-15 alone which has not been analyzed/published yet to the best of our information.

Although histologic picture and surgical reentry has been considered a reliable tool to assess the periodontal regeneration in treated cases, mostly, it is not possible because of ethical concerns and nonacceptability of the patients. To overcome all these deficiencies, the present split-mouth study was designed for the estimation the regeneration potential of PepGen P-15 unaided or in blend with PRF in periodontal intraosseous defects clinically and radiographically, utilizing high-resolution computed tomography [Philips Ingenuity MDCT, Netherland (§)] scan-assisted volumetric analysis.

**MATERIALS AND METHODS**

Fifteen patients of chronic periodontitis with bilateral deep intrabony defects were enrolled out of 417 patients who were referred to the institutional outpatient department of periodontology, based on the inclusion criterion. All the enrolled patients underwent Phase I periodontal therapy, but only 12 (10 males, 2 females; of age range between 25 and 55 years with a mean age of 40 years) patients submitted written signed consent and they were treated as per the revised Helsinki Declaration (2008). The selected patients were randomly allocated utilizing sequential numbered, opaque, and sealed envelopes to each treatment group just before the surgery by a noninvestigating examiner.

**Inclusion criterion**

Chronic periodontitis patients with normal platelet count concentration, age between 25-60 years of either gender, having minimal two intra osseous defect in each/contra lateral arch with probing depth (PPD) ≥ 5mm as well as osseous defect well observed on IOPA x-ray taken using parallel profile radiography technique, orthopantomogram, and then confirmed by using ingenuity; 128 Slice MDCT, Philips Medical Systems, Netherland software at baseline were the inclusion criterion for the study as shown in Figures 1a-c and 2a-c for CT scan evaluation of defect; Figures 3a and 4a for pre-operative PD and Figures 3d and 4d for osseous defect observed on IOPA X-ray).

**Exclusion criterion**

Adverse habits such as smoking and alcohol consumption, any potential medical complications and any disorder affecting the treatment plan and wound healing, pregnant and nursing women, any known reaction to any of the materials proposed to be utilized in the study, mobility of teeth, furcation defects, and flawed endodontic/conservative treatment were excluded from the study.

**Initial therapy**

All the selected patients had gone thorough oral prophylaxis as well as subgingival root planing followed by oral hygiene instructions. Oral hygiene maintenance therapy and motivation carried out at weekly interval, and the patients responded well with good oral hygiene within 6-8 weeks after the initial therapy.

**Preoperative clinical parameters assessed**

Plaque index (PI) and gingival index (GI) were evaluated with respect to a localized tooth having intraosseous defects, in addition to full-mouth PI, GI and gingival sulcus bleeding index (SBI) were recorded at the baseline (zero time). Occlusal stents were fabricated and grooves were placed to standardize the position of the periodontal probe **(CP 15 UNC, Hu-Friedy Chicago, IL, USA)** and to accurately compare the pre- and postoperative measurements including PPD, relative position of the gingival margin (REC), and relative attachment level (RAL). RAL and REC were measured using the most apical end of the stent as a reference, while PPD was measured from the gingival margin.

Osseous defect morphology was determined using 3D CT with the following technical parameters: slice thickness of 0.67 mm, exposure of 120 kV, and 150 mA with a 0° gantry orientation.
Following image acquisition in three sections consisting of axial, sagittal, and coronal planes, as measured with the help of digital calipers, the images were reconstructed using the software provided with the CT system. The area of interest was extracted, and threshold processing was performed to allow clear visualization of the defect [Figures 1c and 2c preoperatively and Figures 1f and 2f postoperatively]. All linear and volumetric measurements were calculated to the nearest to 0.1 mm. All linear and volumetric measurements were calculated to the nearest to 0.1 mm. The analyzed hard-tissue parameters included depth of bony defect (cementoenamel junction [CEJ] to the base of the defect [BOD] minus CEJ to alveolar crest [AC]), AC level, defect volume, and linear bone defect height (CEJ to the BOD at the baseline A0) and were recorded by another trained blind investigator who was not the part of study, whereas surgeries were performed by a single-trained clinician.

Platelet-rich fibrin preparation
It was carried out just immediately before the surgical intervention from patients own 10 ml blood sample collected in pre sterile test tube and centrifuged at 2700 rpm, for 10 min as per the Choukroun’s protocol, in a centrifuge unit (REMI, India).

Surgical procedures/intrasurgical measurements
Under a septic surgical protocol, surgical sites were anesthetized using 2% local anesthesia with adrenaline. Full-thickness periodontal flaps were reflected followed by thorough root planing and the defect was debrided. The open defect measurements from the BOD to the apical end of the stent (BD-AS) as shown [Figures 3b and 4b] and from AC-AS were measured utilizing UNC-15 probe. The defect depth was calculated as the difference between the two, that is, AS to BD minus AS to AC.

PepGen P-15 graft alone or in blend with PRF clot fragments were packed till the crest of bone defects in Group A and B, respectively. The patients were instructed regarding the postoperative oral hygiene measures.

PI, GI, SBI, PPD, RAL were recorded at 3 and 6 month interval [Figure 3c and 4c showed PPD 6 month interval]. IOPA X ray was also taken at 6 month post operatively to observe the bone changes too [Figures 3e and 4e] whereas linear bone growth (LBG), volumetric bone gain (VBG) [Figures 1d-f and 2d-f] and LBG % and VBG% change were recorded by CT scan for both the groups 6 months post operatively groups.

Linear bone growth = Linear bone defect height at 6 months A1– Linear bone defect height at baseline A0
Linear bone growth%change = A1-A0/A0 X 100

All the data obtained from the different parameters assessed at respected time intervals of the study protocol were analyzed utilizing IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY., USA). The Wilcoxon signed-rank test was performed for intragroup comparison value); independent ‘t’ test for intergroup comparison of clinical parameters (t) where paired ‘t’ and independent ‘t’ was performed for LBG as well as VBG intra and intergroup comparison. P < 0.05/>0.05 was considered statistical significant/nonsignificant, respectively.
RESULTS

All the 12 patients selected for the surgical procedure had completed the study without any complication. Out of full mouth PI, GI, and SBI scores as well as PI and GI at teeth with the intrabony defect, only PI and GI scores only on intragroup comparison showed statistically significant changes \((P < 0.002)\) [Table 1].

The reduction in PPD, RAL, and REC on intragroup comparison in Group A and B at 3 and 6 months postoperatively found to be statistically significant \((P = 0.002)\), respectively, but only significant improvement \((P < 0.008)\) was observed in RAL at 6-month interval on intergroup comparison [Table 2].

Both Group A and Group B reported significant intragroup improvements \((P < 0.001)\) in terms of mean amount and \% of changes in linear bone gain (LBG) and VBG, but more, pronounced changes observed in mean difference \(2.17 \pm 0.72\) (LBD), \(7.02 \pm 4.23\) (VBG) and \(30.33 \pm 8.36\) (%LBG) as well as \(58.08 \pm 18.14\) (%VBG) in group B. LBG, VBG, \% of LBG and VBG were also reported to be statistically significant \((P = 0.018, 0.06, 0.17 and 0.08)\) respectively on intragroup comparison too [Table 3 and 4].

Table 1: Mean and mean differences in plaque index, gingival index, and sulcular bleeding index of Group A, Group B, and Group A versus Group B at different intervals

| Assessment interval | PI (localized at tooth with intraosseous defect) Mean±SD | GI (localized at tooth with intraosseous defect) Mean±SD | SBI (full mouth) Mean±SD |
|---------------------|--------------------------------------------------------|--------------------------------------------------------|--------------------------|
|                     | Mean difference from baseline Z or t P                | Mean difference from baseline Z or t P                  | Mean difference from baseline Z or t P |
| Group A             |                                                        |                                                        |                          |
| Baseline            | 0.00±0.00                                              | 0.00±0.00                                              | 0.58±0.51                |
| 3 months            | 0.32±0.15                                              | 0.32±0.15                                              | 0.32±0.15                |
| 6 months            | 0.54±0.27                                              | 0.54±0.27                                              | 0.50±0.16                |
| Group B             | 0.00±0.00                                              | 0.00±0.00                                              | 0.58±0.51                |
| Baseline            | 0.35±0.15                                              | 0.35±0.15                                              | 0.31±0.18                |
| 6 months            | 0.51±0.24                                              | 0.51±0.24                                              | 0.47±0.18                |
| Group A versus B    | -                                                      | -                                                      | -                        |
| Baseline - 3 months | 0.02±0.06                                              | 0.01±0.06                                              | 0.01±0.06                |
| Baseline - 6 months | 0.02±0.10                                              | 0.02±0.07                                              | 0.02±0.07                |

DISCUSSION

Conventional intraoral radiographs provided only the buccal and lingual view of intrabony defects\([10,20]\), whereas CT scan has advantages over conventional radiographs because of its skill for 3D analysis of bone defect image with high precision and resolution\([14,15]\) as well as it is a noninvasive way to assess the bone regeneration in the periodontal bone defects reported by Naito et al.,\([16]\) Ito et al.,\([17]\) and Pradeep et al.,\([18]\), etc. Therefore, advance high-resolution CT was selected in the present study.

PepGen P-15 xenograft has been considered in the present study due to its favorable clinical and histologic profile\([16,20]\) and enhanced attachment of cells in vivo\([20]\) since it is an anorganic bovine-derived hydroxyapatite (HA) bone matrix representing a regular HA skeleton and appears to behave more physiologically during wound healing. It has been shown that the P-15 helps in the binding of cells particularly fibroblasts and osteoblasts.\([21]\) Different researchers have been reported clinical efficiency and superiority of ABM/P-15 to other bone graft materials\([22,23]\) and open-flap debridement.\([24]\)

The PRF coagulate boosts cellular migration through its fibrin framework, accelerated wound healing, neovascularization,
Table 2: Mean and mean differences in probing pocket depth, relative attachment level, and relative position of gingival margin of Group A, Group B, and Group A versus Group B at different intervals

| Assessment interval | PPD | RAL | REC |
|---------------------|-----|-----|-----|
|                     | Mean±SD | Mean difference from baseline | Z or t | P | Mean±SD | Mean difference from baseline | Z or t | P | Mean±SD | Mean difference from baseline | Z or t | P |
| Group A Baseline    | 6.91±0.90 | - | - | - | 10.42±1.83 | - | - | - | 5.63±0.78 | - | - | - |
| 3 months            | 4.30±0.77 | 2.58±0.67 | 3.12 | 0.002 | 7.83±1.95 | 2.58±0.67 | 3.12 | 0.002 | 4.75±0.96 | 0.91±0.28 | 3.31 | 0.001 |
| 6 months            | 2.80±0.57 | 4.08±0.79 | 3.12 | 0.002 | 6.41±1.83 | 4.00±0.85 | 3.09 | 0.002 | 4.58±0.90 | 1.08±0.28 | 3.35 | 0.001 |
| Group B Baseline    | 7.41±0.79 | - | - | - | 11.41±1.44 | - | - | - | 6.08±1.24 | - | - | - |
| 3 months            | 4.50±0.52 | 2.91±0.79 | 3.16 | 0.002 | 8.50±1.24 | 2.91±0.79 | 3.10 | 0.002 | 5.08±1.16 | 1.00±0.42 | 3.20 | 0.001 |
| 6 months            | 2.83±0.38 | 4.58±0.67 | 3.16 | 0.002 | 6.50±1.31 | 4.91±0.67 | 3.13 | 0.002 | 5.0±1.20 | 1.08±0.29 | 3.35 | 0.001 |
| Group A versus Group B Baseline-3 months | - | 0.33±0.29 | 1.11 | 0.27 | - | 0.33±0.29 | 1.11 | 0.28 | - | 0.14±0.21 | 0.56 | 0.58 |
| Baseline-6 months   | - | 0.50±0.29 | 1.67 | 0.10 | - | 0.91±0.31 | 2.93 | 0.008 | - | 0.00±0.11 | 0.00 | 1.00 |

P>0.05 – Nonsignificant; P<0.05 – Significant; P<0.001 – Highly significant changes observed on intra and intergroup comparison statistically; PPD – Probing pocket depth; RAL – Relative attachment level; REC – Relative position of gingival margin; SD – Standard deviation; Z – Value for non parametric data utilizing Wilcoxon’s signed rank test on intra group comparison; t – Independent ‘t’ test value of inter group comparison; P – Probability value

Table 3: Mean, mean differences, and percentage of linear bone growth (DENTASCAN) of Group A, Group B, and Group A versus Group B at different intervals

| Assessment interval | Percentage of linear bone growth (LBG) | Mean±SD | Mean difference from baseline | t | P | LBG (%) |
|---------------------|---------------------------------------|--------|-----------------------------|---|---|--------|
| Group A Baseline    |                                       | 6.86±2.18 | - | - | - | - |
| 6 months            |                                       | 5.44±1.94 | 1.42±0.67 | 7.26 | 0.001 | 21.25±8.93 |
| Group B Baseline    |                                       | 7.17±1.45 | - | - | - | - |
| 6 months            |                                       | 5.00±1.18 | 2.15±0.72 | 10.26 | 0.001 | 30.30±8.34 |
| Group A LBG versus Group B Baseline-6 months | - | 0.73±0.28 | 2.555 | 0.018 | - | - |
| LBG (%)             |                                       | 9.08±3.53 | 2.573 | 0.017 | - | - |

P>0.05 – Nonsignificant; P<0.05 – Significant; P<0.001 – Highly significant; LBG – Linear bone growth; SD – Standard deviation; t – t value of paired ‘t’ test for intragroup comparison of LBG; P – Probability value

Table 4: Mean, mean differences and percentage of volumetric bone gain (DENTASCAN) of Group A, Group B and Group A versus Group B at different intervals

| Assessment interval | Percentage of volumetric bone gain | Mean±SD | Mean difference from baseline | t | P | Defect volume gain (%) |
|---------------------|------------------------------------|--------|-----------------------------|---|---|------------------------|
| Group A Baseline    |                                    | 11.43±4.37 | - | - | - | - |
| 6 months            |                                    | 7.11±3.23 | 4.31±2.08 | 7.17 | 0.001 | 37.83±15.5 |
| Group B Baseline    |                                    | 11.95±5.62 | - | - | - | - |
| 6 months            |                                    | 4.93±3.28 | 7.01±4.23 | 5.631 | 0.001 | 58.08±18.14 |
| Group A versus Group B defect volume gain Baseline - 6 months | - | 2.7±1.36 | 1.98 | 0.060 | - | - |
| Volume gain (%)     |                                    | 20.25±6.90 | 2.93 | 0.008 | - | - |

P>0.05 – Nonsignificant; P<0.05 – Significant; P<0.001 – Highly significant; SD – Standard deviation; t - t value of independent ‘t’ test value of inter group comparison; P – Probability value

and cicatricial tissue remodeling.[8] PRF secure and take care of the implanted material by acting as a genetic connector between implanted graft particles. During resorption phase, PRF steadily released cytokines, thereby generating a long-lasting process of healing. Finally, the presence of different leucocytes and cytokines within the fibrin web plays an extensive role in the self-regulation of inflammatory and infectious phenomena within the imbedded material.[23] Greater improvement reported in the periodontal soft-tissue parameter (PPD, CAL, etc.) and radiographic bone gain with the use of unaided PRF in comparison to conventional flap surgery in three-wall periodontal bone defects.[26,27] Grade II furcal defect,[28] PRF in blend with bone grafts in the treatment of three-wall osseous defects,[27] and comparable regenerative potential of PRF to DFDBA in periodontal intraosseous defects,[28] in marginal tissue recession coverage.[29] Periodontal regeneration of three-wall intraosseous defect by the use of ABM/P-15 unaided and in blend with PRF was not published yet to the best of our information achieved through the web of literature search. Thus, it has been reserved in thoughts that no direct comparative assessment is available. The study results showed that the mean PPD reduction was marginally greater in the Group B than Group A, which is
Comparatively, greater gain in RAL was observed in Group B in comparison to Group A from 0- to 6-month interval, respectively, with a significant intergroup difference which is consistent with the reports of Pradeep et al., but they have observed the gain in clinical attachment level with PRP and PEBG and fusion of PRF with HA bone graft for the management of three-wall intrabony defects in the patients suffering from chronic periodontitis. The report of Piemontese et al. treated intraosseous defects with DFDBA in blend with PRP, DDFBA in blend with PRF, and partially in consistency to the report of Fatima et al. as they observed significant difference only on intragroup comparison only. The gain in RAL in each group of our study may be attributed to the periodontal regeneration associated with ABM/P-15 which is in consistency with the report of Yukna et al., which further enhanced when blend of ABM/P-15 and PRF was utilized. The gain in RAL (clinical attachment gain) in both the groups is in consistency with the reports of Pradeep et al. but have compared different implanted materials; Mishra et al. evaluated open-flap therapy with or without ABM/P-15. Juneja and Bharti utilized PRF and HA in the intrabony defects in vivo. Greater and significant mean LBG and VBG were observed in the ABM/P-15 PRF group after 6 months, as compared to ABM/P-15 group which was in consistency with the report Pradeep et al., but they evaluated the defect fill and original defect resolution till 9 months postoperatively utilizing spiral 3D CT scan. The significant intergroup comparison may be attributed due to multiple reasons (i) synchronized effect of PepGen P-15 and PRF, as precedent surfaces imitate the role of native collagen matrix in wound healing; and its deposition is an important component of repair in tissue. It also promotes matrix mineralization by exciting the osteoblastic activity by improving the BMP-2, BMP-7, alkaline phosphatase, and osteogenic factors expression which might help in regenerating the periodontal tissues; (ii) PRF due to their distinguishing properties enhances the regenerative effect when used in combination with bone graft, which might be because two diverse healing processes may take place collectively which may probably result in their synergistic effect and (iii) increased sensitivity, specificity determination, and quantification through CT scan as compared to conventional radiographs.

CONCLUSIONS
PepGen P-15 bone graft in conjunction with flap surgery was an effective periodontal regenerative potential in terms of linear bone growth and VBG for the management of three-wall bone defects. However, the outcome achieved further enhanced when the same treatment protocol is used in blend with PRF.

Footnotes
†PepGen P-15® (250–420 μ) (DENTSPLY Friadent CeraMed, Lakewood, CO, USA).

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Conflicts of interest
There are no conflicts of interest.

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