Bone Regeneration in Maxillary Sinus Augmentation using Advanced Platelet-Rich Fibrin (A-PRF) and Plasma Rich in Growth Factors (PRGF): A Pilot Randomized Controlled Trial

Panagiotis Dragonas, DDS, MS1/Hari S. Prasad PhD2/Qingzhao Yu, PhD3/Elizabeth T. Mayer, RDH1/Paul L. Fidel Jr., PhD4

1Department of Periodontics, Louisiana State University-Health, School of Dentistry, New Orleans, Louisiana, USA;
2Hard Tissue Research Laboratory, University of Minnesota, Minneapolis, MN, USA.
3Biostatistics Program, School of Public Health, Louisiana State University-Health, New Orleans, Louisiana, USA;
4Department of Oral and Craniofacial Biology, Louisiana State University Health - School of Dentistry, New Orleans, Louisiana, USA

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Correspondence to: Dr. Panagiotis Dragonas, LSU-H School of Dentistry, 1100 Florida Ave, New Orleans, LA, 70119, USA, Email: pdrag1@lsuhsc.edu, Fax: 504-941-8279

The purpose of this pilot randomized controlled trial was to analyze and compare the effects of advanced platelet-rich fibrin (A-PRF) and plasma rich in growth factors (PRGF) combined with deproteinized bovine bone mineral (DBBM) on bone regeneration outcomes in maxillary sinus augmentation (MSA) procedures. A total of 15 patients in need of MSA were consecutively recruited. Maxillary sinuses were grafted with DBBM alone (control group), DBBM mixed with A-PRF (PRF group), or DBBM mixed with PRGF (PRGF group). After a 6-month healing period, bone core biopsy
samples were collected prior to implant placement for histologic and histomorphometric analyses. The mean percentage of mineralized tissue (MT) was 20.33 ± 11.50 in the control group, 32.20 ± 7.29 for the PRF group, and 34.80 ± 6.83 for the PRGF group, with no statistically significant differences across the three groups ($P > .05$). The mean percentage of remaining bone grafting material (RBGM) was 24.00 ± 7.94 for the control group, 26.00 ± 7.78 for the PRF group, and 15.80 ± 8.23 for the PRGF group, with no statistically significant differences across the three groups ($P > .05$). Finally, the mean percentage of nonmineralized tissue (NMT) was 55.66 ± 7.77 for the control group, 41.40 ± 8.32 for the PRF group, and 49.60 ± 5.68 for the PRGF group, with no statistically significant differences across the three groups ($P > .05$). These findings suggest that the addition of A-PRF and PRGF to DBBM does not enhance new bone formation outcomes in maxillary sinus augmentation procedures. Neither of the two platelet concentrates were superior to the other in any of the variables assessed. *Int J Periodontics Restorative Dent* 2022. doi: 10.11607/prd.5491
Introduction

Tooth replacement therapy with dental implants in the posterior maxilla often requires maxillary sinus augmentation (MSA), due to alveolar ridge atrophy. A number of bone grafting materials have been successfully used through the lateral window approach, often in combination with platelet concentrates (PC’s) in an effort to enhance the regenerative potential. Two of the most frequently used PC’s in sinus grafting are the Platelet-rich fibrin (PRF) in its various commercial forms and the Plasma rich in Growth factors (PRGF®-Endoret®). These PC’s follow different preparation protocols, however they both produce diverse forms of clinically applicable products, such as liquids that allow them to be mixed with various biomaterials as well as membranes. Advanced-PRF (A-PRF™) and Leukocyte-PRF (L-PRF) have both been reported to contain higher amount of growth factors with a longer release pattern when compared to PRGF (1, 2). However, PRGF preparation intentionally involves the exclusion of leukocytes, with the purpose of minimizing local pro-inflammatory effects, thus enhancing wound healing and bone regeneration (3, 4). In terms of clinical outcomes, the addition of L-PRF and PRGF to deproteinized bovine bone mineral (DBBM) has been reported to increase the amount of new bone formation (NBF) when compared to DBBM alone (5, 6). However, two recent systematic reviews on the effects of these PC’s reported that the addition of L-PRF and PRGF did not produce any more favorable outcomes in terms of % of NBF and residual graft material (RGM), concluding that current evidence supporting the use of these PC’s in MSA is limited (7, 8). Also, only one study to date has compared the use of PRF and PRGF in MSA, reporting no differences in terms of % of NBF, RGM and soft tissue at 6 months, when both combined with beta-tricalcium phosphate (β-TCP)(9). To the authors’ knowledge, no studies have been published so far comparing these two PC’s when combined with DBBM. Thus, the aim of this study was to assess and compare, though histologic and histomorphometric analysis, the effects of A-PRF™ and PRGF®, combined with DBBM, in bone regeneration outcomes, 6 months after MSA procedures.
Materials and methods

Study design

This study was designed as a pilot randomized controlled trial. All participants in the study were recruited and treated at the Department of Periodontics, Louisiana State University Health (LSUH) – School of Dentistry, between November 2017 and December 2019. The clinical study protocol was approved by the LSUH – New Orleans Institutional Review Board (IRB # 9727). The trial was conducted in compliance with the CONSORT guidelines (Consolidated Standards of Reporting Trials) (10). The CONSORT flowchart illustrating the timeline and study design is depicted in Figure 1.

Outcomes of interest

Percentage of mineralized tissue (%MT) at 6 months
Percentage of remaining bone grafting material (%RBGM) at 6 months
Percentage of non-mineralized tissue (%NMT) at 6 months

Eligibility criteria

The following inclusion criteria were applied: Age >18 years, partial or complete edentulism in the posterior maxilla, in need of unilateral or bilateral maxillary sinus augmentation with delayed implant placement, residual crestal bone height (RBH) ≤ 6mm assessed on a pre-surgical cone beam computed tomography (CBCT), physical status according to the American Society of Anesthesiologists (ASA) I or II and local conditions compatible with sinus floor elevation. The patients were excluded on the basis of use of medications that affect bone metabolism, smoking more than 10 cigarettes a day, uncontrolled diabetes mellitus or other systemic disorders prohibiting extensive surgery, history of head and neck radiation, untreated periodontal disease and acute or chronic sinus pathology. In case a patient was in need of bilateral maxillary sinus grafting, each site was randomly assigned to one of the three treatment groups.

Randomization
The statistical unit was each individual maxillary sinus. Each available sinus was randomly assigned to three treatment groups: (1) PRF, (2) PRGF and (3) control by use of the online statistical computing web program www.randomization.com. The software randomizes each site to a single treatment by using the method of randomly permuted blocks. The randomization plan is not affected by the order in which the treatments are entered.

Interventions

Surgeries were performed under intravenous sedation and local anesthesia. In all cases, sinus augmentation was performed following a lateral approach. A full thickness mucoperiosteal flap was raised in order to expose the lateral wall of the maxillary sinus. Antrostomy was then performed by means of high speed diamond burs and/or Piezosurgery (Piezotome® Solo ACTEON®) under copious sterile saline irrigation. The window of the lateral wall was preserved and folded with the Schneiderian membrane into the sinus cavity. The sinus membrane was then elevated using piezoelectric tips and hand instruments. Based on the group assignment, the following protocols were followed:

Control Group: Deproteinized bovine bone mineral (DBBM) (1-2mm particle size; Bio-Oss®, Geistlich, Wolhusen, Switzerland) was used to fill in the maxillary sinus. In case of a sinus membrane perforation, a collagen membrane (Bio-Gide®, Geistlich, Wolhusen, Switzerland) was used to seal the perforation. A second collagen membrane (BioGide®, Geistlich) was placed over the lateral window, prior to flap closure.

PRF Group: For the PRF fabrication, Choukroun’s A-PRF™ protocol was used. More specifically, peripheral blood of patients was drawn intraoperatively into six (6) 10ml-sterile plain glass-based vacuum tubes without anticoagulant (A-PRF™+). Tubes were immediately centrifuged at 1300rpm for 5 min. At the end of the spin, 2 tubes were removed and the upper liquid layer (2-3ml) was immediately collected with a syringe and mixed with DBBM (1-2mm particle size; Bio-Oss®, Geistlich). The A-PRF-DBBM mix was used to fill the maxillary sinus. The remaining 4 tubes were centrifuged at 1300rpm for additional 3 minutes for a total of 8 minutes. At the end of the second spin,
the tubes were placed on a tube holder for 5 minutes. Then, the PRF clots were carefully retrieved from
the tubes and placed on a specially designed box ("PRF-box") where they were compressed into
membranes. In case of a membrane perforation, a collagen membrane (BioGide®, Geistlich) was used
in combination with two (2) A-PRF membranes, to seal the perforation. A second collagen membrane
(BioGide®, Geistlich) was placed over the lateral window and was subsequently covered with 2-4
more A-PRF membranes prior to flap closure.

PRGF Group: For the PRGF preparation, the manufacturer’s protocol was followed (PRGF®-
Endoret® BTI Biotechnology Institute). More specifically, peripheral blood of patients was drawn
intraoperatively into six (6) 9 mL-blood-collecting tubes® (Biotechnology Institute [BTI], Vitoria,
Spain) that contain 3.8% sodium citrate as anticoagulant. PRGF was prepared by centrifugation at
460g for 8 minutes at room temperature. Plasma not including the buffy coat above red blood cells,
was pipetted out in two fractions. Fraction 1, closest to the red and white blood cell containing
sediment, was mixed with calcium chloride on a dose dependent quantity and then mixed with DBBM
(1-2mm particle size; Bio-Oss®, Geistlich). The mix was incubated at 37C until a gel like consistency
was formed. The PRGF-DBBM viscous mix was then used to fill the maxillary sinus. Fraction 2,
immediately above fraction 1, was also mixed with calcium chloride on a dose dependent manner
producing a PRGF membrane. In case of a membrane perforation, a collagen membrane (BioGide®,
Geistlich) was used in combination with a PRGF membrane, to seal the perforation. A second collagen
membrane (BioGide®, Geistlich) was placed over the lateral window and was subsequently covered
with a PRGF membrane prior to flap closure. All participants were asked to follow a pharmacologic
protocol consisting of antibiotics (Augmentin 875mg BID for 7-10 days), oral corticosteroids
(Methylprednisolone for 6 days in decreasing daily dosages: 24, 20, 16, 12, 8, and 4mg respectively)
and non-steroidal anti-inflammatory drugs (Ibuprofen 600mg) to control post-operative swelling and
discomfort. Patients returned for post-operative follow up at 2 weeks and were seen at regular intervals
during the 6-month healing period. After a 6 month healing period, during surgery for implant
placement, 2.0 (internal diameter) x 15mm trephines (ACE Surgical supply Co., Inc.) were used to collect bone biopsies in the same surgical location where the implants were placed. The biopsies were left inside the trephine burs to maintain the orientation of the bone cores and were immediately fixed in 10% buffered formalin at room temperature for subsequent histologic and histomorphometric analysis.

Histologic Processing and Histomorphometric Analysis

Blinded histologic and histomorphometric assessment of all specimens was performed by an experienced pathologist (H.S.P.) at the Hard tissue Research Laboratory, University of Minnesota, Minneapolis, Minnesota, USA. Upon receipt, specimens were dehydrated with a graded series of alcohols for 9 days. Following dehydration, the specimens were infiltrated with a light-curing embedding resin (Technovit 7200 VLC, Kulzer). Following 20 days of infiltration with constant shaking at normal atmospheric pressure, the specimens were embedded and polymerized by 450-nm light (the temperature of the specimens never exceeded 40oC) and then cut and ground. Two slides per specimen were cut in a longitudinal section and prepared to a thickness of 150µm on a grinding system (EXAKT Technologies). The cores were polished to a thickness of 45 to 65µm with a series of polishing sandpaper disks from 800 to 2,400 grit, using microgrinding system, followed by a final polish with 0.3µm alumina polishing paste. The slides were stained with Stevenel’s blue and Van Gieson’s picro fuchsin and coverslipped for histologic analysis using Brightfield and polarized microscopy. The following variables were measured: (i) percentage of mineralized tissue (%MT), (ii) percentage of remaining bone grafting material (%RBGM) and (iii) percentage of non-mineralized tissue (%NMT). The analysis was performed at the same magnification using a Nikon Eclipse 50i microscope (Nikon Corporation, Japan) and a Spot Insight 2 mega sample digital camera (Diagnostic instruments Inc., USA). Histomorphometric measurement were completed by a combination of spot insight program and Adobe Photoshop (Adobe Systems, Inc.) and were recorded as the average of the 2 slides from each specimen.

Statistical analysis
As this was a pilot study, no formal sample size calculation was performed. All statistical analyses were performed using SAS® (Statistical Analysis System) version 9.4. All recorded variables (%MT, %RBGM and %NMT) were expressed as mean ± standard deviation. One-way ANOVA was used to compare study variables among groups and Tukey’s method was used for pairwise comparisons. The significance level was set a priori at 0.05.

Results

Study population and Clinical findings

Fifteen (15) patients were recruited for this study and subsequently underwent sinus augmentation. Among these subjects, 1 patient was excluded due to a large sinus membrane perforation that could not be repaired, 1 patient due to a post-operative sinus infection, 1 patient due to medical reasons occurring after the initial surgery and 2 patients dropped out for financial reasons. The final sample consisted of 10 patients contributing with 13 maxillary sinus grafts, as 3 patients underwent bilateral maxillary sinus augmentation. The distribution among the three treatment groups included, five (5) maxillary sinuses on the PRF group, five (5) on the PRGF group and three (3) on the control group.

The subjects consisted of 6 females and 4 males with a mean age of 60.4 years (range: 49 to 71 years). Two patients were smokers (<10 cigarettes a day). Mean baseline radiographic RBH was 3.1 ± 1.2 mm ranging from 1 to 5.1 mm. The incidence of sinus membrane perforation was 54% (7 out of 13). Two perforations occurred in the PRF group, 3 on the PRGF group and 2 on the control group. Out of the 7 sinus membrane perforations, 6 of them presented with a maximum diameter of ≤ 5mm and 1 of them (PRF group) with a maximum diameter of 7mm as measured with a UNC periodontal probe intraoperatively. All perforations were sealed intraoperatively, following the protocol established for each of the treatment groups.

Histomorphometric outcomes
Thirteen bone biopsies were obtained and processed for analysis. The mean % of MT was 20.33±11.50 in the control group, 32.20±7.29 for the PRF group and 34.80±6.83 for the PRGF group with no statistically significant differences (NSSD) across the 3 groups (p-value of 0.0875). The mean % of RBGM was 24.00±7.94 for the control group, 26.00±7.78 for the PRF group and 15.80±8.23 for the PRGF group with NSSD across the 3 groups (p-value of 0.161). Finally, the mean % of NMT was 55.66±7.77 for the control group, 41.40±8.32 for the PRF group and 49.60±5.68 for the PRGF group with NSSD across the 3 groups (p-value of 0.0573) (Tables 1, 2 and 3) (Figures 2-9).

Discussion

The purpose of this study was to compare A-PRF™ and PRGF® in parallel, when combined with DBBM. The histologic and histomorphometric analysis revealed no differences between the two PC’s in terms of % MT, RBGM and NMT at 6 months post MSA. Also, no differences were found between A-PRF™/DBBM and PRGF®/DBBM when compared to DBBM alone, despite the %MT in the control group being less than in the other two groups (20.3±11.5 vs. 32.2±7.3 and 34.8±6.8). However, the unequal sample size as well as the large standard error for the control group, could have influenced the results. Adjunctive effects of PRF on bone regeneration in DBBM-grafted maxillary sinuses, have been evaluated in a number of clinical studies reporting no differences in % NBF when compared to DBBM alone (18.35±5.62 vs. 12.95±5.33 and 21.38±8.78 vs. 21.25±5.59 respectively)(11, 12). These results are in line with the present data. However, % MT seems to be higher in the present study for the PRF group (32.20±7.29), which could be explained by differences in the study design, population characteristics as well as PRF/DBBM mixture preparation protocols. Limited evidence also exists on the effects of PRGF on bone regeneration outcomes in DBBM-grafted maxillary sinuses with studies either reporting greater (31±5 vs. 21.3±4.5) (13) or similar (30.7±7 vs. 22.72±9.2) (14), (35.6 ± 8.3 vs. 37.8 ± 3.2)(15) % NBF with PRGF/DBBM mixtures versus DBBM alone respectively. In the present study, the %MT in PRGF-treated sites (34.8±6.8) is similar to what has been reported in the
aforementioned studies, which could be partly explained by a more uniform protocol associated with PRGF preparation (PRGF®-Endoret® BTI Biotechnology Institute). There are some limitations present on this study. First, the initially small sample size was further diminished by 5 patients dropping out (33% of initial sample), resulting in an even smaller sample size that does not easily allow for generalization of outcomes. Also, a high incidence of SM perforation was noted in the study, which could be attributed to the procedures being performed by three (3) surgeons in training. Whether this complication, which was even more prevalent on the control group, could have potentially affected the reported histomorphometric outcomes cannot be fully assessed. Finally, due to the very similar histomorphometric outcomes that were observed across groups, it is unlikely that another investigation involving a larger sample size would result in significantly different findings.

Conclusion

The results of this study suggest that the addition of A-PRF™ and PRGF® to DBBM does not enhance new bone formation outcomes in maxillary sinus augmentation procedures. None of the two platelet concentrates was found to be superior to the other in any of the variables assessed.

Acknowledgements

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References


Figure Legends

Figure 1: CONSORT flowchart
Figure 2: PRF group. Low-power photomicrograph shows a fairly solid core with good new bone (NB) formation around xenograft (XG) particles. The cancellous network is well formed with good, thick trabeculae bridging among the XG particles. (X20 Stevenel’s blue and Van Gieson’s picro fuchsin)

Figure 3a: PRF Group (from same core as Fig.2). The medium power photomicrograph shows excellent views of NB formation surrounding particles of XG. XG particles make up a substantial portion of the cancellous bone pattern and NB. Formation of green-staining osteoid (OD) along the surface of NB. (X40 Stevenel’s blue and Van Gieson’s picro fuchsin)

Figure 3b: PRF group (from same core as Fig.2). The medium power polarized view, shows a view of NB formation as well as bone remodeling. (x40 Stevenel’s blue and Van Gieson’s picro fuchsin)

Figure 4: PRF group (from same core as Fig.2). High-power photomicrograph shows numerous particles of XG of various sizes surrounded by NB. NB formation bridges among the particles in areas where the particles are close to each other, forming a cancellous bone pattern. Green-staining osteoid (OD) along the surface of the new bone (NB) and osteocyte (OC) in the lacunae are present. (X100 Stevenel’s blue and Van Gieson’s picro fuchsin)

Figure 5: PRGF group. Low-power photomicrograph shows a fairly solid core with good NB formation around XG particles. The cancellous network is well formed with good, thick trabeculae bridging among the XG particles. (X20 Stevenel’s blue and Van Gieson’s picro fuchsin)

Figure 6a: PRGF group (from same core as fig 5). The medium power photomicrograph shows cancellous NB formation that has formed around XG particles. Virtually every particle of XG is surrounded by newly formed bone. The image shows new bone formation with osteoid (OD). (X40 Stevenel’s blue and Van Gieson’s picro fuchsin)
Figure 6b: PRGF group (from same core as fig 5). The medium power polarized view, shows a view of NB formation as well as bone remodeling. XG particles are surrounded by newly bone formation (x40 Stevenel’s blue and Van Gieson’s picro fuchsin)

Figure 7: PRGF group (from same core as fig 5). The very high power photomicrograph shows that bone had grown in contact with the large XG particle and a very good example of the various phases of NB formation. The image shows NB formation with osteoid (OD), osteocytes (OC) and osteoblasts (OB) within the core. (X200 Stevenel’s blue and Van Gieson’s picro fuchsin)

Figure 8: Control group. The low power photomicrograph shows this core consists of well-formed trabeculae, connective tissue and various particles of xenograft XG. Various areas of NB surrounding the particles of XG can be seen within the core. The cancellous network is well formed with good, thick trabeculae bridging among the XG particles. (X20 Stevenel’s blue and Van Gieson’s picro fuchsin)

Figure 9a: Control group (from same core as Fig.8). The medium power image shows a core comprised of very thick NB surrounding the XG particles. The bone exhibits maturity and remodeling, thick trabeculae with a background of delicate marrow (MS). The cancellous network is well formed with good, thick trabeculae bridging among the XG particles. (x40 Stevenel’s blue and Van Gieson’s picro fuchsin)

Figure 9b: Control group (from same core as Fig.8). The polarized medium power image emphasizes the immature, woven bone pattern. Polarized view also shows new bone formation as well as mature and remodeled bone. A few particle of XG surrounded by newly formed bone. (x40 Stevenel’s blue and Van Gieson’s picro fuchsin)

Figure 10: Control group (from same core as Fig.7) The high-power photomicrograph shows NB formation bridges among the particles, delicate marrow space (MS), bone calcifying within the osteoid (OD). Image shows osteoblasts (OB) forming green-staining osteoid (OD) along the surface of the NB formation. It seems to be a line of green connective tissue at the peripheral border of the new bone
formation. The osteocyte (OC) in the lacunae are numerous and irregularly arranged (x200 Stevenel’s blue and Van Gieson’s picro fuchsin)
Tables

Table 1: Histomorphometric data values after 6 months of healing per maxillary sinus.

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<th>%MT</th>
<th>%RBGM</th>
<th>%NMT</th>
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MT: Mineralized tissue RBGM: Remaining bone graft material NMT: Non-mineralized Tissue
Symbols x, y, z, refer to same patient interventions.

Table 2: Mean % of vital bone, residual graft material and soft tissue and their intergroup comparisons using one-way ANOVA.

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<td>%RBGM</td>
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<td>%NMT</td>
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MT: Mineralized tissue RBGM: Remaining bone graft material NMT: Non-mineralized Tissue

Table 3: Pairwise comparisons between groups using Tukey’s Method

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MT: Mineralized tissue RBGM: Remaining bone graft material NMT: Non-mineralized Tissue
Figures

![Diagram of study enrollment, allocation, follow-up, and analysis with details on PRF and Control groups with respective sample sizes and reasons for exclusions.]

Fig 2