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**ORIGINAL ARTICLE**

# Clinical and radiographic evaluation of the efficacy of platelet-rich plasma combined with hydroxyapatite bone graft substitutes in the treatment of intra-bony defects in maxillofacial region

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**Abstract**

***Objective.*** The aim of this study is to evaluate the efficacy of platelet-rich plasma (PRP) clinically and radiographically when combined with bovine derived hydroxyapatite (HA) bone grafting materials and resorbable collagen membranes for the treatment of intra-bony defects frequently seen at the distal aspect of mandibular second molars following the surgical extraction of fully impacted mandibular wisdom teeth. ***Study design.*** Eighteen patients were scheduled for post-operative visits at 1, 3 and 6 months post-operatively, probing depths were measured and digital panoramic radiographs were taken. ***Results.*** There were no significant differences on probing depths among two groups. Radiographic assessment also showed no significant difference among groups at 1st and 6th month intervals, while 3 months post-operatively the amount of radiographic density at the PRP side was significantly higher. ***Conclusion.*** Combined use of PRP and bovine-derived HA graft materials for the treatment of intra-bony defects might be an appropriate approach when the main goal is providing earlier bone regeneration.

**Key Words:** *platelet rich plasma, hydroxyapatite, bone healing*

## Introduction

Desired clinical outcomes with oral implants, maxillofacial reconstructions and periodontal treatments are highly dependent on successful bone regeneration [1]. In an aid to improve healing of large bone defects, autologous bone grafting is accepted as gold standard. Autologous bone grafts possess optimal osteoinductive, osteoconductive and osteogenic properties that are the requirements for an ideal graft. Synthetic graft materials being only osteoconductive are among the alternatives for autogenous bone grafts, but do not have superior biologic or mechanical properties [2,3].

Hydroxyapatite (HA) has been the widely used synthetic graft material for bone reconstruction due to its biocompatibility, bone-resembling mineral composition apart from easy availability and for being non-allergic [4–6]. Recently, bovine bone derived hydroxyapatite has been produced and used as an alternative to synthetic HA with the advantages of being more compatible with human bone, abundant availability, low cost and reducing the volume of biological waste [7–9]. However, hydroxyapatite cement when used for secondary craniofacial reconstruction resulted with high infection rates leading to discontinuation of its use. An organic bovine-derived hydroxyapatite matrix has not been found as a suitable graft for the treatment of critical-sized segmental defects in long bones [10,11].

Platelet Rich Plasma (PRP) is an autologous concentrate of platelet, suspended in plasma. It is a proven source of growth factors like Platelet Derived Growth Factors (PDGF) and Transforming Growth Factors (TGF-$\beta$1-$\beta$2) which is obtained by sequestering and concentrating platelets by gradient density centrifugation. PRP either used alone or in combination with autologous bone or synthetic bone grafts in extraction sockets has been found to improve soft tissue healing, bone regeneration, increase bone density, decrease probing depth and patients experienced

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less pain following surgery [12–16]. On the contrary, Sanchez et al. [17] have pointed out the lack of evidence on the efficacy of PRP in combination with bone grafts during augmentation procedures in a review. In another study by Arenaz-Bua et al. [18], acceleration in bone formation has not been observed when PRP is placed in third molar extraction sites and it was concluded that PRP ease manipulation and acts as a perfect carrier when used in combination with other graft materials. In a Cochrane systematic review of randomized controlled clinical trials no reliable evidence has been found on promotion of bone healing with platelet-rich plasma, in conjunction with implant treatment [19].

Removal of impacted third molars is a very common oral surgical procedure. Inadequate bone healing may result in periodontal defects on the distal side of the adjacent second molar teeth. This complication is more frequent in older patients or when there is already an existing periodontal defect on the distal side of the second molar [15].

In our operating room settings we usually prefer to use HA in bone defects not exceeding the critical size like extraction cavity of impacted third molars. The promising results obtained with growth factors like PRP, promoting both soft tissue and bone healing, lead us to study the bone healing with HA that is combined with PRP in an extraction wound study model. We aimed to observe the effects of HA alone or when combined with PRP comparatively on bone healing of fully impacted third molar extraction sockets. Quantitative analysis of bone healing was done by radiographical analysis. Periodontal healing at the distal side of the adjacent second molars was evaluated both clinically and radiographically.

## Materials and methods

This study was conducted on 18 patients comprising of six men and 12 women who were referred to the Gazi University, Faculty of Dentistry Department of Oral & Maxillofacial Surgery, for surgical removal of bilateral, fully impacted wisdom teeth. Patients who had any systemic disease and/or smoking habit were excluded from this study.

### *Preparation of PRP*

PRP was prepared from patient's own blood using Curasan PRP kit (Pharma Gmbh AG, Lindigstrab, Germany) by double centrifugation. A 10 ml volume of autologous peripheral venous blood was drawn from each patient 30 min before surgery and stored in red marked monovettes containing 0.5 mL citrate (10% trisodium citrate). Citrated blood was centrifuged in a laboratory centrifuge (Heraeus Labofuge 300, Kendro Laboratory Products, D-37520 Osterrade, Germany) at 2400 rpm for 10 min. After being

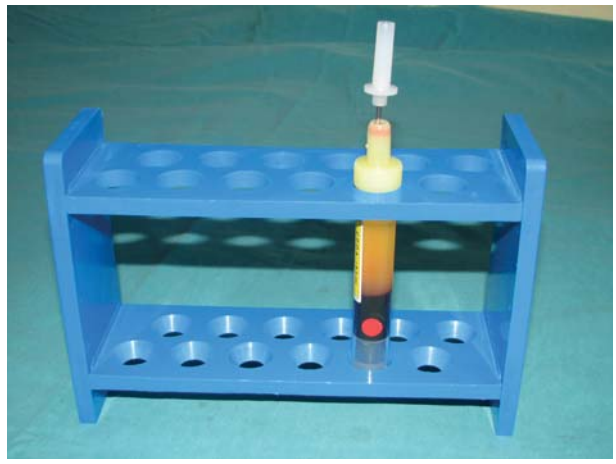

Figure 1. The upper yellow layer consisted of platelet rich and poor plasma and the lower red layer consisted of erythrocytes and leukocytes.

centrifuged, blood was separated into two fractions visible in two parts; the upper yellow part consisting of platelet rich plasma (PRP) and platelet poor plasma (PPP) and the lower part blood cells (Figure 1).

A mark was made 2 mm below the line that separates the two parts in the tube. All the content above this point was collected in yellow marked monovettes and centrifuged again at 3600 rpm for 15 min [20,21] (Figure 2). The part containing platelet poor plasma was discarded and the remaining 0.7 mL of plasma at the bottom of the yellow marked monovette was

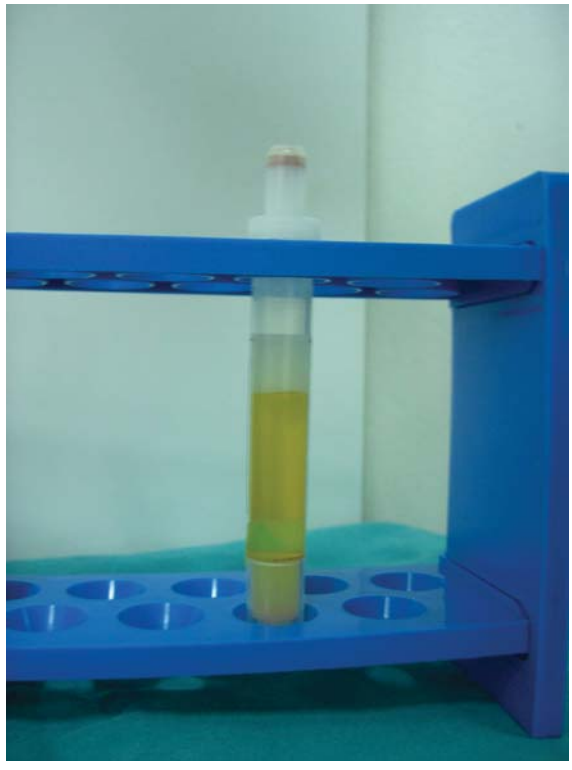

Figure 2. After second centrifugation, platelet rich plasma and platelet poor plasma.

Figure 3. PRP was transferred into a green marked application injector.

transferred into green marked application injector (Figure 3).

All surgeries were performed by the same surgeons. Impacted third molars on both sides were removed simultaneously by a standard, atraumatic surgical technique.

*Grafting the extraction socket*

Hydroxyapatite was transferred into a sterile glass jar that is ready to use or combined with PRP. The extraction cavity on one side was grafted with HA and PRP combination serving as the experimental group. The other side was grafted with hydroxyapatite (Apatos Mix 1 g, 500–1000 μm, Ref: AS1005FE, OsteoBiol, Tecnoss, Torino) alone serving as control. Since the aim of the study was to observe if there is a difference in bone healing between HA used alone and in combination with PRP, no further control group with extraction cavity filled with blood clot was constituted.

Following the grafting procedure, both sockets were covered with resorbable collagen membrane (Biocollagen, collagen membrane ($2 \times 2 \times 0.2$ mm), Bioteck, Italy) in order to maintain guided tissue regeneration. Flaps were returned to their original positions and closed by primary intension.

The patients were discharged after being given post-surgical instructions; sutures were removed 2 weeks after surgery.

All patients were scheduled for post-operative visits at 1, 3 and 6 months. Probing depths were measured and recorded at the follow-up visits. For radiographical evaluation, digital panoramic radiographs were taken and then transferred to image analysis software for computer-aided evaluation of bone regeneration.

*Radiographical assessment*

For quantitative analysis of new bone formation, digital panoramic radiographs (Orthoralix 9200 DDE, Gendex Dental Systems, Milano, Italy) were taken on the operation day and post-operatively at 1, 3 and 6 months.

Digital images were recorded as 8 bytes Tagged Image File Format (TIFF) to avoid data loss. The digital panoramic radiographs were displayed on the computer screen using Adobe Photoshop program (Adobe Photoshop® CS2, Version: 9.0, Adobe Systems Incorporated, 1990–2005), USA for histogram analysis (Figure 4).

With the use of the Adobe Photoshop program, the most radiolucent area and the most radiopaque area was cropped in each radiograph. For each radiograph, a score was created, with the value 0 being conferred on the most radiolucent area and the value on the most radiopaque area. The lesion area and an adjacent bone area in each radiograph were also cropped by means of the Adobe Photoshop program. The ratio between the radiographic density of the lesion area and the adjacent bone area was obtained in each group [18].

Four standard areas, two on the left side and two on the right side of the panoramic radiographs, were determined as control areas for making a comparison of histogram values of newly forming bone in the extraction cavity. However, at the initial measurements it was noticed that the histogram values of one side were highly greater than the other side. This difference was thought to be caused by imposition of soft tissue over bone. For verification, the values of the control area on one side were compared with the extraction cavity at the same side. It was found that there were no significant differences between groups when the initial calculation method was used; however, when the later calculation method was used, there was a significant difference at 3 months, in the group where HA was combined with PRP. No difference was found at 1 and 6 months between groups.

The objective of this study was to compare bone healing with HA alone or in combination with PRP in extraction wounds and to determine the effect of PRP on bone healing with digital radiographs by histogram. For standardization of the measurements, histogram values of the extraction socket were compared

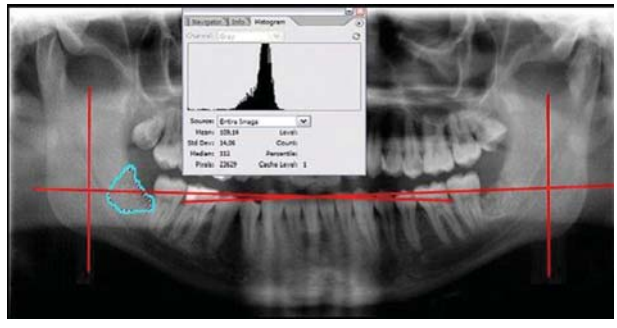

Figure 4. Histogram measurement of right mandibular third molar extraction socket.

Table I. Histogram measurements of defects.

| | HA* | PRP+HA* | Significance (*p*-value) |
|---|---|---|---|
| Post-operative 1 months | 1.27 ± 0.31 | 1.26 ± 0.34 | > 0.05 |
| Post-operative 3 months | 1.13 ± 0.21 | 1.26 ± 0.30 | < 0.05 |
| Post-operative 6 months | 1.39 ± 0.82 | 1.38 ± 0.41 | > 0.05 |

Data are expressed as the means ± standard deviation of means.
HA, Hydroxyapatite; PRP, Platelet rich plasma.
*No significant difference between the values of the groups ($p > 0.05$).

Table II. PPD measurements of defects.

| | HA* | PRP+HA* | Significance (*p*-value) |
|---|---|---|---|
| Post-operative 1 months | 3.00 ± 1.20 | 3.11 ± 1.20 | > 0.05 |
| Post-operative 3 months | 3.22 ± 1.13 | 3.00 ± 1.11 | > 0.05 |
| Post-operative 6 months | 2.89 ± 0.87 | 2.83 ± 1.07 | > 0.05 |

Data are expressed as the means ± standard deviation of means.
HA, Hydroxyapatite; PRP, Platelet rich plasma.
*No significant difference between the values of the groups ($p > 0.05$).

with healthy bone. Bone density in the extraction cavity filled either with HA alone or in combination with PRP was compared to the density of the healthy bone by comparing the histogram values of the extraction cavity one side with the mean histogram value of control areas at the same side. These measurements were done post-operatively at 1, 3 and 6 months.

*Clinical assessment*

The probing pocket depth (PPD) and clinical attachment level (CAL) were measured immediately before the surgery and at 1, 3 and6 months post-operatively by using a Williams periodontal probe (Nordent Manufacturing Inc., Elk Grove Vilage, IL). PPD was measured as the distance from the gingival margin to the base of the periodontal pocket. CAL was recorded by combining the distance from the cemento-enamel junction to the gingival margin with probing pocket depth. All clinical examinations were performed by the same calibrated investigator.

## Results

Eighteen patients from both sexes underwent extraction of third molars. The ages were varying between 18–30 years and there were no differences in sexes. The results were evaluated based on radiographic analysis and densitometric analysis by grey level histogram, probing depth and alveolar bone level distal to second molar in the post-operative follow-up visits on the 1st, 3rd and 6th months.

The results of this study indicate that radiological assessment of bone healing via digital panoramic images and image analysis software is an easy and cost-effective method and combined used of PRP and bovine-derived HA graft materials for the treatment of intra-bony defects might be an appropriate approach when the main goal is providing earlier bone regeneration.

Both groups showed optimal periodontal healing but, on the other hand, statistical analysis revealed no significant difference on probing depths among two groups (Table I).

Radiographic assessment also showed no significant difference among groups at 1st and 6th month intervals, while 3 months post-operatively the amount of radiographic density at the PRP side was significantly higher (Table II).

## Discussion

Bone density of experimental and control groups at 1 and 6 months were comparable on digital radiographs. There was a significant increase in density at 3 months in the experimental group, where HA was combined with PRP in our study.

PRP was studied in extraction sockets in many studies [22,23]. Autologous PRP application to the extraction cavity of third molars resulted in significantly faster bone formation when compared to extraction cavities filled with a blood clot. Measurements on radiographs showed significant bone formation in the first month, 3 and 6 months post-operatively. Accelerated bone formation was significant as early as 1 month in extraction cavities filled with autologous PRP [22]. Histologic studies also revealed increased bone healing as early as 1 month in other studies when HA was combined with PRP. We did not observe any difference in bone healing at 1 month in our study.

There may be several reasons for that. First of all, the type and amount of the carrier for growth factors influence bone healing. Second, the results obtained by different evaluation methods also differ. The histologic findings demonstrate early tissue reactions at a cellular level, whereas radiographic evaluation shows bone healing when calcification begins. We observed a significant difference in bone healing between groups at 3 months when calcification has been apparent on digital radiographs. Histogram values were comparable again at 6 months; there was no significant difference in bone density.

Calcium phosphate compounds, particularly hydroxyapatite, have widely been used as a bone substitute due to their compatibility and bone resembling mineral composition. Enhanced bone healing was observed when they are combined with growth factors. When HA is combined with autologous PRP, being one of the growth factors, significantly enhanced bone formation was observed at 3 months. This may be suggested to combine HA with PRP to promote bone formation, especially at early stages of bone healing [4,14].

In the present study there was a significant difference in the mean values of the histogram at the 3rd month. There was no significant difference at the 1st month, that is supported by another study [24].

Periodontal complications distal to the root of the 2nd mandibular molar after extraction of the adjacent 3rd molar are very common. In 44 (4%) cases, extraction of impacted 3rd mandibular molars resulted in bony periodontal defects on the distal surface of adjacent second molars [24].

Bone regenerative techniques including graft material, protein and barrier membranes are often used to solve this problem [1–25]. We used PRP, a growth factor, as an adjunct to HA. We used HA alone or in combination with PRP in mandibular 3rd molar extraction sockets that are covered with resorbable collagen membrane to enhance soft tissue healing as well as bone regeneration and to avoid bone defects distal to mandibular 2nd molars. There was a reduction in probing depth in both groups, but there was no statistically significant difference in any of the investigated parameters between the two groups.

There are studies on the efficacy of alloplastic bone grafts, mainly HA combined with PRP, allografts like demineralized bone, barriers for guided tissue regeneration either alone or in combination with above mentioned graft materials on bone and periodontal healing [26–29].

In patients with chronic periodontal disease displaying one intra-bony defect, PRP combined with an organic bovine bone mineral application did not show a difference in parameters like bleeding on probing, probing depth, gingival recession and clinical attachment level compared to an organic bovine bone mineral application alone [28]. Dodson [26] studied efficacy of grafting third molar extraction sites with demineralized bone powder on periodontal healing. There was a statistically significant difference in attachment levels between controls without any treatment with DBP and, guided tissue regeneration treated groups at 6 months. DBP proved an enhanced periodontal healing, whereas guided bone regeneration did not show a significant difference when compared with controls.

In a 12-month prospective clinical study, healing of periodontal intra-bony defects treated with PRP and HA were compared to HA mixed with saline. Clinical and radiographic measurements showed a significant improvement in both groups; however, probing depth reduction and clinical attachment level gain was significantly greater in PRP+HA treatment group [30].

In another study, PRP gel was placed in one of the extraction sockets after removal of bilateral impacted mandibular third molars. PRP grafted sockets showed dehiscence in 8% of cases. Although probing depth reduced significantly in 3 and 6 months in both the groups, the decrease was greater in PRP grafted sockets [24].

In a 4-year follow-up study, intra-osseous periodontal defects surgically treated with porous hydroxyapatite combined with PRP were compared with the mixture of hydroxyapatite and saline. No significant difference was observed at 1 year in both groups when compared with baseline. However, significant changes were found in the porous HA+PRP treated group in probing depth reduction, clinical attachment gain and defect fill [31].

These studies show that PRP improves soft tissue, bone and periodontal healing. However, this effect was reported to be statistically significant when compared to controls in longer follow-up studies exceeding 4 years. Some contradictory results in findings may be related to a lack of standardization of intrabony defects, evaluation methods, evaluation parameters, differences in initial depth of the defects as well as physiologic factors related to the patients.

Inadequate periodontal healing and formation of a periodontal pocket in the distal side of the second molars is also an undesirable clinical condition. To avoid such complications and to contribute to the bone healing mechanism, a biocompatible graft material, improving bone healing with little cost to the patient and society, should be selected. We aimed to observe bone healing with commonly used graft material HA either alone or in combination with PRP in the experimental model of extraction sockets to help clinical decision-making when use of bone grafts is needed.

## Conclusion

PRP offers a valuable adjunct to graft materials in promoting bone and soft tissue healing with its ease of

preparation and lack of antigenic activity. However, further randomized controlled trials with standardized methods and long follow-up are required to gain more understanding of the role of PRP in the healing process.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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