

The Efficiency of Hyaluronic Acid with Platelet Rich Fibrin (PRF) on Bone Surrounding Dental Implants Placed in Posterior Maxilla: A Split-Mouth Randomized Control Trial

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ABSTRACT

Implant placement in the posterior maxilla is often complicated by thin cortical bone and low-density trabecular bone, which may affect initial stability and early bone healing. Advanced platelet-rich fibrin (A-PRF) and hyaluronic acid (HA) have been used as local adjuncts to promote peri-implant regeneration. This study compared osteoblastic activity around implants treated with A-PRF combined with HA and those treated with A-PRF alone. Twelve adults requiring bilateral posterior maxillary implants were included in a split-mouth randomized controlled trial. At the test site, the osteotomy received A-PRF mixed with 0.1% HA, while the corresponding contralateral site received A-PRF alone. The same implant dimensions and surgical protocol were used at both sites. Bone activity was evaluated by scintigraphy, while alkaline phosphatase in peri-implant crevicular fluid was measured using an enzyme-linked immunosorbent assay. Data were analysed using SPSS version 21, with statistical significance set at $p < 0.05$. Osteoblastic activity was higher at the test sites at every assessment ($p < 0.001$). It increased during early healing, reached its highest value at the intermediate assessment and declined slightly by 90 days. Alkaline phosphatase increased throughout follow-up in both groups, but values remained higher at the test sites ($p < 0.001$). The addition of HA to A-PRF was associated with greater early peri-implant bone activity. Further studies should determine whether this difference improves long-term implant outcomes.

KEYWORDS: Platelet-Rich Fibrin; Alkaline Phosphatase; Radionuclide Imaging; Dental Implants; Hyaluronic Acid; Osseointegration.

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INTRODUCTION:

Dental implants are routinely used to replace missing teeth, and their long-term success largely depends on achieving stable osseointegration (1). Successful integration depends not only on the implant itself, but also on the surgical procedure, loading conditions, and the quality and quantity of bone at the recipient site. Bone quality is especially relevant during the early healing period because it affects the initial mechanical engagement of the implant and the later development of biological stability. Lekholm and Zarb described four bone types based on the relative proportions of cortical and trabecular bone. Among these, Type IV bone, which consists mainly of low-density trabecular bone covered by a thin cortical layer, is considered the least favourable for implant placement (2).

Implant stability is commonly described as primary and secondary stability. Primary stability is achieved at the time of placement through mechanical contact between the implant and the surrounding bone. Secondary stability develops later as new bone is formed and remodelled around the implant (3). Although the two phases are distinct,

adequate primary stability provides a suitable foundation for subsequent biological healing. Reduced bone density, particularly in Type IV bone, has been linked to a higher risk of implant failure (4). For this reason, considerable attention has been given to materials and techniques that may improve the local environment for bone formation.

Advanced platelet-rich fibrin (A-PRF) is an autologous platelet-rich concentrate obtained by low speed centrifugation. It forms a fibrin matrix that may help cell migration and the sequestration of biologically active mediators. This matrix releases growth factors involved in angiogenesis, tissue repair and osteogenic activity. A-PRF has a slow release so it may be beneficial in the early stages of bone healing around dental implants (5).

Another material that may be of interest in peri-implant healing is hyaluronic acid (HA). A glycosaminoglycan that occurs naturally in the extracellular matrix of soft and mineralised tissues. HA is involved in tissue hydration, inflammation control, angiogenesis, extracellular matrix organization and bone regeneration (6). The

biological effect is dependent on molecular weight and concentration. It has been demonstrated that low molecular weight HA can increase proliferation of bone marrow derived mesenchymal stem cells and high molecular weight HA may promote expression of osteogenic genes (7). These properties have encouraged its use as adjunct in regenerative procedures.

The posterior maxilla is a difficult area for implant placement. The cortical bone is often thin, the trabecular bone is less dense and the bone height available might be limited by the maxillary sinus. These features can reduce primary stability and may delay early osseointegration. HA has been evaluated around implants placed in the posterior maxilla, but evidence on its combined use with A-PRF is still limited (8). Available experimental studies suggest that combining HA with platelet-rich fibrin may improve bone formation, although much of this evidence has been obtained from animal models (9).

A-PRF and HA may act through different but related mechanisms. A-PRF acts as a fibrin scaffold and a sustained source of growth factors while HA might contribute to extracellular matrix organization, cell migration, angiogenesis and osteogenic differentiation. Hence, the combination of both may be beneficial in sites with less favourable bone quality. However, there is a lack of clinical evidence for posterior maxillary implant sites.

The present split-mouth randomised controlled trial compared A-PRF combined with HA against A-PRF alone in implants placed in the posterior maxilla. Peri-implant bone healing was evaluated through bone scintigraphy and alkaline phosphatase activity as indicators of osteoblastic activity and bone formation.

MATERIALS AND METHODS

This split-mouth randomized controlled trial was conducted at Sri Ramachandra Institute of Higher Education and Research after approval from the Institutional Ethics Committee (CSP/25/FEB/17/102). The study was designed and reported in accordance with the CONSORT extension for within-person randomized trials (10). Written informed consent was obtained from all participants before enrolment.

Twelve participants aged 21–60 years with bilaterally missing posterior maxillary teeth and willing to receive implant-supported prostheses were included. Participants of either sex were eligible when their glycated haemoglobin level was below 8.0%. Smokers, patients receiving bisphosphonate therapy, individuals with psychological disorders and pregnant or lactating women were excluded.

Before surgery, all participants underwent extraoral and intraoral photographic documentation, routine haematological investigations, fasting and postprandial blood glucose assessment, bleeding

time, clotting time and HbA1c estimation. Cone-beam computed tomography was performed to evaluate the quality and quantity of bone at the edentulous sites and to exclude retained roots, impacted teeth, or other local pathology. Following completion of the preoperative assessment, the treatment protocol was explained to the participants and informed consent was confirmed.

Venous blood (about 10 mL) was drawn for the preparation of advanced platelet-rich fibrin (A-PRF). The blood was centrifuged at 1500 rpm for 14 minutes (**Figure 1a**). Following centrifugation, separation of the blood components was observed within the collection tubes (**Figure 1b**). The resulting A-PRF clot was removed under sterile conditions and placed in a sterile container (**Figure 1c**). At the test site, A-PRF was combined with 0.1% hyaluronic acid before placement into the osteotomy (**Figure 1d**). At the control site, A-PRF alone was placed into the osteotomy.

Under local anaesthesia, a full-thickness mucoperiosteal flap was elevated at both posterior maxillary sites. Osteotomies were prepared using sequential drills of 2.0, 2.7, 3.0, and 3.2 mm to a depth of 10 mm. Test osteotomy was treated with A-PRF and 0.1% hyaluronic acid while contralateral control osteotomy was treated only with A-PRF. Implants measuring 4.0 × 10 mm were inserted using a torque wrench, followed by placement of healing collars (**Figure 2a, b**). The flaps were repositioned and closed using simple interrupted sutures. Participants were recalled after one week for suture removal.

Bone scintigraphy was carried out before prosthetic rehabilitation to monitor bone activity around the implants. Scans were obtained at 15, 45 and 90 days after implant placement. Participants were positioned in the supine position, and 10 mCi of technetium-99m methylene diphosphonate was administered intravenously. Static blood-pool images of the head and neck were obtained 10 minutes later. Before delayed imaging, participants were instructed to remain well hydrated and drink at least two glasses of water. Regions of interest were then outlined around the implant, the adjacent bone and the mandibular ramus, and changes in regional tracer uptake were compared across the three follow-up visits.

Peri-implant crevicular fluid was collected to assess alkaline phosphatase activity as a biochemical marker of osteoblastic activity using open-ended capillary tubes that were 75 mm long and collecting it over 10 minutes (**Figure 2c, d**). The samples that were obtained were quickly put into sterile Eppendorf tubes that held 300 µL of phosphate-buffered saline (PBS). The samples were allowed to equilibrate at room temperature for about 30 minutes and the capillary tubes were removed carefully. Then the materials were stored at –70°C for further laboratory research.

PICF samples collected on days 30, 60 and 90 after implant placement were analyzed using a manufacturer-supplied enzyme-linked immunosorbent assay (ELISA) kit to determine alkaline phosphatase (ALP) levels, which served as a biochemical indicator of osteoblastic activity. The reference range for ALP detection as a biomarker was 0.156–10 IU.

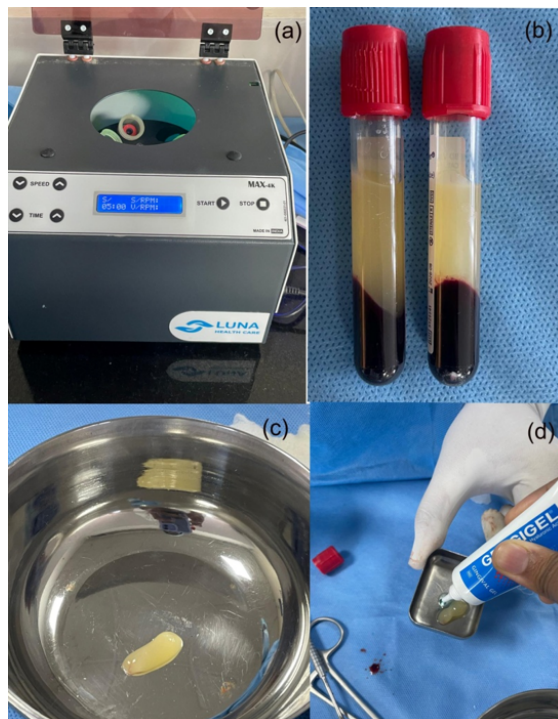


Figure 1: Preparation of advanced platelet-rich fibrin combined with hyaluronic acid (a) Centrifugation of the collected venous blood; (b) blood samples after centrifugation; (c) retrieved A-PRF clot; and (d) incorporation of 0.1% hyaluronic acid into A-PRF for application at the test site.



Figure 2: Clinical procedure and peri-implant crevicular fluid collection. (a) Preoperative maxillary occlusal view showing bilateral posterior edentulous sites; (b) postoperative view following

bilateral implant placement and placement of healing collars and (c, d) collection of peri-implant crevicular fluid from the implant sites using open-ended capillary tubes.

STATISTICAL METHODS

Data were analysed using SPSS version 21. Continuous variables were summarized as mean and standard deviation. Normality was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Changes in osteoblastic activity and alkaline phosphatase levels across the three follow-up periods within each treatment group were evaluated using one-way analysis of variance followed by Tukey’s honestly significant difference test for pairwise comparisons. Comparisons between the A-PRF plus hyaluronic acid and A-PRF alone groups at each follow-up period were performed using independent-samples *t* tests. Mean differences and 95% confidence intervals were reported where available. Statistical significance was set at a two-sided $p < 0.05$.

RESULTS

Osteoblastic activity was consistently higher at sites treated with A-PRF plus HA than at sites treated with A-PRF alone. At 15 days, mean osteoblastic activity was 50.37 ± 3.63 in the A-PRF plus HA group and 45.84 ± 1.99 in the A-PRF alone group with a mean difference of 4.53 ($p = 0.001$). The corresponding values were 54.65 ± 1.19 and 49.35 ± 0.93 at 45 days with a mean difference of 5.29 ($p < 0.001$), and 53.13 ± 0.60 and 49.05 ± 1.52 at 90 days with a mean difference of 4.08 ($p < 0.001$) (Table 1). Within the A-PRF plus HA group, osteoblastic activity increased significantly between 15 and 45 days ($p < 0.001$) and between 15 and 90 days ($p = 0.013$), while the difference between 45 and 90 days was not significant ($p = 0.234$). In the A-PRF alone group, significant differences were observed between 15 and 45 days and between 15 and 90 days (both $p < 0.001$), whereas the difference between 45 and 90 days was not significant ($p = 0.880$) (Table 2).

Peri-implant crevicular fluid alkaline phosphatase levels increased progressively during follow-up in both groups and remained higher at the A-PRF plus HA sites. Mean levels at 30 days were 13.33 ± 0.91 and 10.23 ± 0.69 in the A-PRF plus HA and A-PRF alone groups respectively with a mean difference of 3.09 ($p < 0.001$). At 60 days, the corresponding values were 17.02 ± 0.53 and 12.13 ± 0.58 with a mean difference of 4.89 ($p < 0.001$). At 90 days, values were 24.70 ± 1.04 and 14.03 ± 0.55 with a mean difference of 10.67 ($p < 0.001$) (Table 3). Pairwise comparisons showed significant increases in alkaline phosphatase levels between all follow-up periods within both treatment groups (all $p < 0.001$) (Table 4).

Table 1: Osteoblastic activity at different follow-up periods according to treatment

Follow-up	A-PRF + HA, mean $\pm$ SD	A-PRF alone, mean $\pm$ SD	Mean difference	<i>p</i> value
15 days	50.37 $\pm$ 3.63	45.84 $\pm$ 1.99	4.53	0.001
45 days	54.65 $\pm$ 1.19	49.35 $\pm$ 0.93	5.29	<0.001
90 days	53.13 $\pm$ 0.60	49.05 $\pm$ 1.52	4.08	<0.001

A two-sided $p < 0.05$ was considered statistically significant

Table 2: Pairwise changes in osteoblastic activity during follow-up

Treatment	Comparison	Mean difference	95% CI	<i>p</i> value
A-PRF + HA	15 vs 45 days	-4.28	-6.52 to -2.05	<0.001
	15 vs 90 days	-2.77	-5.00 to -0.53	0.013
	45 vs 90 days	1.52	-0.72 to 3.75	0.234
A-PRF alone	15 vs 45 days	-3.52	-5.06 to -1.97	<0.001
	15 vs 90 days	-3.21	-4.76 to -1.67	<0.001
	45 vs 90 days	0.30	-1.24 to 1.85	0.880

A two-sided $p < 0.05$ was considered statistically significant

Table 3: Peri-implant crevicular fluid alkaline phosphatase levels according to treatment and follow-up

Follow-up	A-PRF + HA	A-PRF alone	Mean difference	<i>p</i> value
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	mean $\pm$ SD	mean $\pm$ SD		
30 days	13.33 $\pm$ 0.91	10.23 $\pm$ 0.69	3.09	<0.001
60 days	17.02 $\pm$ 0.53	12.13 $\pm$ 0.58	4.89	<0.001
90 days	24.70 $\pm$ 1.04	14.03 $\pm$ 0.55	10.67	<0.001

A two-sided $p < 0.05$ was considered statistically significant

Table 4: Pairwise changes in peri-implant crevicular fluid alkaline phosphatase levels during follow-up

Treatment	Comparison	Mean difference	95% CI	<i>p</i> value
A-PRF + HA	30 vs 60 days	-3.69	-4.54 to -2.83	<0.001
	30 vs 90 days	-11.37	-12.22 to -10.51	<0.001
	60 vs 90 days	-7.68	-8.53 to -6.83	<0.001
A-PRF alone	30 vs 60 days	-1.90	-2.51 to -1.29	<0.001
	30 vs 90 days	-3.79	-4.40 to -3.18	<0.001
	60 vs 90 days	-1.90	-2.51 to -1.29	<0.001

A two-sided $p < 0.05$ was considered statistically significant

DISCUSSION

The use of hyaluronic acid (HA) in addition to advanced platelet-rich fibrin (A-PRF) was associated with a greater peri-implant osteoblastic activity and ALP level than A-PRF alone. This difference was seen during the first 90 days after implant placement in the posterior maxilla. Osteoblastic activity was increased in the early period of healing reaching its peak at the

intermediate assessment. It then showed a slight decline. In contrast, ALP levels continued to increase up to 90 days. These findings suggest that HA may enhance the regenerative effect of A-PRF during early osseointegration, although both groups showed a broadly similar descriptive temporal pattern of healing.

The early rise in osteoblast activity is in accordance with the biological sequence of peri-implant bone healing. Inflammatory and proliferative events are followed by osteoid formation, mineralisation and remodelling after implant placement. Osteoblastic activity generally increases during the first several weeks and then plateaus as newly formed bone matures (11). The modest reduction at 90 days may therefore represent progression from active bone formation to remodelling rather than loss of regenerative activity. The consistently higher values at test sites indicate that adding HA may have improved the local osteogenic environment throughout this period.

A-PRF provides a fibrin scaffold that supports cellular migration and matrix deposition while permitting sustained release of platelet-derived growth factor, transforming growth factor-beta, and vascular endothelial growth factor. Fujioka-Kobayashi et al. showed a sustained release of growth factors from A-PRF prepared by the low-speed centrifugation concept (5). These mediators can induce osteoblast proliferation, angiogenesis and progenitor-cell recruitment. The present findings are compatible with this biological activity and suggest an incremental benefit when HA is added to A-PRF.

HA may contribute through extracellular matrix stabilisation, tissue hydration, modulation of inflammation, and promotion of cell migration and angiogenesis. It has also been associated with osteogenic differentiation and increased expression of bone-related markers, including ALP (12). The continued increase in ALP at test sites may reflect ongoing mineralisation and maturation of peri-implant bone. However, the study did not include an HA-only group. The findings therefore support an additional effect of HA when combined with A-PRF but do not establish biological synergism between the two materials.

The posterior maxilla is a challenging site for implant placement due to the thin cortical plate, low density trabecular bone and proximity to the maxillary sinus. These characteristics may reduce primary stability and delay osseointegration. Regenerative adjuncts are therefore of particular interest in this region. Previous work has emphasised the need for methods that improve bone formation in sites with reduced bone density (13). The greater biological activity at test sites supports the potential value of HA as an adjunct to A-PRF, although clinical outcomes such as implant stability, marginal bone change, and long-term survival are

required before firm therapeutic conclusions can be drawn.

The progressive rise in ALP is clinically relevant because ALP is associated with osteoblastic differentiation and mineral deposition. In contrast to the slight reduction in osteoblastic activity after the intermediate assessment, ALP continued to increase up to 90 days, suggesting that mineralisation remained active during the later healing phase. Simonpieri et al. reported favourable bone maturation following the use of platelet concentrates in oral and maxillofacial procedures (14). The present findings are consistent with this observation while indicating higher biochemical activity when HA was added to A-PRF.

Previous studies of platelet concentrates in posterior maxillary regeneration have produced variable results. Aoki et al. reported successful bone formation after sinus augmentation with PRF alone, although the evidence was based on a limited case series (15). Mozzati et al. reported improved early healing and greater socket closure in extraction sites treated with concentrated growth factors compared with untreated control sites (16). However, differences in platelet concentrate preparation, clinical indication and outcome assessment limit direct comparison with the present findings. The stronger response observed here may relate to the addition of HA, differences in the clinical indication, or use of biochemical and scintigraphic outcomes rather than histomorphometric endpoints. Direct comparison should therefore remain cautious.

Dominiak et al. found broadly comparable bone integrity after PRF- and xenograft-based sinus augmentation, without establishing a clear advantage for PRF (17). Pathak et al. reported more favourable regenerative outcomes with A-PRF than with platelet-rich plasma (18). Collectively, these studies support the regenerative potential of platelet concentrates but show that their effect depends on the comparator, defect characteristics, and outcome measure. The present study adds evidence that HA may enhance early peri-implant biological activity when combined with A-PRF.

Although osteoblastic activity was consistently higher at the test sites, both treatments showed a broadly similar descriptive temporal pattern, with an increase during early healing followed by relatively little change between 45 and 90 days. These findings suggest a greater biological response at sites receiving HA with A-PRF but should not be interpreted as evidence of accelerated or superior clinical osseointegration.

A major strength was the split-mouth randomized design where each participant served as his or her own control which reduced confounding due to systemic health, bone metabolism, age and individual healing capacity. Assessment at several time points permitted evaluation of the early healing trajectory and scintigraphic and biochemical

parameters offered complementary information on regional bone activity and osteoblastic function.

The small sample size may have limited the ability of the study to detect true differences between the groups and decreased the precision of the estimated effects. Bone scintigraphy and ALP are markers of bone activity, but they do not give the direct tissue level information that can be obtained by histomorphometric analysis. Follow-up was terminated at 90 days and results pertain only to early healing. Absence of HA-only group did not allow to conclude on the independent contribution of HA. Moreover, longer term clinical outcomes such as implant stability, marginal bone loss, prosthetic success and implant survival were not evaluated.

An additional limitation is that the statistical analyses did not account for the within-participant correlation inherent in the split-mouth design and repeated assessments. The inferential findings should therefore be interpreted cautiously. Future studies should include larger samples, longer follow-up and analytical methods that explicitly account for paired and repeated measurements together with additional clinical and radiographic outcomes.

CONCLUSION

The addition of 0.1% hyaluronic acid to A-PRF was associated with greater peri-implant osteoblastic activity and higher alkaline phosphatase levels during the first 90 days of healing compared with A-PRF alone. Although the descriptive temporal pattern of osteoblastic activity was broadly similar between treatments, the consistently greater biological activity at the test sites suggests a potential adjunctive effect of hyaluronic acid during early peri-implant healing. These findings should be interpreted cautiously because of the small sample size, short follow-up and absence of direct clinical measures of osseointegration. Larger randomized studies with longer follow-up and clinical and radiographic outcomes are required to determine whether this early biological response translates into improved implant outcomes.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

The study was approved by the Institutional Ethics Committee of Sri Ramachandra Institute of Higher Education and Research (CSP/25/FEB/17/102). Written informed consent was obtained from all participants before enrolment and participation in the study

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