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EFFICIENCY OF HYALURONIC ACID VERSUS RED INJECTABLE PLATELET-RICH FIBRIN (I-PRF) IN TREATMENT OF STAGE III PERIODONTITIS: RANDOMIZED CONTROLLED CLINICAL TRIAL

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Introduction: This study aims to compare clinical efficacy of red injectable platelet-rich fibrin (i-PRF) and hyaluronic acid (HA) as adjuncts to professional mechanical plaque removal (PMPR) in non-surgical management of stage III periodontitis.

Methods: 75 patients were split into groups: group one (G1) received HA, group two (G2) received red i-PRF, and group three (G3), received only PMPR. Periodontal evaluation was done at baseline, 4th, 8th, and 12th weeks following treatment.

Results: The plaque index, gingival index, and bleeding on probing were significantly improved in all groups. Moreover, the probing depth in all three groups displayed lower levels over the three months, with G1 and G2 experiencing the greatest declines. Additionally, G1 and G2 showed a considerable increase in clinical attachment level, while G3 showed no improvement.

Conclusions: Thus, the application of HA and red i-PRF in conjunction with PMPR significantly improves all periodontal metrics, however, there is no statistically significant distinction between them.

Trial Registration: This trial is registered in ClinicalTrials.gov, ID: NCT05768243.

Keywords: hyaluronic acid, non-surgical, periodontitis, professional mechanical plaque removal, red injectable platelet-rich fibrin, stage III.

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The authors declare no conflicts of interest.

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EFFICACITÉ DE L'ACIDE HYALURONIQUE PAR RAPPORT À LA FIBRINE RICHE EN PLAQUETTES INJECTABLE ROUGE (I-PRF) DANS LE TRAITEMENT DE LA PARODONTITE DE STADE III : ESSAI CLINIQUE CONTRÔLÉ RANDOMISÉ

Introduction: Cette étude vise à comparer l'efficacité clinique de la fibrine riche en plaquettes injectable rouge (i-PRF) et de l'acide hyaluronique (HA) en tant que compléments à l'élimination mécanique professionnelle de la plaque (PMPR) sans une intervention chirugical de la parodontite de stade III.

Méthodes: 75 patients ont été divisés en groupes : le groupe un (G1) a reçu de l'HA, le groupe deux (G2) a reçu de l'i-PRF rouge et le groupe trois (G3) n'a reçu que du PMPR. Une évaluation parodontale a été effectuée au départ, 4e, 8e et 12e semaines après le traitement.

Résultats: L'indice de plaque, l'indice gingival et le saignement au sondage ont été significativement améliorés dans tous les groupes. La profondeur de sondage dans les trois groupes a affiché des niveaux inférieurs au cours des trois mois, G1 et G2 connaissant les plus fortes baisses. De plus, G1 et G2 ont montré une augmentation considérable du niveau d'attachement clinique, tandis que G3 n'a montré aucune amélioration.

Conclusions: Ainsi, l'application de HA et d'i-PRF rouge en conjonction avec PMPR améliore de manière significative toutes les métriques parodontales, cependant, il n'y a pas de différence statistiquement significative entre elles.

Registration de l'essais: ClinicalTrials.gov, ID: NCT05768243.

Mots clés : acide hyaluronique, non chirurgical, parodontite, élimination mécanique professionnelle de la plaque dentaire, fibrine rouge injectable riche en plaquettes, stade III.

Introduction

Chronic periodontitis is an irreversible multifactorial inflammatory disease causing progressive destruction of periodontal supporting tissues. [1] Primarily, it is identified by the loss of periodontal tissue support, represented clinically by clinical attachment loss (CAL), periodontal pockets, gingival bleeding, and radiographically by alveolar bone loss.

Professional mechanical plaque removal (PMPR) is the gold standard treatment for most patients with periodontitis. However, recently, several strategies have been developed to improve PMRP results and thus avoid the need for periodontal surgical intervention in some cases. [2] These new strategies include systemically or locally administered antibiotics and antiseptics (ex: hyaluronic acid, metronidazole, minocycline...), or the use of platelet concentrates.

Hyaluronic acid (HA) is a linear polysaccharide naturally found in the extracellular matrix of connective tissue, synovial fluid, and other tissues. [3] It has many physiological as well as structural functions that help maintain tissue structure and haemostatic integrity. It has the potential to control the inflammatory response, which occurs when chronically irritated tissues break down high molecular weight HA into lower molecular weight molecules. These low-molecular-weight molecules help to identify tissue damage and mobilize immune cells, while high-molecular-weight molecules slow down the immune response, preventing inflammation from worsening too much. [4] Additionally, HA has viscoelastic qualities that reduce the ability of germs and viruses to penetrate the tissue. Nevertheless, HA is a naturally hygroscopic molecule. When HA is added to an aqueous solution, hydrogen bonding between adjacent carboxyl and N-acetyl groups occurs; this characteristic enables HA to maintain conformational stiffness and water retention. Therefore, due to the multiple functions that HA has in the healing of wounds, gingiva, and bones, it has been used to repair both mineralized and non-mineralized periodontal tissues. [5]

Furthermore, injectable platelet rich fibrin (i-PRF) is one of the recently introduced platelet concentrates. It comes in an injectable form and coagulates after minutes of administration. A slower and shorter centrifugation spin is used, thus resulting in regenerating cells with increased concentrations of growth factors and cytokines that may enhance the healing potential of both bone and soft tissues. [6] Moreover, its preparation techniques vary depending on the different fractions from various areas based on the junction between the enriched fibrin plasma and red blood cell layers. Yellow i-PRF is harvested at the upper yellow zone above the junction, while red i-PRF is harvested at the interface with the buffy coat layer. The use of Red i-PRF is superior to the yellow i-PRF as it promotes early-stage wound healing and bone regeneration. In addition, it is unlikely to prevent bone regeneration or induce premature bone formation outside the desired area. [7]

Several studies and clinical trials concerning the efficiency of HA or PRF in treating periodontal disease are available, but few are the articles that assess the efficiency of i-PRF in the non-surgical treatment of periodontal disease. [8-16] Thus, the aim of this clinical trial is to compare the efficacy of HA used as an adjunctive to PMPR and red i-PRF (for the first time to our best knowledge) in the non-surgical treatment of stage III periodontitis.

Materials and methods

Seventy-five patients aged between 20 and 60 years were recruited for the study in March 2021. All the selected patients had clinical periodontal loss and radiographic bone loss of stage III/grades A and B with no history of systemic disease. They had at least four periodontal sites with a pocket depth of six mm or greater, radiographic evidence of bone loss extending to the middle third of the root, and clinical attachment loss of five mm or more. Moreover, patients were excluded from this study if they had had: uncontrolled systemic conditions (uncontrolled diabetes or uncontrolled hypertension), bleeding disorders, or were on anticoagulant therapy; alcohol users; pregnant or lactating females; heavy smokers (more than ten cigarettes per day); underwent chemo or radiotherapy; or used antibiotic/anti-inflammatory drugs over the last three months before treatment.

Before starting the clinical trial, an institutional review board (IRB) was obtained (2019-H-0075-D-R-0293) and the trial was registered in the clinicaltrial.gov (NCT05768243). After that, complete medical and dental histories as well as informed consent were collected from each patient, and periodontal charting was done for them.

The selected patients were allocated into three groups (each containing 25) with the help of a computerized randomizer (Randomizer.org):

- **Group one (G1)**: 25 patients were treated with hyaluronic acid gel as an adjunct to PMRP by applying **one ml of 0.8% HA** to the base of the pocket (subgingivally) and **0.2 ml of 0.2% HA** topically (applied by the patient).
- **Group two (G2)**: 25 patients were treated with red i-PRF as an adjunct to PMRP.
- **Group three (G3)**: 25 patients were treated with PMRP only.

The clinical examiner was not informed of the treatment groups' distribution.

Before the baseline examination, a full mouth supragingival PMRP was performed under local anesthesia in one or two sessions (over a 24-hour period). Patients were informed on self-performed plaque control measures including using the modified Bass brushing technique using a soft toothbrush and regular toothpaste twice a day and interdental cleaning using interdental brushes once a day. Note that patients received the same toothbrushes, toothpaste, and interdental brushes. Oral hygiene was reinforced at every visit.

The clinical periodontal parameters were recorded by one blinded examiner from the mesio-buccal, mid-buccal, disto-buccal, disto-lingual, mid-lingual, and mesio-lingual surfaces of each tooth and checked by another blinded examiner. Examiners were calibrated to ensure intra-examiner as well as inter-examiner agreement when measuring PD and CAL values. Twenty patients were examined twice before the trial, 24 hours apart. Calibration was considered accepted if both measurements at the baseline and after 24 hours were similar to one mm at the 90% level.

Clinical measurements included the clinical attachment level (CAL), probing depth (PD), plaque index (PI), gingival index (GI), and bleeding on probing (BOP). First, the PI and the GI were measured from four sites per tooth. Gingival bleeding was recorded within 15 seconds. Afterwards, patients were asked to rinse with water so as not to misinterpret gingival bleeding as BOP. Following that, all teeth were probed at six different locations per tooth. Moreover, CAL was measured as the distance from the cemento-enamel junction (CEJ) to the depth of the pocket, while the PD was measured as the distance from the gingival margin to the base of the pocket. Regarding the BOP, it was recorded 15 seconds after probing. Note that the clinical parameters were recorded at the baseline (1st visit) before the treatment and were repeated in the fourth week (2nd visit), eighth week (3rd visit), and twelfth week (fourth visit). During this period, reinforcement of plaque control and additional instructions were given to maintain good oral hygiene.

The sample size is calculated with the help of this formula: [17]

$$= \frac{(z\frac{\alpha}{2} + z\beta)\,\sigma}{\delta}\ 2\ \frac{1}{Q1} + \frac{1}{Q2}\ ^{\pi}$$

Data from previous studies were used to calculate the sample size regarding the PD change measurement. [18] It was found that the difference in PD (δ) is around 0.3mm, whereas the standard deviation in groups (σ) was around 0.2mm. Our aim was to achieve a statistical power of > 90% as well as a 0.05 significance level. Thus, 18 participants per group were needed. However, as some dropouts may be expected, a minimum of *25 patients per group* were recruited.

Regarding the preparation of red I-PRF, first, 20 mL of patient's blood was collected by venipuncture of the median cubital vein. Then, the blood was distributed into two ten mL glass tubes (containing no anticoagulant). The tubes were shaken before being placed into a centrifuge to prevent clots from developing. The centrifuge was set for 700 rpm for three min (60 g force) at room temperature using a Choukroun PRF Duo Centrifuge. After centrifugation, three layers were formed in each tube: the red blood cells in the bottom, the PRF layer in the middle, and the platelet poor plasma at the top. After that, one mL was taken from the upper liquid red and yellow layer with the buffy coat (demonstrate the red i-PRF) (Figure 1). Note that the bevel edge of the harvesting needle as used as a reference point. [19, 20]

After that, topical anesthesia was applied to the site of injection. Then, the obtained red i-PRF was placed in a 2.5 cc dental injector (27-gauge needle). The red i-PRF was injected into the pocket at the point of interdental space (Figure 2). Moreover, to control bleeding due to the needle tip after the procedure, a saline-soaked sponge was placed between the lip and the gingiva and removed after 15 minutes. A total of four sessions of i-PRF were administered to patients at a ten-day interval. On the other hand, after PMRP, hyaluronic acid (GENGIGEL®) was applied in the following forms (one ml of 0.8% HA was injected subgingivally once every four weeks), topically (0.2 ml of 0.8% HA was applied by the patient twice daily for the following 14 days after the subgingival application) (Figure 3*).*

Figure 1: one mL taken from the upper liquid red and yellow layer with the buffy coat

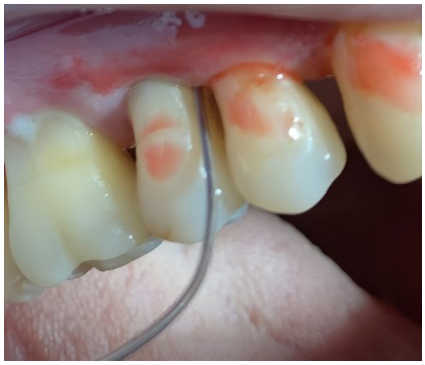

Figure 2 : The red i-PRF injected into the pocket at the point of interdental space Note that the red color on teeth is the topical anesthesia gel.

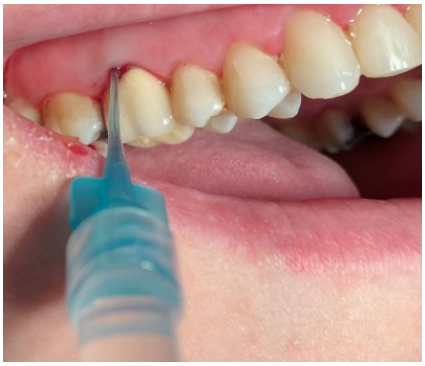

Figure 3: subgingival injection of 0.8% HA.

Statistical analysis was done using SAS 9.4 Software (SAS Institute Inc., Cary, NC, USA). Means and standard deviations (SD) were calculated for all continuous variables (periodontal parameters: CAL, PD, BOP, GI, PI) at the baseline, fourth week, eighth week, and twelfth week. Repeated linear mixed-effects models (PROC MIXED in SAS) were used to examine the changes in all periodontal parameters over the four-time points within each group and between groups. An unstructured covariance matrix was used, residual plots were visually reviewed to check model fit, and extreme outliers were eliminated using the restricted likelihood distance. A Tukey-Kramer correction was applied to all pairwise comparisons. One-way ANOVA was used to examine group differences in PD reduction and CAL. A p-value of 0.05 was considered statistically significant.

Results

Patient recruitment began in March 2021 and data collection ended in June 2022. A total of 138 patients were checked for eligibility of which 75 had met the inclusion criteria. However, 12 were lost throughout the study. Therefore, complete data analysis was possible for 63 patients who finished the study (Figure 4). Note that no teeth were lost throughout the study period. In addition, no postoperative systemic deficits were reported by any of the patients, and no postoperative problems were observed.

The gingivitis and plaque indices are shown in Table 1. At the follow-up visits, all treatment groups showed a statistically significant reduction in both indices compared to the baseline ($p<0.05$). At any of the observation intervals, there was no statistically significant difference in PI and GI.

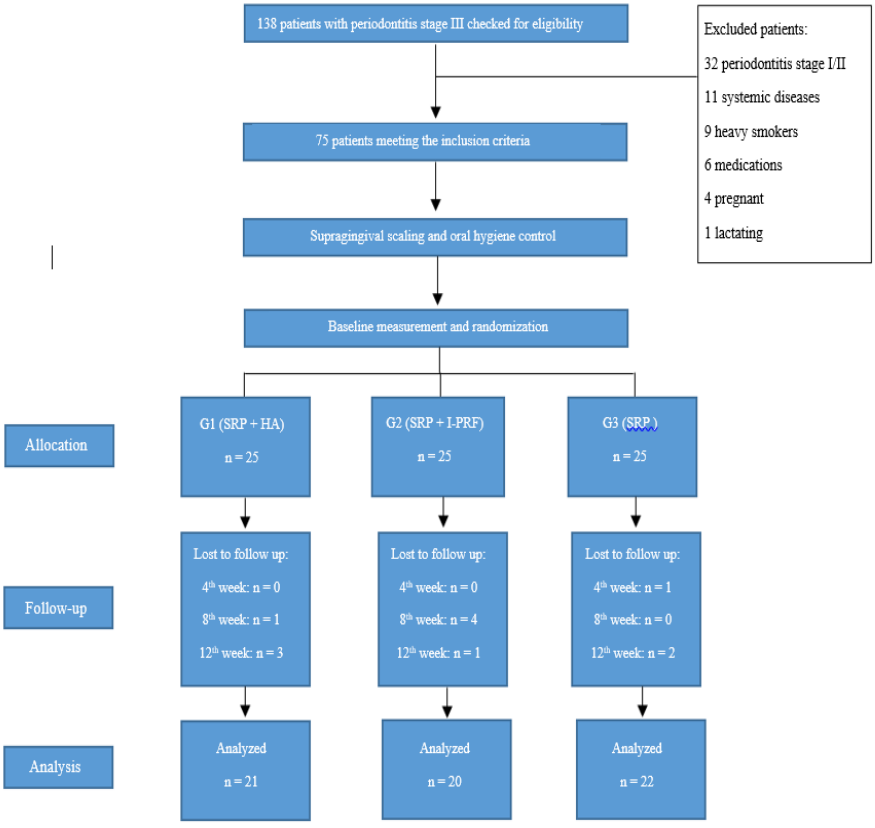

Figure 4: Diagram depicting the process of selecting and allocating study participants.

Moreover, both groups G1 and G2 demonstrated a statistically significant reduction in the mean PD values postoperatively when compared to the baseline ($p<0.05$), which was largely based on improvements within the first four weeks of treatment. However, a slight reduction in the PD was noticed in G3 where PMPR was done without any adjunctive treatment (Table 1). Moreover, after three months, patients treated with HA as an addition to PMPR had a significantly higher PD reduction than patients treated with PMPR alone ($p<0.05$). Similarly, patients treated with red i-PRF as an adjunct to PMPR had a significantly higher PD reduction than those treated with PMPR only ($p<0.05$). However, there was no statistically significant difference between both groups, G1 (HA + PMPR) and G2 (i-PRF + PMPR). (Table 2)

Furthermore, throughout the trial period, significant gains in clinical attachment (CAL gain) were observed in both groups G1 and G2 where adjunctive treatment is applied to PMPR, while in G3, where PMPR is done solely, no significant gain was noticed ($p<0.05$) (Table 1). However, no statistically significant difference between G1 and G2 was observed. (Table 2)

Nonetheless, in all three treatment groups, the proportion of sites with BOP significantly decreased after three months ($p<0.05$) (Table 1).

Table 1: Patient's characteristics and full-mouth clinical parameters at the baseline and follow-up visits (mean ± standard deviation).

Variable	Time point	G1 (PMPR + HA)	G2 (PMPR + I-PRF)	G3 (PMPR)
Age (years)	Baseline	57.8 ± 11.1	51.8 ± 10.8	49.9 ± 11.9
Gender (female/ male)	Baseline	12 / 9	9 / 11	12 / 10
PI	Baseline	1.2 ± 0.6	1.0 ± 0.6	0.9 ± 0.7
	4th week	0.8 ± 0.7*	0.79 ± 0.6*	0.6 ± 0.6*
	8th week	0.76 ± 0.6*	0.67± 0.6*	0.5 ± 0.4*
	12th week	0.72± 0.6*	0.52 ± 0.5*	0.43 ± 0.4*
GI	Baseline	1.1 ± 0.7	1.2 ± 0.6	1.0 ± 0.6
	4th week	0.75 ± 0.4*	0.8 ± 0.5*	0.64 ± 0.5*
	8th week	0.73 ± 0.5*	0.62 ± 0.4*	0.59 ± 0.4*
	12th week	0.69 ± 0.5*	0.78 ± 0.4*	0.57 ± 0.4*
PD (mm)	Baseline	7.27 ± 0.73	7.38 ± 0.71	7.12 ± 0.73
	4th week	6.03 ± 0.90*	5.88 ± 0.94*	6.92 ± 0.91*
	8th week	5.10 ± 0.75*	4.98 ± 0.50*	6.57 ± 0.75*
	12th week	4.51 ± 1.25*	4.55 ± 0.57*	6.23 ± 0.67*
CAL (mm)	Baseline	6.04 ± 0.80	6.42 ± 0.76	6.35 ± 0.78
	4th week	5.17 ± 0.81*	5.38 ± 0.67*	6.27 ± 0.82*
	8th week	4.89 ± 0.58*	5.01 ± 0.56*	6.13 ± 0.76*
	12th week	4.06 ± 1.01*	4.38 ± 0.74*	5.99 ± 0.87*
BOP (%)	Baseline	47.6 ± 28.50	48.64 ± 26.50	43.79 ± 23.15
	4th week	23.2 ± 20.11*	18.06 ± 13.29*	18.17 ± 13.48*
	8th week	20.3 ± 17.88*	18.47 ± 13.88*	15.3 ± 10.29*
	12th week	19.87 ± 16.49*	19.00 ± 14.43*	14.47 ± 9.88*

** statistically significant difference ($p<0.05$) within one treatment group as compared to the baseline*

Table 2: comparison of mean changes between baseline and visits in group 1,2 and 3.12

PD mean changes	4th week visit	8th week visit	12th week visit	CAL mean changes	4th week visit	8th week visit	12th week visit
G1	1.24 ± 0.85	2.17 ± 0.81*	2.76 ± 1.08*	G1	0.85 ± 0.64	1.15 ± 0.70*	1.98 ± 0.83*
G2	1.5 ± 0. 66	2.4 ± 0.67*	2.83 ± 1.26*	G2	1.04 ± 0.81	1.41 ± 0.84*	2.04 ± 0.85*
G3	0.2 ± 0.43	0.55 ± 0.51*	0.89 ± 0.61*	G3	0.08 ± 0.55	0.22 ± 0.49*	0.36 ± 0.72*

** statistically significant difference ($p<0.05$) within one treatment group as compared to the baseline*

Discussion

In the current clinical trial, two different treatment strategies have been investigated in order to prove their clinical benefit as an adjunct to PMPR and to compare them in efficiency.

Since the introduction of locally delivered drugs in the dental field, several studies have been conducted to examine their efficacy in treating dental diseases, including chronic periodontitis. Some studies found that these substances (such as HA) when used as an adjunct to PMPR had no actual significant difference compared to PMPR alone. [8], [9], [10] However, other studies showed that there was significant improvement in the periodontal parameters when HA was used as an adjunct to PMPR rather than when PMPR was performed solely. [11-15]

In this clinical trial, the results of the group where HA was used as an adjunct to PMPR (G1) were consistent with the latter research studies. A significant difference was noticed in G1 where around 1.98 mm gain in CAL and a 2.76 mm reduction in the PD were noticed, whereas in G3 where only PMPR was performed, only around 0.36 mm of CAL gain and a 0.89 mm PD reduction was observed.

On the other hand, other treatment protocols were introduced as an adjunct to PMPR. One of these protocols includes the use of i-PRF. There is no doubt that the PRF causes enhancement in all periodontal parameters when used to treat periodontal problems as it contains growth factors. All the studies done on it confirm this fact. However, the use of i-PRF in the non-surgical treatment of periodontitis was done by Vučković et al. in 2020 for the first time. [16] It showed significant improvements in the periodontal parameters.

Recently, research has started to differentiate between red and yellow i-PRF. But, to our best knowledge, to date, the clinical efficacy of red i-PRF in treating periodontal diseases has not been investigated. Thus, our concern was to examine the clinical efficiency of the red i-PRF in treating stage III periodontitis non-surgically for the first time and to compare it to the HA, which has been more familiar in the field for the past few years.

Moreover, the randomization strategy used allowed for an evenly dispersed number of patients at the baseline. However, some dropouts were noticed in the three treatment groups. Most of these dropouts occurred as a result of patients' postponing or canceling some of their multiple weekly appointments, resulting in treatment intervals of more than four weeks between visits.

Nonetheless, the three treatment groups were demographically balanced, and the final sample size in each group was greater than the minimum required (n = 18) for sufficient statistical power.

After conducting the treatment for the three groups, the results came out to show that there was no statistically significant difference in the plaque and gingival indices between them all at any time period. This could be due to the fact that all patients were given the same oral hygiene recommendations and used the same oral hygiene equipment.

Similarly, there was no statistically significant difference in the reduction of BOP between the three groups despite the significant reduction in the PD. This has been discussed in previous studies (Fang et al., 2016). The removal of the major biofilm mass during PMPR may be the reason behind the resolution of tissue inflammation and vasodilation, thus leading to a decrease in the BOP. [21]

Regarding the CAL gain, both groups G1 and G2, where adjunctive treatment was done in addition to PMPR, showed significant improvement during the three-month period. Around 1.98 mm of gain in CAL was noticed in G1 where HA was used. Similarly, around 2.04 mm of gain in CAL was observed in G2 where red i-PRF was applied. However, G3, where only PMPR was done, showed no significant gain (only 0.36 mm). This shows that both adjunctive treatments, HA and i-PRF, cause significant improvement in the CAL in comparison to PMPR alone, with no significant difference between them.

Likewise, for the PD reduction, both groups G1 and G2, where adjunctive treatment was done in addition to PMPR, showed significant improvement during the three-month period. A 2.76 mm reduction in PD was noticed in G1 where HA was used. Similarly, a 2.83 mm decrease in PD was observed in G2 where red i-PRF was applied. However, no significant reduction was observed in G3 where only PMPR was done (almost 0.36 mm). This means that both treatments, HA and i-PRF, lead to a significant reduction in the PD in comparison to PMPR alone, with no significant difference between them.

Note that there were some limitations to the study. Blinding of the therapists was not possible due to the typical specification of the number of appointments (HA applied every four weeks whereas red i-PRF was applied within a ten-day interval) and content of the treatment (special measures should be taken after the application of red i-PRF such as the sponge soaked in saline). However, this didn't affect the double blindness of the study since the examiners who were collecting data as well as the patients were blinded.

Conclusion

In conclusion, when used in conjunction with PMPR to treat stage III periodontitis non-surgically, both treatment modalities, HA and the red i-PRF, significantly improve all periodontal metrics compared to when used alone, especially in terms of CAL gain and PD decrease. However, when comparing these two therapy modalities, there is no statistically significant difference between them, and they both practically have the same efficacy.

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