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Comparison Between Hyaluronic Acid and Chlorhexidine in the Treatment of Orthodontically Induced Gingival Enlargement.

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Cover Page Footnote

First, I'm grateful to our mentor, my dean Professor Essam Osman for his advice, continuous support and patience during this study. i would also acknowledge and give my warmest thanks to Professor Nayer Abo Elsaad and Assistant professor Aly Osman who guided me to complete this work.

ORIGINAL ARTICLE / *ARTICLE ORIGINAL*

Orthodontics / *Orthodontie*

COMPARISON BETWEEN HYALURONIC ACID AND CHLORHEXIDINE IN THE TREATMENT OF ORTHODONTICALLY INDUCED GINGIVAL ENLARGEMENT: A RANDOMIZED CONTROLLED TRIAL

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Introduction: The study aimed to assess and compare the effectiveness of chlorhexidine and hyaluronic acid when used as an adjuvant to professional mechanical plaque removal (PMPR) in the treatment of orthodontically induced gingival enlargement.

Methods: The study conducted was a randomized controlled clinical trial involving 45 patients. The patients will be categorized into 3 groups; control group receiving conventional PMPR, study 1 group receiving PMPR and chlorhexidine (CHX), and study 2 group receiving PMPR and hyaluronic acid (HA). Probing depth (PD), Gingival overgrowth index (GOI), gingival bleeding index (GBI), and plaque index (PI), will be recorded at baseline, 1 month, 2 months, and 4 months' post therapy. A bivariate analysis was conducted to evaluate the parameters in function of the three study groups, and to evaluate the changes in PD and GBI between baseline, month 1, month 2 and month 4 in the three study groups.

Results: A significant reduction in probing depth and gingival bleeding was observed in the three groups ($p<0.05$) at all stages of the study except for month 1. No significant differences were found regarding GOI and PI values ($P>0.05$). The change in PD, PI, GBI and GOI was more in Group 1 and Group 2 than in the control group. Hyaluronic acid demonstrated the same effect of chlorhexidine.

Conclusions: HA is just as effective as CHX in treating gingival enlargement. Based on the acceptance of HA by patients generally and the negative effects of CHX, HA may be a potential alternative to CHX.

Keywords: Hyaluronic acid, Chlorhexidine, gingival enlargement, orthodontics, PMPR.

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The authors declare no conflicts of interest.

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COMPARAISON ENTRE L'ACIDE HYALURONIQUE ET LA CHLORHEXIDINE POUR LE TRAITEMENT DES GINGIVITES INDUITES ORTHODONTIQUEMENT : UN ESSAI CLINIQUE RANDOMISÉ

Introduction: L'étude visait à évaluer et à comparer l'efficacité de la chlorhexidine et de l'acide hyaluronique lorsqu'ils sont utilisés comme adjuvant à l'élimination mécanique professionnelle de la plaque (PMPR) dans le traitement de l'hypertrophie gingivale induite par l'orthodontie. **Méthodes**: L'étude menée est un essai clinique contrôlé randomisé impliquant 45 patients. Les patients seront classés en 3 groupes; le groupe témoin recevant le PMPR conventionnel, le groupe de l'étude 1 recevant le PMPR et la chlorhexidine (CHX) et le groupe de l'étude 2 recevant le PMPR et l'acide hyaluronique (HA). La profondeur de sondage (PD), l'indice de prolifération gingivale (GOI), l'indice de saignement gingival (GBI) et l'indice de plaque (PI) seront enregistrés au début, 1er mois, 2ème mois et 4ème mois après le traitement. Une analyse bivariée a été menée pour évaluer les paramètres en fonction des trois groupes d'étude, et pour évaluer les changements de PD et de GBI entre le début, le mois 1, le mois 2 et le mois 4 dans les trois groupes d'étude. **Résultats**: Une réduction significative de la profondeur des poches et des saignements gingivaux a été observée dans les trois groupes ($p<0,05$) à tous les stades de l'étude sauf pour le mois 1. Aucune différence significative n'a été trouvée concernant les valeurs de GOI et PI ($P > 0,05$). Le changement de PD, PI, GBI et GOI était plus important pour les groupes 1 et 2 que pour le groupe témoin. L'acide hyaluronique a démontré le même effet que la chlorhexidine. **Conclusions**: HA est tout aussi efficace que CHX dans le traitement de l'hypertrophie gingivale. Sur la base de l'acceptation de l'HA par les patients en général et des effets négatifs de la CHX, l'HA peut être une alternative potentielle à la CHX.

Mots Clés: acide Hyaluronic, Chlorhexidine, élargissememnt gingival, orthodontie, PMPR.

Introduction

Dental plaque is the most important etiological factor for periodontal diseases. The most common type of periodontal diseases is plaque induced gingivitis affecting around 50 to 90% of people in the world. Many orthodontic cases of untreated gingivitis may result in gingival enlargement. Gingival enlargement is defined as an overgrowth or increase in the size of the gingiva [1].

Gingival overgrowth and gingival enlargement are the same expressions that are used interchangeably with gingival fibrosis and gingival hypertrophy. Gingival hyperplasia is an increase in the number of tissue cells resulting in increased tissue volume [2]. GE is a very common condition in orthodontic patients characterized by gingival overgrowth, which leads to pseudo-pocketing with or without attachment loss. Traditionally, gingival enlargement was considered an inflammatory reaction due to the accumulation of bacterial plaque [3].

Almost all patients with fixed orthodontic appliances can encounter gingival enlargement at some point during their treatment. Many studies have shown that patients with orthodontic appliances are at high risk of developing periodontal and gingival diseases due to the orthodontic brackets, ligatures wires, orthodontic bands, and elastics that enhance the accumulation of food debris and microbial flora. Moreover, the longer the treatment of the orthodontics may contribute to the progression of the gingival enlargement [4].

In addition, the cytotoxic effects and the oxidative stresses of materials in the fixed orthodontic appliances and the bonding agents have been considered another causative factor for gingival inflammation [4].

Typically, gingival treatment is generally directed through decreasing the etiological factors in order to reduce the inflammation process, thus allowing the healing of gingival tissues. This can be managed by an effective plaque control measures and tooth debridement combined with continuous periodontal maintenance procedures in order to prevent the re-initiation of gingival inflammation [5].

The orthodontic appliances create many retentive areas for plaque accumulation aroud the teeth favouring the colonization of mainly periodonto-pathogens such as, Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans Tannerella forsythia, Treponema denticola Prevotella intermedia, Prevotella nigrescens, and in sub-gingival plaque [6].

Mechanical plaque control measures are usually inadequate for providing a level of plaque control reliable with normal oral health over long time. Bacteria present in the soft tissue has the ability to recolonize the surfaces of teeth even after mechanical plaque control measures. Dental products as mouth rinses and topical gels that contain chemical agents with anti-plaque and antimicrobial activities have shown to be more effective in controlling plaque mediated gingival diseases [7].

In 2020, Ramanauskaite and Machiulskiene found in their study that adjunctive antiseptics with a sustained release that are delivered subgingivally have a major proven benefits compared to scaling and root planning alone [8].

Chlorhexidine has been used successfully as the most effective topical antiseptic in treating gingival disease and remains the gold standard of all chemical antimicrobial agents. Yet, CHX has many side effects that affects the patient's compliance such as tongue and teeth staining, mucosal erosions and taste alteration [9].

Chlorhexidine adsorbed to dental tissues is released gradually into the oral cavity. Therefore, the slow CHX release will prolong its antibacterial activity for long hours, depending on many factors such as the dose, percentage, temperature, usage intervals and the presence of natural teeth or other prosthesis and the PH of saliva [10].

A study done in 2020 by Han Zhao et al, concluded that the adjunctive subgingival application of chlorhexidine at individual selected sites in nonsurgical periodontal therapy has appeared to provide a light difference in periodontal pocket reduction compared to non-surgical periodontal therapy alone for chronic gingivitis [11].

HA has various important biological and physiological functions playing an important role in the functioning of the periodontium extracellular matrix. This shows its valuable role in tissue healing through its anti-inflammatory and bacteriostatic properties [12].

The topical administration of a high-molecular weight exogenous hyaluronic acid gel has been suggested to induce periodontal healing in patients with inflammatory gingivitis. Hyaluronic acid gel used intrasulcularly and extrasulcularly is beneficial in treating gingivitis [13].

In 2016, Srishti Anil Shah et al. found in his study that the sub-gingival application of 0.8% hyaluronan gel in combination with S/R may present a positive effect on treating patients with gingival enlargement. A significant decrease in the pockets probing depth as well as gain of attachment level was shown in hyaluronan treated gingival pockets [14].

In the light of these evidences and because of independent research data are insufficiently available, comparing the efficiency between HA and CHX in the treatment of orthodontically induced gingival enlargement is necessary.

Methodology

The following study was approved by the ethical review committee and institutional review board at Beirut Arab University with IRB code: 2023-H-0119-D-M-0520.

A Randomized Controlled Clinical Trial was conducted including 45

patients attending the department of periodontology in Beirut Arab University and undergoing orthodontic treatment with orthodontically-induced grade II and III gingival enlargement. Written informed consent was obtained from all patients prior to their participation in this study to be approved by ethical committee.

Different eligibility criteria were followed. In fact, this study included patients aged between 18-25 years; having acceptable oral hygiene, motivated, having fixed orthodontics and having grade II and III gingival enlargement. Moreover, males and females equally selected.

Furthermore, we excluded smoker, medically compromised patients, pregnant and lactating women, patients allergic to drugs and medications, patients who had taken antibiotic therapy in the month, teeth with severe mobility and severe bone loss, advanced periodontitis or rampant caries, removable orthodontic appliances or removable oral prostheses.

Patients were divided into 3 treatment groups (study and control).

- The study 1 group G1: 15 patients received PMPR followed by the intra-sulcular and topical application of 0.20% chlorhexidine gel (Perio Kin) and 0.12% chlorhexidine home mouth wash (Kin Gingival).
- The study 2 group G2: 15 patients received PMPR followed by the intra-sulcular and topical application of hyaluronic acid gel (GENGIGEL) and hyaluronic acid home mouth rinse (GENGIGEL).
- The control group GC: 15 patients received PMPR only.

The clinical parameters Probing depth (PD), Gingival overgrowth index (GOI), gingival bleeding index (GBI), and plaque index (PI), were recorded at baseline, 1 month, 2 months, and 4 months' post therapy. Moreover, the study comprised 3 phases: pre-therapeutic phase, therapeutic phase and post therapeutic phase. First, all patients were assessed and evaluated by proper history taking and thorough clinical examination. PMPR was done for all three groups, followed by postoperative hygiene instructions. Moreover, intrasulcular applications of the gel was done for each test group during their weekly visit. After the gel application, the patients will wait 30 minutes and use the mouth rinse and will be instructed to avoid eating, drinking, or rinsing for 1 h.

Patients in groups 1 and 2 were instructed to use the topical gel and the mouth rinse twice daily for 2 weeks. Follow up was done after 1 month, 2 months and 4 months and measurements and maintenance of oral hygiene were recorded.

All the data that were collected from the study and statistically analyzed using the Statistical Package for Social Science (SPSS) version 25 were summarized and represented in suitable tables and graphs. By taking the means and variance of a similar study conducted by Amoian et al [15], the confidence level was set to 95% and the power was set on 80% and the calculated sample size was 45 patients.

Bivariate analysis was conducted in order to evaluate the four study outcomes Probing Depth (PD), Gingival Bleeding Index (GBI), gingival overgrowth Index (GOI) and Plaque Index (PI), in function of the three study groups. Tests used were Chi-square test and Fisher exact test to statistically analyze the nominal or categorical variables such as indices (GOI and PI) , Mann-Whitney test and Kruskal Wallis test to analyze ordinal or continuous variables such as numbers and percentages (GBI and PD). In addition, bivariate analysis was conducted to evaluate the changes in PD and GBI between baseline, month 1, month 2 and month 4 in the three study groups. Wilcoxon signed rank test was used to test the difference between the measurements among the time points (continuous variables not normally distributed). A correlation was considered statistically significant if the P value is less than 0.05.

Results

1- **Study Groups**

The study population included 45 patients distributed between 3 groups: 15 patients in the group 1 (PMPR + CHx - PMPR and CHX gel applied into gingival sulcus), 15 patients in the group 2 (PMPR + HA - PMPR and HA gel applied into gingival sulcus), and 15 patients in the control group (GC) (Figure 1).

2- **Demographics**

The study included 23 males (51.1%) and 22 females (48.9%). The group control included 7 males (46.7%) and 22 females (53.3%). Group 1 included 7 males (46.7%) and 8 females (53.3%). Group 2 included 9 males (60%) and 6 females (40%) (Figure 1).

The average age of the 45 patients was 18.9 ± 2.8 years. The mean age of the control group was 19.3 ± 2.9 years, the mean age of group 1 was 18.6 ± 2.3 years, and the mean age of group 2 was 18.9 ± 3.2 years (Figure 2).

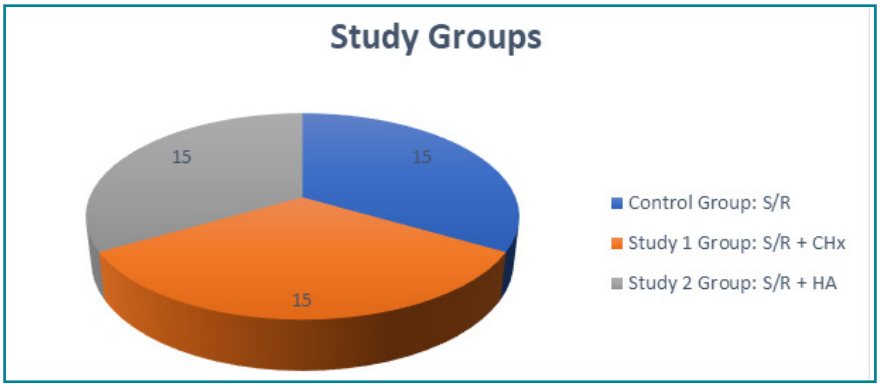

Figure 1: Representation of the study population

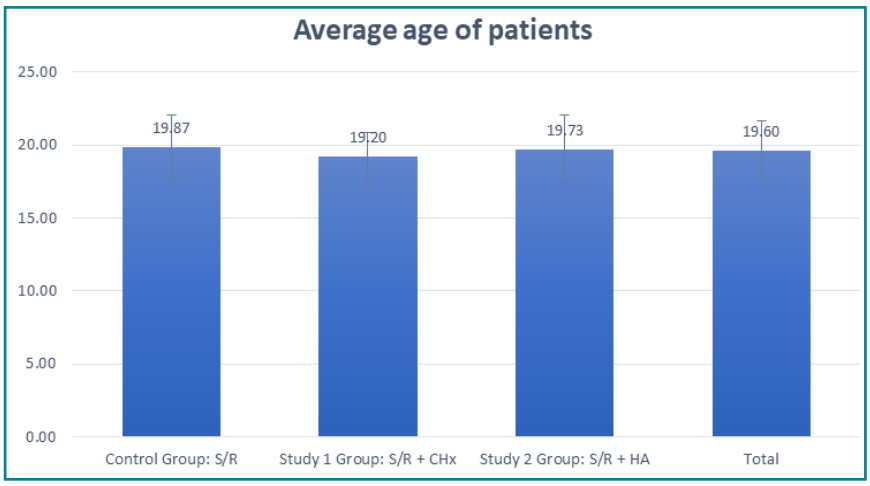

Figure 2: Representation of the study population per age

3- **Probing Depth (PD)**

At baseline, mean PD was 5.133 ± 0.743 in group 1 and 4.933 ± 0.799 in group 2, and 4.867 ± 0.743 in the control group. There was no statistically significant difference between the three groups (p = 0.601), between GC and G1 (p = 0.326), between GC and G2 (p = 0.824), and between G1 and G2 (p = 0.478).

At month 1, mean PD was 4.733 ± 0.799 in group 1 and 4.600 ± 0.737 in group 2, and 4.667 ± 0.617 in the control group. There was no statistically significant difference between the three groups (p = 0.874), between GC and G1 (p = 0.928), between GC and G2 (p = 0.663), and between G1 and G2 (p = 0.650).

At month 2, mean PD was 3.933 ± 0.704 in group 1 and 4.133 ± 0.516 in group 2, and 4.400 ± 0.632 in the control group. There was no statistically significant difference between the three groups (p = 0.182), between GC and G1 (p = 0.084), between GC and G2 (p = 0.267), and between G1 and G2 (p = 0.384).

At month 4, mean PD was 3.667 ± 0.724 in group 1 and 3.867 ± 0.516 in group 2, and 4.267 ± 0.704 in the control group. There was no statistically significant difference between the three groups (p = 0.055), between GC and G2 (p = 0.095), and between G1 and G2 (p = 0.302). There was a statistically significant difference between GC and G1 (p = 0.028) showing that PD at M4 was lower in G1 comparing to GC.

In group 1, a statistically significant decreasing was shown in PD between baseline and Month 1, where mean PD decreased from 5.133 ± 0.743 mm at baseline to 4.733 ± 0.799 mm at month 1 (p = 0.014) (Table 1). In addition, a statistically significant decreasing was shown in PD between baseline and Month 2, where mean PD decreased from 5.133 ± 0.743 mm at baseline to 3.933 ± 0.704 mm at month 2 (p = 0.001). Furthermore, a statistically significant decreasing was shown in PD between base-

Table 1: Changes in Probing Depth (PD) in the study groups during the study period

		Mean	SD	Paired Differences		P.value
				Mean	SD	
G1	Probing Depth (PD) (in mm)	5.133	0.743	0.400	0.507	**0.014**
	Probing Depth (M1) (in mm)	4.733	0.799			
	Probing Depth (PD) (in mm)	5.133	0.743	1.200	0.561	**0.001**
	Probing Depth (M2) (in mm)	3.933	0.704			
	Probing Depth (PD) (in mm)	5.133	0.743	1.467	0.834	**0.001**
	Probing Depth (M4) (in mm)	3.667	0.724			
G2	Probing Depth (PD) (in mm)	4.933	0.799	0.333	0.488	**0.025**
	Probing Depth (M1) (in mm)	4.600	0.737			
	Probing Depth (PD) (in mm)	4.933	0.799	0.800	0.775	**0.006**
	Probing Depth (M2) (in mm)	4.133	0.516			
	Probing Depth (PD) (in mm)	4.933	0.799	1.067	0.799	**0.003**
	Probing Depth (M4) (in mm)	3.867	0.516			
Control	Probing Depth (PD) (in mm)	4.867	0.743	0.200	0.414	0.083
	Probing Depth (M1) (in mm)	4.667	0.617			
	Probing Depth (PD) (in mm)	4.867	0.743	0.467	0.640	**0.020**
	Probing Depth (M2) (in mm)	4.400	0.632			
	Probing Depth (PD) (in mm)	4.867	0.743	0.600	0.632	**0.007**
	Probing Depth (M4) (in mm)	4.267	0.704			

a. Wilcoxon Signed Ranks Test

line and Month 4, where mean PD decreased from 5.133 ± 0.743 mm at baseline to 3.667 ± 0.724 mm at month 4 (p = 0.001).

In group 2, a statistically significant decreasing was shown in PD between baseline and Month 1, where mean PD decreased from 4.933 ± 0.799 mm at baseline to 4.600 ± 0.737 mm at month 1 (p = 0.025) (Table 1). In addition, a statistically significant decreasing was shown in PD between baseline and Month 2, where mean PD decreased from 4.933 ± 0.799 mm at baseline to 4.133 ± 0.516 mm at month 2 (p = 0.006). Furthermore, a statistically significant decreasing was shown in PD between baseline and Month 4, where mean PD decreased from 4.933 ± 0.799 mm at baseline to 3.867 ± 0.516 mm at month 4 (p = 0.003).

In the control group, there was no statistically significant change in PD between baseline and Month 1, where mean PD was 4.867 ± 0.743 mm at baseline and 4.667 ± 0.617 mm at month 1 (p = 0.083) (Table 1). In addition, a statistically significant decreasing was shown in PD between baseline and Month 2, where mean PD decreased from 4.867 ± 0.743 mm at baseline to 4.400 ± 0.632 mm at month 2 (p = 0.020). Furthermore, a statistically significant decreasing was shown in PD between baseline and Month 4, where mean PD decreased from 4.867 ± 0.743 mm at baseline to 4.267 ± 0.704 mm at month 4 (p = 0.007).

4- **Gingival Bleeding Index (GBI)**

At baseline, mean GBI was 0.627 ± 0.068 in group 1, 0.593 ± 0.075 in group 2, and 0.583 ± 0.126 in the control group. There was no statistically significant difference between the three groups (p = 0.456), between GC and G1 (p = 0.375), between GC and G2 (p = 0.916), and between G1 and G2 (p = 0.210).

At month 1, mean GBI was 0.547 ± 0.077 in group 1, 0.533 ± 0.070 in group 2, and 0.567 ± 0.118 in the control group. There was no statistically significant difference between the three groups (p = 0.305), between GC and G1 (p = 0.310), between GC and G2 (p = 0.140), and between G1 and G2 (p = 0.581).

At month 2, mean GBI was 0.467 ± 0.062 in group 1, 0.563 ± 0.058 in group 2, and 0.537 ± 0.117 in the control group. There was a statistically significant difference between the three groups (p = 0.026), between GC and G1 (p = 0.024), between GC and G2 (p = 0.016), and no statistically significant difference between G1 and G2 (p = 0.966). Therefore, results showed that GBI was lower at month 2 in Group 1 comparing to control group, and lower at month 2 in Group 2 comparing to control group, but statistically same between Group 1 and Group 2.

At month 4, mean GBI was 0.423 ± 0.050 in group 1, 0.420 ± 0.056 in group 2, and 0.520 ± 0.113 in the control group. There was a statistically significant difference between the three groups (p = 0.005), between GC and G1 (p = 0.006), between GC and G2 (p = 0.005), and no statistically significant difference between G1 and G2 (p = 0.965). Therefore, results showed that GBI was lower at month 4 in Group 1 comparing to control group, and lower at month 4 in Group 2 comparing to control group, but statistically same between Group 1 and Group 2.

Table 2: Gingival Bleeding Index (GBI) in the study groups during the study period

		Mean	Std. Deviation	Paired Differences		P.value
				Mean	Std. Deviation	
G1	Gingival Bleeding Index (GBI)	0.627	0.068	0.080	0.037	**0.000**
	Gingival Bleeding Index (GBI) (M1)	0.547	0.077			
	Gingival Bleeding Index (GBI)	0.627	0.068	0.160	0.051	**0.001**
	Gingival Bleeding Index (GBI) (M2)	0.467	0.062			
	Gingival Bleeding Index (GBI)	0.627	0.068	0.203	0.061	**0.001**
	Gingival Bleeding Index (GBI) (M4)	0.423	0.050			
G2	Gingival Bleeding Index (GBI)	0.593	0.075	0.060	0.034	**0.001**
	Gingival Bleeding Index (GBI) (M1)	0.533	0.070			
	Gingival Bleeding Index (GBI)	0.593	0.075	0.130	0.065	**0.001**
	Gingival Bleeding Index (GBI) (M2)	0.463	0.058			
	Gingival Bleeding Index (GBI)	0.593	0.075	0.173	0.073	**0.001**
	Gingival Bleeding Index (GBI) (M4)	0.420	0.056			
Control	Gingival Bleeding Index (GBI)	0.583	0.126	0.017	0.024	**0.025**
	Gingival Bleeding Index (GBI) (M1)	0.567	0.118			
	Gingival Bleeding Index (GBI)	0.583	0.126	0.047	0.044	**0.004**
	Gingival Bleeding Index (GBI) (M2)	0.537	0.117			
	Gingival Bleeding Index (GBI)	0.583	0.126	0.063	0.061	**0.005**
	Gingival Bleeding Index (GBI) (M4)	0.520	0.113			

a. Wilcoxon Signed Ranks Test

In Group 1, a statistically significant decreasing was shown in GBI between baseline and Month 1, baseline and Month 2, and baseline and Month 4 (Table 2). Mean GBI was 0.627 ± 0.068 mm at baseline and decreased to 0.547 ± 0.077 mm at Month 1 ($p < 0.001$), 0.467 ± 0.062 mm at Month 2 ($p = 0.001$), and 0.423 ± 0.050 mm at Month 4 ($p = 0.001$).

In Group 2, a statistically significant decreasing was shown in GBI between baseline and Month 1, baseline and Month 2, and baseline and Month 4 (Table 2). Mean GBI was 0.593 ± 0.075 mm at baseline and decreased to 0.533 ± 0.070 mm at Month 1 ($p = 0.001$), 0.463 ± 0.058 mm at Month 2 ($p = 0.001$), and 0.420 ± 0.056 mm at Month 4 ($p = 0.001$).

In the control group, a statistically significant decreasing was shown in GBI between baseline and Month 1, baseline and Month 2, and baseline and Month 4 (Table 2). Mean GBI was 0.583 ± 0.126 mm at baseline and decreased to 0.567 ± 0.118 mm at Month 1 ($p = 0.025$), 0.537 ± 0.117 mm at Month 2 ($p = 0.004$), and 0.520 ± 0.113 mm at Month 4 ($p = 0.005$).

5- **Gingival overgrowth Index (GOI)**

Gingival overgrowth Index (GOI) was scoring index 2 in 20% of G1 patients, 27.6% of G2 patients, and 40% of GC patients. In addition, GOI was scoring index 2-3 in 80% of G1 patients, 73.3% of G2 patients, and 60% of GC patients. There was no statistically significant difference between the three groups ($p = 0.469$), between GC and G1 ($p = 0.427$), between GC and G2 ($p = 0.439$), and between G1 and G2 ($p = 1.000$) (Table 3).

At month 1, GOI scoring index 2-3 in 40% of G1 patients, 46.7% of G2 patients, and 53.3% of GC patients. There was no statistically significant difference between the three groups ($p = 0.668$), between GC and G1 ($p = 0.509$), between GC and G2 ($p = 0.715$), and between G1 and G2 ($p = 0.584$) (Table 3).

At month 2, GOI was at level 2-3 in 13.3% of G1 patients, 20% of G2 patients, and 40% of GC patients. There was no statistically significant difference between the three groups ($p = 0.209$), between GC and G1 ($p = 0.215$), between GC and G2 ($p = 0.427$), and between G1 and G2 ($p = 1.000$) (Table 3).

At month 4, GOI was at level 2-3 in 13.3% of G1 patients, 6.7% of G2 patients, and 33.3% of GC patients. There was no statistically significant difference between the three groups ($p = 0.139$), between GC and G1 ($p = 0.390$), between GC and G2 ($p = 0.169$), and between G1 and G2 ($p = 1.000$) (Table 3).

Table 3: Gingival overgrowth Index (GOI) in the study groups

Study 1 Group: PMPR + CHx		Patient's Group: Study 2 Group: PMPR + HA	Patient's Group: Control Group: PMPR		Total	P1	P2	P3	P4
GOI	GOI: 2	3	4	6	13	0.469	0.427	0.439	1.000
		20.0%	26.7%	40.0%	28.9%				
	GOI: 2-3	12	11	9	32				
		80.0%	73.3%	60.0%	71.1%				
GOI M1	GOI: 1-2	1	0	0	1	0.668	0.509	0.715	0.584
		6.7%	0.0%	0.0%	2.2%				
	GOI: 2	8	8	7	23				
		53.3%	53.3%	46.7%	51.1%				
	GOI: 2-3	6	7	8	21				
		40.0%	46.7%	53.3%	46.7%				
GOI M2	GOI: 2	13	12	9	34	0.209	0.215	0.427	1.000
		86.7%	80.0%	60.0%	75.6%				
	GOI: 2-3	2	3	6	11				
		13.3%	20.0%	40.0%	24.4%				
GOI M4	GOI: 2	13	14	10	37	0.139	0.390	0.169	1.000
		86.7%	93.3%	66.7%	82.2%				
	GOI: 2-3	2	1	5	8				
		13.3%	6.7%	33.3%	17.8%				

a. Chi-square Test (P1)
b. Fisher exact test (P2, P3, and P4)
P1: P.value (C / G1 / G2); P2: P.value (C / G1); P3: P.value (C / G2); P4: P.value (G1 / G2)

6- **Plaque Index (PI)**

At baseline, PI was shown moderate accumulation in 73.3% in G1 patients, 66.7% in G2 patients, and 73.3% of GC patients. There was no statistically significant difference between the three groups (p = 0.897), between GC and G1 (p = 1.000), between GC and G2 (p = 1.000), and between G1 and G2 (p = 1.000) (Table 4).

At month 1, PI was shown moderate accumulation in 46.7% in G1 patients, 53.3% in G2 patients, and 60% of GC patients. There was no statistically significant difference between the three groups (p = 0.765), between GC and G1 (p = 0.715), between GC and G2 (p = 1.000), and between G1 and G2 (p = 1.000) (Table 4).

At month 2, PI was shown moderate accumulation in 46.7% in G1 patients, 40% in G2 patients, and 53.3% of GC patients. There was no statistically significant difference between the three groups (p = 0.765), between GC and G1 (p = 1.000), between GC and G2 (p = 0.715), and between G1 and G2 (p = 1.000) (Table 4).

At month 4, PI was shown moderate accumulation in 40% in G1 patients, 40% in G2 patients, and 53.3% of GC patients. There was no statistically significant difference between the three groups (p = 0.698), between GC and G1 (p = 0.715), between GC and G2 (p = 0.715), and between G1 and G2 (p = 1.000) (Table 4).

Table 4: Plaque Index (PI) in the study groups

Study 1 Group: PMPR + CHx		Patient's Group			Total	P1	P2	P3	P4
		Study 2 Group: PMPR + HA	Control Group: PMPR						
Plaque Index (PI)	Moderate accumulation	11	10	11	32	0.897	1.000	1.000	1.000
		73.3%	66.7%	73.3%	71.1%				
	Plaque film	4	5	4	13				
		26.7%	33.3%	26.7%	28.9%				
Plaque Index (PI) (M1)	Moderate accumulation	7	8	9	24	0.765	0.715	1.000	1.000
		46.7%	53.3%	60.0%	53.3%				
	Plaque film	8	7	6	21				
		53.3%	46.7%	40.0%	46.7%				
Plaque Index (PI) (M2)	Moderate accumulation	7	6	8	21	0.765	1.000	0.715	1.000
		46.7%	40.0%	53.3%	46.7%				
	Plaque film	8	9	7	24				
		53.3%	60.0%	46.7%	53.3%				
Plaque Index (PI) (M4)	Moderate accumulation	6	6	8	20	0.698	0.715	0.715	1.000
		40.0%	40.0%	53.3%	44.4%				
	Plaque film	9	9	7	25				
		60.0%	60.0%	46.7%	55.6%				

a. Chi-square Test (P1)
b. Fisher exact test (P2, P3, and P4)
P1: P.value (C / G1 / G2); P2: P.value (C / G1); P3: P.value (C / G2); P4: P.value (G1 / G2)

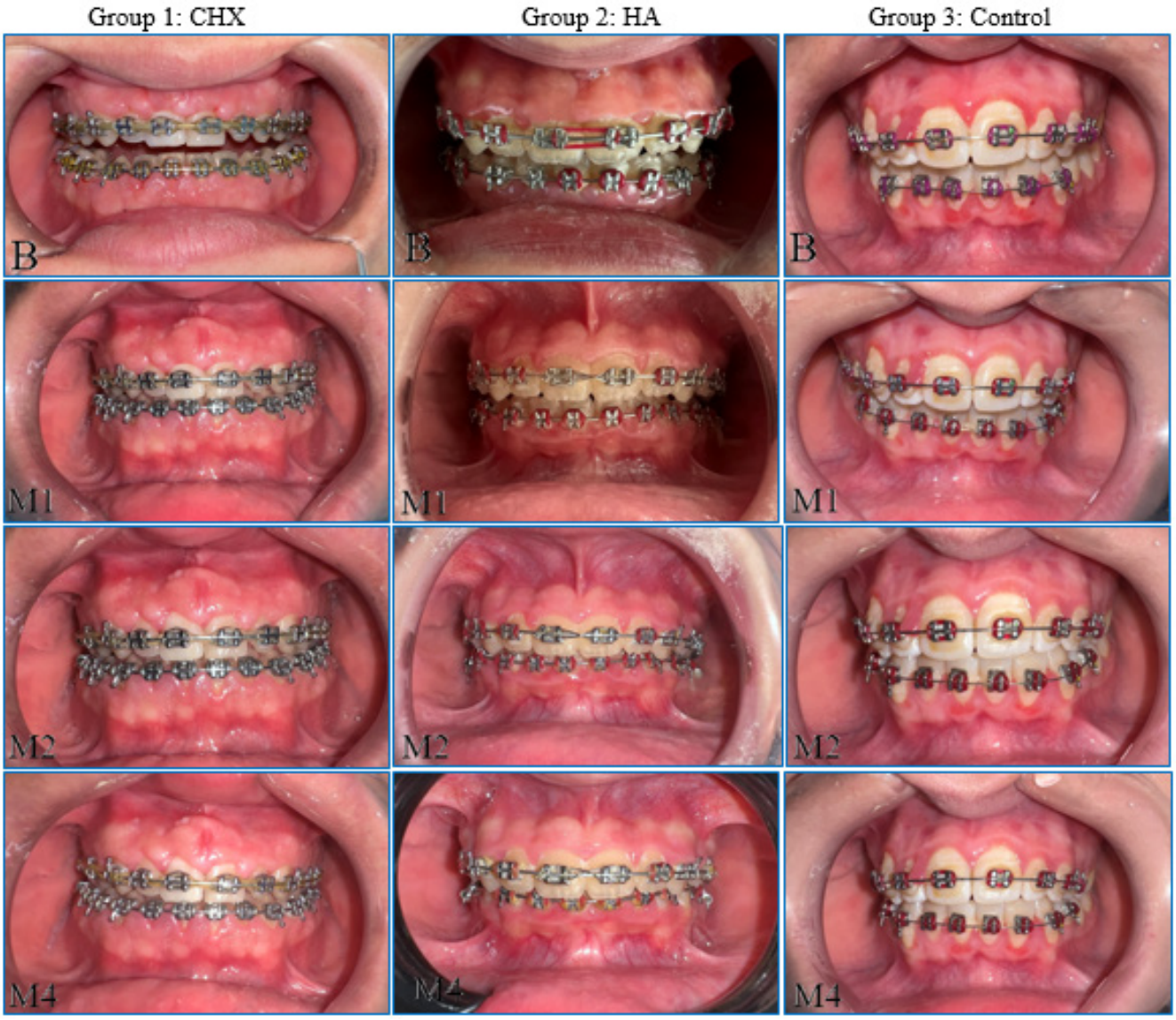

Figure 1: Changes in the gingival enlargement clinically in the 3 groups at baseline (B), 1 Month (M1), 2 months (M2), and 4 months (M4)

Discussion

We performed a randomized controlled clinical trial including 45 patients with orthodontically-induced grade II and III gingival enlargement distributed between 3 groups, PMPR, PMPR plus chlorhexidine, and PMPR plus hyaluronic acid, and evaluated for different parameters. Probing depth (PD), Gingival overgrowth index (GOI), gingival bleeding index (GBI), and plaque index (PI), were recorded at baseline, 1 month, 2 months, and 4 months' post therapy. A bivariate analysis was conducted to evaluate the parameters in function of the three study groups. In addition, bivariate analysis was conducted to evaluate the changes in PD and GBI between baseline, month 1, month 2 and month 4 in the three study groups. A significant reduction in probing depth and gingival bleeding was observed in the three groups (p 0.05). The change in PD, PI, GBI and GOI was more in Group 1 and Group 2 than in the control group. Hyaluronic acid demonstrated the same effect of chlorhexidine. Our findings demonstrated that the hyaluronic acid has an analogous effect to chlorhexidine in the management of plaque-induced gingival enlargement in fixed orthodontic appliance patients. They both have the same effect in reducing probing depth, gingival bleeding, gingival overgrowth and plaque index although. Using hyaluronic acid or chlorhexidine as an adjunctive to PMPR resulted in clinical benefits in the treatment of gingival overgrowth.

Gingival enlargement affects adolescent patients undergoing orthodontic treatment. This is due to the changes of hormone levels accompanied by poor oral hygiene leading to inflammatory gingival changes. This will clinically result in a nodular

or globular enlargement of the interdental papilla accompanied by BOP and gingival marginal thickening. In severe cases, inflammatory gingival enlargement will continue to cover a great part of the teeth and orthodontic brackets and bands as well, affecting the progress of the orthodontic treatment negatively [15].

Gingival enlargement usually happens one to two months after initiation of the orthodontic treatment. Different factors can stimulate and increase gingival inflammation leading to fibrosis and hypertrophy. These factors include plaque accumulation, physical and chemical effect of bondings and adhesive materials, food impaction and mechanical band stimulation [16].

The applied orthodontic forces and ensuing periodontal remodeling may also be related to gingival enlargement, despite the fact that plaque is frequently thought to be the primary cause of gingival enlargement. Gingival enlargement has been reported to occur in patients with good oral hygiene as well. As an illustration, Surlin et al. (2010) discovered that 15 of the 22 patients who had fixed orthodontics experienced gingival expansion. These individuals had considerably greater levels of (MMP)-8 than the group receiving conventional orthodontic treatment who had no periodontal lesions. The degree of gingival enlargement and the expression of MMP-9/IV collagen in orthodontic patients without inflammation were found to be positively correlated by the authors. Based on these findings, they hypothesize that one of the causes of gingival enlargement may be the rise in MMP levels brought on by orthodontic forces [17]. However, whether or not pure orthodontic pressures directly contribute to GE needs to be further examined.

Additionally, it was established that one of the primary causes of gingival enlargement during orthodontic treatment is the continuous stimulation of low concentration nickel ions in some orthodontic appliances. By encouraging T-lymphocytes to produce interferon and interleukin (IL)-2, IL-5, and IL-10, nickel ions may promote the growth of epithelial cells and the proliferation of keratinocytes, which may result in gingival hypertrophy. A type IV allergic reaction can be caused by time dependent nickel ion release. To prevent gingival enlargement during orthodontic treatment, a proper medical history should be obtained from the patient to know whether he has a history of nickel allergy or not [18].

Comparing the mean of probing depth in the study groups during the period of the study, our results showed no significant difference between GC/G1/G2, GC/G1, GC/G2 or G1/G2 at baseline, month 1 and month 2. However, after 4 months of treatment there was no statistically significant difference between the three groups. Only a statistically significant difference was shown between control group and CHX group at month 4, which indicates that PD at M4 was lower in CHX group comparing to control group. Thus using CHX as an adjunctive to PMPR results in a significant reduction in PD when compared to the treatment with PMPR only. In line with our results, different studies showed the efficiency of CHX in the treatment of ginigival enlargement when used as an adjunct to PMPR [19-20].

Comparing G1 with G2 the PD is almost the same, thus the HA has demonstrated a similar effect to CHX in decreasing the probing depth and the difference is not statistically significant. Hyaluronic acid is probably better than CHX although not being statistically improved. In 2015, Polepalle et al evaluated the clinical and microbiological effect of a HA application in the treatment of mild chronic gingivitis. They demonstrated a significant decrease of probing depth upon the use of hyaluronic acid with PMPR [21].

The gingival bleeding index (marker of periodontal inflammation) was assessed in the three groups. At baseline and month 1, there was no statistically significant difference between the three groups, GC and G1, GC and G2, and between G1 and G2. However, at month 2, a statistically significant difference was underlined between the three groups, between GC and G1, between GC and G2, but there was statistical equality between Groups 1 and 2. At month 4, our analysis showed a statistically significant difference between the three groups, between GC and G1, between GC and G2, but not between G1 and G2. Therefore, results showed that GBI at month 2 and month 4 was lower in Group 1 and in group 2 when compared to control group, but statistically same between Group 1 and Group 2. Thus CHX and HA seems to have the same efficiency in treating gingival bleeding when used as adjunctive to PMPR, and are more efficient than treating gingival enlargement by PMPR only.

Furthermore, assessing the GBI decrease during the treatment period showed that in the control group, a statistically significant decrease was shown between baseline and Month 1, baseline and Month 2, and baseline and Month 4. Moreover, a statistically significant decreasing was shown in group 1 between baseline and Month 1, baseline and Month 2, and baseline and Month 4. Similarly to CG and G1, a statistically significant decreasing in GBI was proved between baseline and Month 1, baseline and Month 2, and baseline and Month 4. Thus all the three methods are significantly effective in treating the gingival bleeding. However, GBI was higher in control group than other groups at month 4 underlying a greater efficiency of CHX and HA compared to PMPR. The gingival bleeding score was reduced in both study groups, and was significantly higher in the group of hyaluronic acid than group of chlorhexidine after one week and no substantial difference found after three weeks between both groups 10, that finding was similar to the results of Chauhan et al. (2013) [22] and de Araujo Nobre et al (2007)

[23]. These findings can result from the anti-inflammatory, anti-edematous, and scavenger effect of hyaluronic acid. Both gels showed anti-bacterial action, that was consistent with both YI et al. 2016 [24] and Pirnazar et al. 1999) [25].

Consistent with the study findings, Calderini et al showed that the use of chlorhexidine as an adjunctive to PMPR reduce gingival bleeding and has clinical and microbiological advantages in the treatment of generalized periodontal diseases [26]. In their study conducted in 2015, Jose et al. have also demonstrated that chlorhexidine mouth rinse greatly lowers bleeding scores [10].

To evaluate the seriousness of gingival inflammation, we assessed the gingival overgrowth index. The higher the gingival growth index, the more gingival hyperplasia extends over the entire crown of the tooth. During the treatment period, we noticed that the number of patients with GOI scoring 2-3 decreases and those with GOI scoring 2 increase, indicating a decrease in gingival overgrowth during the treatment phase. In fact, hyaluronic acid gel has anti-inflammatory and anti-edematous properties [27] and has been demonstrated to be an optimal choice in the treatment of gingivitis and periodontitis mainly characterized by gingival overgrowth [27-28].

The last parameter assessed in the study is the plaque index (PI). The study results demonstrate that the plaque index decreases over time in each group, thus the number of patient with moderate plaque accumulation declines. By comparing the different groups to each other to detect which treatment was the most effective, we did not indicate any statistically significant difference between the three groups, between control group and CHX, between control group and HA, and between CHX and HA. All the three techniques decreased the plaque index during this study, however the plaque index decrease was more important in group 1 and group 2 than in the control group. Therefore, CHX and HA improves the plaque treatment; plaque index in both groups improved significantly after the intervention, this result was identical to that of Batavia (2016) [29] and Pagnacco (1997) [30].

The plaque score reduction can be due to adequate oral hygiene maintenance, proficiently removing of all deposits by PMPR and polishing and antibacterial effect of both gel.

In contrast with our findings, Jain et al evaluated in their study the clinical efficiency of locally delivered xanthan-based Chlosite® gel (two CHX compounds combined) as an adjunctive to PMPR in treating chronic periodontitis and a significant difference was demonstrated between CHX group and PMPR only group for plaque index [31].

Shah et al conducted a research study in 2016 to evaluate the clinical properties of the subgingival application of 0.8% hyaluronic acid gel as an adjunct to PMPR in the treatment of generalized chronic periodontitis. They assessed different parameters including plaque index after 4 and 12 weeks of treatments. In line with our findings, their results showed a decrease in PI in both control group (PMPR) and test group (PMPR +HA) but no significant difference was shown between the two groups [14].

However, the study conducted by Polepalle et al showed that HA+ PMPR treated group showed significant improvement in all parameters including PI when compared with the control group treated with PMPR only [21]. Furthermore, a study done by Johannsen et al. to evaluate the adjunctive impact of the local application of 0.8% HA gel to PMPR in chronic periodontitis treatment found a significant reduction in PI and other parameters in the test group when compared to the PMPR alone [28].

The two study limitations were the limited size of the sampling, where only 15 patients were included in each study arm, and the Short follow-up period in which the study evaluated the patients for only 4 months after the intervention.

Conclusion

When hyaluronic acid administered in association with PMPR, hyaluronic acid was just as effective as chlorhexidine in treating gingival enlargement. Based on the acceptance of hyaluronic acid by patients generally and the negative effects of chlorhexidine, hyaluronic acid may be a potential alternative to chlorhexidine and regarded as a first-choice adjunctive aid for the orthodontic patient with mild to moderate gingival enlargement.

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