



## The Efficacy of a Combination of Hyaluronic acid and Metronidazole as a topical Adjunctive in Non- Surgical Treatment of Periodontitis (Clinical and Biochemical Study)

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### KEYWORDS

*Hyaluronic acid, Metronidazole,  
Topical Adjunctive, periodontitis,  
biochemical parameters*

### ABSTRACT

**Aim:** This study was designed to evaluate the clinical and biochemical effects of combination of hyaluronic acid and metronidazole as an adjunctive treatment of periodontitis. **Subjects and methods:** Forty patients with stage I to stage II, grade A periodontitis were selected from the out-patient clinic, Oral Medicine and Periodontology Department, Faculty of Dental Medicine, Al-Azhar University, Assiut Branch. They were divided into four equal groups. Group I received conventional periodontal therapy alone, group II received conventional periodontal therapy with intra pocket application of hyaluronic acid gel (GENGIGEL) 0.2%, group III received conventional periodontal therapy with intra pocket application of metronidazole (25%) and group IV received conventional periodontal therapy with intra pocket application of combination of hyaluronic acid (0.2%) and metronidazole (25%). All patients were evaluated clinically at baseline, 3 and 6 months and biochemical evaluation was done at baseline, 1 and 3 months to evaluate the IL-1 $\beta$  level in GCF. **Results:** All groups showed statistically significant differences at the different intervals in all clinical parameters (PI, GI, PD, CAL) and IL-1 $\beta$  level in GCF. Inter-groups comparison with respect to clinical and biochemical changes showed that Combination gel was the best. **Conclusion:** The combination of hyaluronic acid and metronidazole achieve superior effects as adjunctive therapy in improving the clinical and biochemical parameters in the treatment of periodontitis.

### INTRODUCTION

Periodontitis is a multifactorial inflammatory condition, caused by the interaction between oral bacteria organized in complex communities that form biofilms, adhering to the dental structures and the local host defense response<sup>(1)</sup>. This interaction lead to destruction of connective tissue attachment and alveolar bone loss. The ultimate outcome of untreated periodontal disease is tooth loss<sup>(2)</sup>.

Periodontopathic bacteria induce host immune response to secrete pro-inflammatory cytokines that play a role in periodontal tissue destruction<sup>(3)</sup>.

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Interleukin 1 beta (IL-1 $\beta$ ) is one of pro-inflammatory mediator which involved in cell proliferation, differentiation, and apoptosis. It is produced by various cell types including macrophages, fibroblasts and neutrophil. The inflammatory response mediated by IL-1 $\beta$  play an important role in periodontal tissue destruction<sup>(4)</sup>.

Non-surgical therapy includes plaque control by mechanical removal of supra and subgingival plaque and calculus deposits (scaling, root planing), and the adjunctive use of chemotherapeutic agents. It aims to reduce bacterial colonization and arrest the progression of periodontal disease<sup>(5)</sup>. But in some cases mechanical therapy have not the ability to eradicate all pathogenic bacteria so there is need to use one of the adjunctive treatment in some cases<sup>(6)</sup>.

Adjunctive periodontal therapy indicated when home care and SRP are not being sufficient to slow or stop the progression of periodontal disease. Adjunctive treatment includes (local and systemic antimicrobial agents, photodynamic therapy, probiotics and host modulating agents). These modalities enhance the healing process and improve periodontal tissue condition by reducing pocket depth and clinical attachment loss (CAL)<sup>(7)</sup>.

Metronidazole is an antimicrobial drug with a bactericidal effect against anaerobic organisms and some facultative anaerobic bacteria which are predominant in sub gingival flora in periodontitis. Its antibacterial action is due to the blocking of nucleic acid synthesis of bacteria leading to stopping of their multiplication and killing of them<sup>(8)</sup>.

Hyaluronic acid is glycolaminoglycan found in the connective tissue of vertebrate, it is essential component of periodontal ligament matrix and play various important roles in cell adhesion, migration and differentiation. It also possess anti-inflammatory, anti-edematous and bacteriostatic effect on different bacterial strains including Aggregatibacter actinomycetemcomitans (Aa) and Porphyromonas gingivalis (P.gingivals)<sup>(9)</sup>. It possess cellular and ex-

tracellular interaction with growth factor and regulation of osmotic pressure and tissue lubrication, all these functions help in maintaining the structure and homeostatic integrity of the tissue<sup>(10)</sup>.

So, the primary research question in the present study was that: upon the proved efficacy of both metronidazole and hyaluronic acid separately as adjunctive periodontal therapy and the antibacterial effect of the combination, does the use of the combination as adjunctive to scaling and root planning can be enhance the clinical and anti-inflammatory effects ?

## PATIENTS AND METHODS

**Patients:** Forty patients of both sex (22 females and 18 males ranged in age from 30 -45 years ) with stage I to stage II, grade A periodontitis. All patients were selected from those attending at the outpatient clinic, Oral Medicine and Periodontology Department, Faculty of Dental Medicine, Al-Azhar University, Assiut Branch. All patients were thoroughly informed of the nature, potential risks and benefits of their participation in the study and signed their informed consent documents. The study protocol was approved by the ethical committee, Faculty of Dentistry, Al-Azhar University.

**Inclusion criteria:** All patients were free from any systemic diseases according to the criteria of Cornell Medical Index and its modification<sup>(11-13)</sup>, with stage I to stage II, grade A periodontitis. Stage I have CAL 1 to 2mm with no tooth loss and probing depth  $\leq 4$  mm. Stage II have CAL 3 to 4mm with no tooth loss and probing depth  $\leq 5$  mm. Grade A: no evidence of CAL or bone loss over 5 years, the patient is nonsmoker and no evidence of diabetes.

**Exclusion criteria:** Uncooperative, pregnant, lactating, smokers patients, who received antibiotics and non-steroidal anti-inflammatory during at least 3 months prior to sample collection, patients subjected to previous periodontal therapy during at least 6 months.



**Patients grouping:** The selected patients were divided randomly into four equal groups:

**Group I:** included 10 patients with stage I to stage II, grade A periodontitis patients were treated by conventional periodontal therapy (scaling and root planing) alone.

**Group II:** included 10 patients with stage I to stage II, grade A periodontitis were treated by conventional periodontal therapy (scaling and root planing) combined with intra pocket application of hyaluronic acid gel (GENGIGEL) 0.2% (fig 1A).

**Group III:** included 10 patients with stage I to stage II, grade A periodontitis patients were treated by conventional periodontal therapy (scaling and root planing) combined with intra pocket application of metronidazole 25%.

**Group IV:** included 10 patients with stage I to stage II, grade A periodontitis were treated by conventional periodontal therapy (scaling and root planing) combined with intra pocket application of combination of hyaluronic acid 0.2% and metronidazole 25%.

**Periodontal treatment:** All patients were received phase I periodontal therapy and full-mouth scaling and root planing was performed in one or two visits without the use of adjunct disinfectants.

After conventional periodontal treatment, the teeth were isolated by cotton rolls for intra pocket application of hyaluronic acid (GENGIGEL) 0.2% in group II, metronidazole gel 25% in group III and combination of hyaluronic acid 0.2% and metronidazole 25% in group IV. Application was repeated after 7 days.

**Clinical evaluation:** The patients of all groups were evaluated clinically at baseline, 3 and 6 months using the following parameters plaque index (PI), gingival index (GI), probing depth (PD) and clinical attachment level (CAL) (fig 1B).

**Biochemical evaluation:** Gingival crevicular fluid (GCF) samples were obtained from the site which showed the highest probing depth (range 3-6 mm) and CAL less than 5mm at baseline, 1 and 3 months. The samples were assayed for IL1  $\beta$  levels using commercially available enzyme-linked immune-sorbent assay (ELISA) according to the manufacturer's instructions.

### Statistical analysis

The mean and standard deviation values were calculated for all groups in each test. The significance level was set at  $P \leq 0.05$ . Statistical analysis was performed with SPSS Statistics version 22 for windows (Fig. 1a&b).



Fig. (1A) A clinical photograph showing intrapocket application of hyaluronic acid gel



Fig. (1b) A clinical photograph showing probing pocket depth measurement by William's probe.

## RESULTS

Forty patients with stage I to stage II, grade A periodontitis with probing pocket depth (PPD)  $\leq 5$  mm and CAL 1-4 mm were selected to be included in the perest study. The patients were divided randomly into four groups; group I received SRP alone, group II received SRP with intra pocket application of HA gel (GENGIGEL) 0.2%, group III received SRP with intra pocket application of MTZ (25%) and group IV received SRP with intra pocket application of combination of HA (0.2%) and MTZ (25%). The results of paired and unpaired sample t-tests of the clinical and biochemical parameters are illustrated in tables 1 and 2.

### Plaque Index

Paired sample t-test showing statistically significant differences in all groups at the different intervals when compared to the baseline while unpaired t-test representing statistically significant differences between (group I) and (group IV) at 6 month, (group II) and (group III) at 3 months and (group II)

and (group IV) at 6 months but there was no statistically significant difference between four groups at base line.

### Gingival Index

Paired sample t-test showing statistically significant differences in all groups at the different intervals when compared to the baseline while unpaired t-test representing no statistically significant differences between the four groups.

### Probing pocket depth

Paired sample t-test showing a statistically significant differences in all groups at the different intervals when compared to the baseline while unpaired t-test representing a statistically significant differences between (group I) and (group II) at 3 and 6 months, (group I) and (group IV) at 3 and 6 months, (group II) and (group IV) at 3 and 6 months, (group III) and (group IV) at 3 and 6 months but there was no statistically significant difference between four groups at base line.

**Table (1)** Illustrating mean  $\pm$  SD values of probing depth, clinical attachment loss, and interleukin 1-beta among studied groups at each evaluation period with significance level using paired t- test.

Clinical parameters	CAL						IL 1Beta												
	Baseline		3 months		6 Months		Baseline		1 month		3 Months								
G1	3.55 $\pm$ 0.42	2.72 $\pm$ 0.32	2.60 $\pm$ 0.29	2.07 $\pm$ 1.73	1.37 $\pm$ 0.24	0.95 $\pm$ 0.32	1.69 $\pm$ 0.51	1.19 $\pm$ 0.36	1.04 $\pm$ 0.29										
G2	3.67 $\pm$ 0.44	2.40 $\pm$ 0.24	2.30 $\pm$ 0.19	2.12 $\pm$ 1.17	1.17 $\pm$ 0.29	0.67 $\pm$ 0.20	1.87 $\pm$ 0.48	0.94 $\pm$ 0.35	0.96 $\pm$ 0.53										
G3	3.62 $\pm$ 0.50	2.45 $\pm$ 0.28	2.37 $\pm$ 0.24	2.10 $\pm$ 1.20	1.20 $\pm$ 0.28	0.70 $\pm$ 0.19	1.86 $\pm$ 0.48	1.00 $\pm$ 0.23	0.94 $\pm$ 0.37										
G4	3.67 $\pm$ 0.57	2.02 $\pm$ 0.21	1.90 $\pm$ 0.17	2.12 $\pm$ 1.07	1.07 $\pm$ 0.20	0.55 $\pm$ 0.19	1.97 $\pm$ 0.32	0.76 $\pm$ 0.24	0.72 $\pm$ 0.29										
Paired t-test	T	P	T	P	T	P	T	P	T	P	T	P	T	P	T	P	T	P	
GI VS Gil	-0.64	0.52	2.55	0.02*	2.68	0.01*	-0.34	0.73	1.76	0.11	2.24	0.03*	-0.77	0.44	1.15	0.13	0.43	0.66	
GI VS Gill	-0.36	0.72	2.02	0.05	1.86	0.07	-0.14	0.88	1.48	0.15	2.06	0.05	-0.76	0.45	1.43	0.16	0.66	0.51	
GI VS IV	-0.55	0.58	5.68	0.00*	6.48	0.00*	-0.34	0.73	2.97	0.008*	3.29	0.004*	-1.44	0.16	3.14	0.006*	2.45	0.02*	
Gil VS Gill	0.23	0.81	-0.42	0.67	-0.75	0.45	0.17	0.86	-0.19	0.84	-0.27	0.78	0.01	0.99	-0.38	0.70	0.07	0.93	
Gil VS IV	0.00	1.00	3.63	0.002*	4.80	0.00*	0.00	1.00	0.88	0.38	1.38	0.18	-0.57	0.57	1.39	0.18	1.23	0.23	
Gill VS GIV	-0.20	0.83	3.75	0.001*	5.01	0.00*	-0.17	0.86	1.12	0.27	1.70	0.10	-0.58	0.56	2.24		1.49	0.15	



**Table (2)** Illustrating significance of probing depth, clinical attachment loss, and interleukin 1-beta among studied groups using unpaired t- test.

Clinical parameters	PD						CAL						IL 1Beta					
	Baseline vs 3 month		Baseline vs 6 months		3 month vs 6 Months		Baseline vs 3 month		Baseline vs 6 months		3 month vs 6 months		Baseline vs 1 month		Baseline vs 3 months		1 month vs 3 Months	
Un Paired t-test	T	P	T	P	T	P	T	P	T	P	T	P	T	P	T	P	T	P
G1	15.46	0.000*	9.77	0.000*	1.86	0.096	9.63	0.000*	7.73	0.000*	3.79	0.004*	2.89	0.018*	3.02	0.014*	0.83	0.427
G2	13.47	0.000*	11.52	0.000*	1.50	0.169	11.63	0.000*	19.95	0.000*	5.07	0.001*	9.38	0.000*	4.61	0.001*	-0.05	0.958
G3	6.29	0.000*	8.66	0.000*	0.66	0.52	9.00	0.000*	11.22	0.000*	6.70	0.000*	6.36	0.000*	5.12	0.001*	0.46	0.656
G4	9.00	0.000*	9.26	0.000*	1.62	0.138	14.45	0.000*	17.18	0.000*	6.67	0.000*	8.80	0.000*	9.24	0.000*	0.46	0.00*

### Clinical attachment level

Paired sample t-test showing a statistically significant differences in all groups at the different intervals when compared to the baseline while unpaired t-test representing a statistically significant differences between (group I) and (group II) at 6 months and (group I) and (group IV) at 3 and 6 months but there was no statistically significant difference between four groups at base line.

### Interleukin 1-beta level

Paired sample t-test showing a statistically significant difference in all groups at the different intervals when compared to the baseline unpaired t-test representing a statistically significant difference between (group I) and (group IV) at 1 and 3 months and (group III) and (group IV) at 1 months but there was no statistically significant difference between four groups at base line.

## DISCUSSION

Periodontitis is an inflammatory disease result from dysbiotic relationship between the host and oral microbiome, causing destruction of soft and hard tissues and eventually lead to tooth loss<sup>(14)</sup>.

Pro-inflammatory cytokines play an important role in initiating and regulating immune responses

in the periodontium which lead to periodontal inflammation and tissue injury<sup>(15)</sup>.

Interleukin-1beta (IL-1 $\beta$ ) is considered a strong stimulator of periodontal tissue destruction. It play a major role in the pathogenesis of periodontitis as a potent inducer of bone resorption and connective tissue degradation via up regulating the secretion of matrix metalloproteinases (MMPs), and increasing osteoclastogenesis. In addition it is an important GCF biomarker strongly associated with periodontitis severity, progression, tooth loss, disease recurrence, and success of periodontal therapy as concluded by another study<sup>(16)</sup>.

Non-surgical periodontal treatment remain the cornerstone and the first approach as the initial phase to control periodontal inflammation, however it was showed to have significant limitations due to difficult to reach deepest sites, not sufficient to completely eradicate the periodontal pathogens and bacterial recolonization occurs soonly<sup>(17)</sup>. So; most studies recommended the use of different types of adjunctive local delivery system in an attempt to support the basic treatment and in the same time to keep the periodontal treatment more effective<sup>(18)</sup>.

Although the local route of drug delivery have a lot of advantages which can attain 100-fold higher concentrations of an antimicrobial agent in sub-gingival sites compared with a systemic drug

regimen but these agents have some limitation because its short term effects and may cause allergic reaction <sup>(19)</sup>.

Hyaluronic Acid (HA) has been used lately as one of the local chemotherapeutic agents in the treatment of oral diseases. It participates in tissue repair and wound healing added to its anti-inflammatory and anti-edematous action as the result obtained by previous studies<sup>(20,21)</sup>.

For long time, MTZ was used for treatment of periodontitis because it specifically has bactericidal action against anaerobic microorganisms, that are well known to be the chief pathogens related to periodontitis as confirmed in most studies <sup>(22)</sup>.

The present study was designed to evaluate the clinical and biochemical effects of combination of hyaluronic acid and metronidazole as an adjunctive treatment of periodontitis, because it has been reported that using HA alone may not be effective enough but a combination with an antimicrobial drugs (e.g., MTZ) may provide a synergistic and a long positive effect <sup>(23)</sup>.

With reference to periodontal probing pocket depth, the results of the present study showed that sub-gingival application of HA after full mouth SRP had statistically significant reduction in PD at 3 and 6 months, as compared to control group this similar to the results were obtained by previous studies which revealed that non-surgical treatment with adjunctive HA resulted in additional PD reduction compared with conventional scaling and root planning <sup>(24,25)</sup>.

The present study found that, there is significant clinical attachment level gain at 6 months observation period in group II when compared with control one. This finding is consistent with the results of a similar study <sup>(26)</sup>.

The present research showed that there is no significant differences in all clinical parameters between group III and control one and this is parallel to the result obtained by similar studies which showed that the local application of 25%

metronidazole gel does not improve the outcome of therapy compared to SRP alone, and in contrary to the findings reported by another studies which concluded that SRP plus sub-gingival application of 25% metronidazole gel was superior to the conventional treatment of SRP alone <sup>(27,28)</sup>.

From the findings of this study, with regard to the studied clinical parameters, there was a statistically significant reduction in all clinical parameters in all studied groups during evaluated periods when compared with baseline but during the inter-group comparison, maximum reduction in probing pocket depth and clinical attachment level were observed in group IV. This maximum change could be attributed to the synergistic and antimicrobial effects of both HA and MTZ in this group <sup>(29)</sup>. Several studies which used combined therapies for the treatment of periodontal infections have been shown to be successful when compared with SRP alone or SRP with HA or MTZ <sup>(30,31)</sup>.

With regard to changes in biochemical parameters, this study found that there was marked decrease in the level of IL-1 $\beta$  in all groups at the different intervals when compared to the base line this result is parallel to the findings of several studies and the maximum reduction of IL-1 $\beta$  level was observed in the group IV, this in agreement with results reported by previous studies<sup>(32,33)</sup>.

## CONCLUSION

The combination of hyaluronic acid and metronidazole achieve the most superior clinical and biochemical outcomes in the treatment of periodontitis. Conventional periodontal therapy alone or with adjunctive periodontal therapy by hyaluronic acid, metronidazole or combination of both have the ability to improve both clinical outcomes and GCF level of IL-1 $\beta$  with variables degrees. Interleukin-1beta (IL-1 $\beta$ ) is a good biomarker to determine periodontal disease activity and to evaluate the outcome following periodontal treatment.



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# الأزهر

## مجلة أسبوط لطب الأسنان

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مصر

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## فعالية الجمع بين حمض الهيالورونيك والميترونيدازول كمساعد موضعي في العلاج غير الجراحي لالتهاب دواعم السن {دراسة إكلينيكية وكيميائية حيوية}

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### الملخص :

**الهدف:** صممت هذه الدراسة لتقييم الآثار السريرية والكيميائية الحيوية لتوليفة حمض الهيالورونيك والميترونيدازول كعلاج مساعد لالتهاب دواعم السن.

**المواد والاساليب:** تم اختيار أربعين مريضاً من المرحلة الأولى إلى الثانية من التهاب دواعم الأسنان من الدرجة الأولى من العيادة الخارجية . قسم طب الفم والأسنان . كلية طب الأسنان . جامعة الأزهر . فرع أسيوط. تم تقسيمهم إلى أربع مجموعات متساوية. تلقت المجموعة الأولى العلاج اللثوي التقليدي وحده . تلقت المجموعة الثانية علاجاً تقليدياً للثة مع تطبيق داخل الجيب لهلام حمض الهيالورونيك (0.2% GENGIGEL) . تلقت المجموعة الثالثة علاجاً تقليدياً للثة مع تطبيق داخل الجيب للميترونيدازول (25%) وتلقت المجموعة الرابعة علاج دواعم الأسنان التقليدي العلاج باستخدام داخل الجيب من مزيج حمض الهيالورونيك (0.2%) وميترونيدازول (25%). تم تقييم جميع المرضى سريرياً في الأساس . 3 و 6 أشهر وتم إجراء التقييم الكيميائي الحيوي في الأساس . 1 و 3 أشهر لتقييم مستوى IL-1B في GCF

**النتائج:** أظهرت جميع المجموعات فروق ذات دلالة إحصائية في فترات مختلفة في جميع المتغيرات السريرية (PI . GI . PD . CAL) ومستوى IL-1B في GCF. أظهرت المقارنة بين المجموعات فيما يتعلق بالمتغيرات السريرية والكيميائية الحيوية أن الهلام المختلط كان الأفضل.

**الخلاصة:** حقق مزيج حمض الهيالورونيك والميترونيدازول تأثيرات فائقة كعلاج مساعد في تحسين المعايير السريرية والكيميائية الحيوية في علاج التهاب اللثة.

**الكلمات المفتاحية:** حمض الهيالورونيك، الميترونيدازول، محفظ موضعي، لالتهاب دواعم السن، المؤشرات الكيميائية الحيوية