

Hyaluronic Acid as an Adjunct to Chlorhexidine Mouthwash in Managing Gingivitis: Randomized Clinical Trial

Ácido hialurónico como coadyuvante del enjuague bucal
con clorhexidina en el tratamiento de la gingivitis: ensayo clínico
aleatorizado

Heba Samir¹ <https://orcid.org/0009-0003-7253-7261>

Ayat Gamal-AbdelNaser^{1*} <https://orcid.org/0000-0003-3564-8539>

Mohamed Osama¹ <https://orcid.org/0009-0007-3554-2474>

Mohamed Kamal¹ <https://orcid.org/0009-0001-1469-1434>

AbdElRahman AbdElAtty¹ <https://orcid.org/0009-0009-5933-923X>

Areej Ahmed¹ <https://orcid.org/0009-0006-4403-9486>

Amira Khaled¹ <https://orcid.org/0009-0002-9769-1428>

Doaa Abdelmonaim¹ <https://orcid.org/0009-0002-3464-1984>

Rania Ahmed¹ <https://orcid.org/0009-0000-8784-4561>

Marwa Elsayed¹ <https://orcid.org/0009-0001-8863-3325>

¹Ahram Canadian University, Faculty of Oral and Dental Medicine, Oral Medicine and Periodontology Department. Giza, Egypt.

*Corresponding author: ayat.gamal@dentistry.cu.edu.eg.

ABSTRACT

Introduction: Gingivitis is one of the most common periodontal diseases. Chlorhexidine represents one of the most frequently used mouthwashes. Hyaluronic acid has anti-inflammatory, anti-edematous and antimicrobial effects beside

improved tissue healing. The combined effect of the two mouthwashes was not investigated before.

Objective: To explore the efficacy of the use hyaluronic acid (HYL) mouthwash as adjunct to Chlorhexidine (CHX) mouthwash compared to Chlorhexidine mouthwash alone in gingivitis patients.

Methods: Sixteen gingivitis patients were randomly assigned to either control group (receiving CHX) or test group (receiving HYL+CHX) after supragingival scaling was performed. Clinical parameters (bleeding on probing (BoP) and plaque index (PI)) and patient-reported outcomes were assessed at baseline and seven days post-operatively.

Results: Intragroup analysis showed significant improvement of BoP (p-value=0.014 for each; intervention and control) and of PI p-value=0.014 for each; intervention and control); but they failed to reach significant level in intergroup analysis (BoP=0.57; PI=0.96). Post-operative questionnaire revealed non-significant results.

Conclusions: Adding HYL to CHX showed comparable results to CHX alone regarding reduction of bleeding on probing and plaque index.

Keywords: mouthwashes; patient satisfaction; gingivitis; taste alteration.

RESUMEN

Introducción: La gingivitis es una de las enfermedades periodontales más comunes. La clorhexidina es uno de los enjuagues bucales más utilizados. El ácido hialurónico tiene efectos antiinflamatorios, antiedematosos y antimicrobianos, además de favorecer la cicatrización de los tejidos. El efecto combinado de ambos enjuagues bucales no se había investigado anteriormente.

Objetivo: Explorar la eficacia del uso de enjuague bucal de ácido hialurónico (HYL) como complemento del enjuague bucal de clorhexidina (CHX) en comparación con el enjuague bucal de clorhexidina solo en pacientes con gingivitis.

Métodos: Se asignó aleatoriamente a dieciséis pacientes con gingivitis al grupo de control (que recibió CHX) o al grupo de prueba (que recibió HYL+CHX) tras realizar

un raspado supragingival. Se evaluaron los parámetros clínicos (sangrado al sondaje [BoP] e índice de placa [PI]) y los resultados comunicados por los pacientes al inicio del estudio y siete días después de la intervención.

Resultados: El análisis intragrupal mostró una mejora significativa del BoP (valor $p = 0,014$ para cada uno; intervención y control) y del PI (valor $p = 0,014$ para cada uno; intervención y control); pero no alcanzaron un nivel significativo en el análisis intergrupar (BoP = 0,57; PI = 0,96). El cuestionario postoperatorio reveló resultados no significativos.

Conclusiones: La adición de HYL al CHX mostró resultados comparables a los del CHX solo en cuanto a la reducción del sangrado al sondaje y del índice de placa.

Palabras clave: enjuagues bucales; satisfacción del paciente; gingivitis; alteración del gusto.

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Introduction

Gingivitis is a highly prevalent inflammatory condition that is limited to the gingival tissue. It manifests as gingival bleeding either spontaneously or upon gentle probing, gingival swelling, redness and edema; but without loss of the tooth supporting tissues or migration of junctional epithelium. If left untreated, it progresses to a more destructive condition -namely, periodontitis- which ultimately results in tooth loss. However, gingivitis is characterized by being a reversible and controllable condition.^(1,2)

Dental plaque represents the main etiological factor causing plaque-induced gingivitis. In this condition, gingival inflammation is driven by microbial dysbiosis, where disruption of the normal oral microbial balance allows pathogenic bacteria to dominate allowing for disease progression. Therefore, plaque control represents the

key strategy of managing gingivitis and preventing periodontitis. It is accomplished through both dental professional supra-gingival scaling and self-practiced plaque control.^(3,4)

Therefore, the patient is educated to perform mechanical plaque control via regular tooth brushing and using interdental cleaning devices. Besides, chemical plaque control through mouthwashes provides an added benefit to tooth brushing especially when it is difficult to some patients to maintain adequate plaque control.^(3,5)

Chlorhexidine digluconate (CHX) mouthwash is regarded as the gold standard of plaque control. This unique effect could be ascribed to its substantivity that belongs to its antibacterial action.⁽⁶⁾ On the other hand, Hyaluronic acid (HYL) has been proposed as an alternative for CHX due to its remarkable anti-inflammatory, anti-edematous and tissue healing capacities.⁽⁷⁾ The topical use of a HYL-containing preparations provides marked clinical improvement in periodontal diseases with no reported adverse effects.^(8,9,10,11)

Adding the anti-inflammatory, anti-edematous and tissue healing capacities of HYL to the potent antibacterial power of CHX is expected to provide more favorable results than either of the mouthwashes when used separately. This combination has been previously tested for tissue healing after various oral surgeries;^(12,13) but not for treating gingivitis. Therefore, this pilot study was conducted to explore the clinical effect and the patient's response to mouthwashes containing a combination of HYL and CHX in the treatment of gingivitis patients compared to mouthwash containing CHX only.

Methods

Study settings

The present pilot randomized clinical trial included 16 patients who were recruited from the outpatient clinic, faculty of Oral and Dental Medicine, Ahram Canadian

University, Egypt; from February to May 2025. The study protocol was registered on *Clinicaltrials.gov* (NCT07366398). The study protocol was approved by the institutional review board (IRB00012891#125). Study steps followed the declaration of Helsinki and its amendments. Informed consents were obtained by all study participants after approving of participating. The study is reported following the CONSORT guidelines.⁽¹⁴⁾

Participants

The study included systemically healthy adult patients (≥ 25 years old) who were diagnosed with plaque-induced gingivitis on intact periodontium according to the latest classification of periodontal diseases.⁽¹⁾ Diagnosis of gingivitis cases were confirmed based on the following criteria:

1. Full mouth bleeding on probing $\geq 10\%$.
2. Full mouth Plaque index recorded.
3. Probing depths ranges (1-3mm) with absence of clinical attachment loss for all sites.
4. Localized gingivitis was defined as BoP 10-30%; while generalized as $>30\%$.
5. Absence of any previous periodontal disease or treatment.

On the other hand, pregnant or lactating females and current smokers were excluded. Besides, cases of periodontitis were excluded based on the following criteria:

1. Evidence of clinical attachment loss and radiographic bone loss.
2. Probing depths ≥ 4 mm with BoP at any site.
3. Previous history of periodontal disease and treatment.

Study groups

Patients were screened consecutively by the order of their entry to the clinic until the

target sample was achieved to prevent selection bias. Eligible patients received clear description of the detailed procedures and follow up periods. After obtaining a signed informed consent, the gingivitis patients were randomly assigned into two equal groups (n=8); both were treated by supra-gingival scaling followed by prescribing a certain mouthwash. Patients assigned to the intervention group (n=8) received mouthwash containing hyaluronic acid and chlorhexidine; while patients assigned to the control group (n=8) received mouthwash containing chlorhexidine only. All patients were re-evaluated after seven days.

Allocation concealment and randomization

A random sequence was prepared before the study using Microsoft Excel software by a third party. Then, the allocations were sequentially placed in opaque sealed envelopes following the random sequence and the outer sides of the envelopes were numbered from one to 16. For each participant, the envelope in order was opened by the supervisor after finishing supragingival scaling to the patient and immediately prior to prescribing the mouthwash. In other words, the operator was blinded to the patient's allocation group till the scaling procedure was finished. The outcome assessor and the statistician were blinded along the study.

Before starting the study, each of the seven operators performed supragingival scaling to five volunteers for calibration. The outcomes were also measured and re-measured by each operator with interval of 40 minutes; and also cross-measured by the other six operators for validation and calibration. Inter-examiner and intra-examiner reliability was within acceptable range (Kappa coefficient >0.8). Measurements indicated validity levels ($r=0.82$) that would support robust outcome measures.

Interventions

Supra-gingival scaling was performed by manual and ultrasonic scalers. Detailed oral hygiene instructions were explained to the patients including the brushing technique used (modified bass) and using a soft tooth brush twice daily.

The control group received CHX mouthwash (0.12%chlorhexidine gluconate; DG- Care wash clove mouth, Al Esraa pharmaceutical Optima, A.R.E); while the intervention group received a mouthwash that contains both HYL with CHX (hyaluronic acid, Chlorhexidine; Orovex- H, MACRO pharmaceuticals- A.R.E). Patients of both groups were instructed to rinse effectively with 20 mL of the undiluted mouthwash (CHX or CHX+HYL) twice daily after 30 minutes from brushing for about 60 seconds; then expectorating. They were also instructed to refrain from eating, drinking or rinsing for another 30 minutes after using the mouthwash. This routine was to be followed for 1 week after scaling.

Outcomes

The study assessed the clinical results of gingivitis and the patients' experience and preference to the mouthwash used. All outcomes were assessed by an independent blinded investigator after following the treatment protocols by seven days.

The primary outcome of the study was bleeding on probing (BoP) evaluated using William's graduated probe with markings at 1, 2, 3, 5, 7, 8, 9, and 10 mm. Probing was conducted with the probe tip parallel to the long axis of the tooth, using a walking stroke technique and a controlled insertion force. BoP was expressed in the form of the percentage of number of sites where bleeding was recorded.⁽¹⁵⁾

Clinical outcomes included O'Leary's plaque index (PI) expressed as percentage of sites of plaque accumulation in the oral cavity.⁽¹⁶⁾

BoP and PI were recorded at 6 sites per tooth (mesio-buccal, mid- buccal, disto-buccal, mesio-palatal, mid- palatal and disto-palatal). All present teeth were examined, including the third molar on condition of being functional or fully erupted. Furthermore, the patient's experience to the mouthwash was assessed by a pre-validated questionnaire of seven questions.^(9,17) Each question was answered on a visual analogue scale in the form of a 10-cm long line; with 0 (far left side of the line) denoting the most negative experience and ten (far right side) indicating the extreme positive response.

Statistical Methods

Statistical analysis was performed using SPSS (version 20). Quantitative variables were described by the mean and standard deviation (SD); while qualitative categorical variables were represented as absolute count and frequency. Normality of data was tested using Shapiro-Wilk test. Mann-Whitney U test was used for comparing means of the two groups at base line and after 7 days. Wilcoxon test was used to compare pre- and post-operative results of the same group. All randomized participants completed follow-up and were included in the final analysis. Significance level is considered at $p < 0.05$.

Sample size was calculated using G power software Version 3.1. Based on the results of a previous study,⁽¹⁸⁾ the mean values of the 2 groups in bleeding on probing (BoP) was 0.75 ± 0.46 for HA and 1.59 ± 0.45 for CHX; providing effect size of 1.85. Adding these parameters with power 80% and 5% significance level, a total sample size of 12 patients (6 patients per group) was required. The sample size was increased by 25% to be total of 16 patients (8 patients per group) to compensate for drop outs during follow up.

Results

Baseline data

The study included 16 patients diagnosed with gingivitis with equal participation of both sexes (8 males and 8 females). The mean age of the intervention group was 25.5 (± 8.73) years; compared to 23.1 (± 5.16) years for the control group with no statistically significant difference between the two groups ($p = 0.9$). All patients completed the follow up period with no drop outs. All participants complied to the assigned mouthwash with no change in protocol. This is clarified in the CONSORT flow diagram (fig.). The follow up period was finished uneventfully with no harm or adverse events to any of the participants.

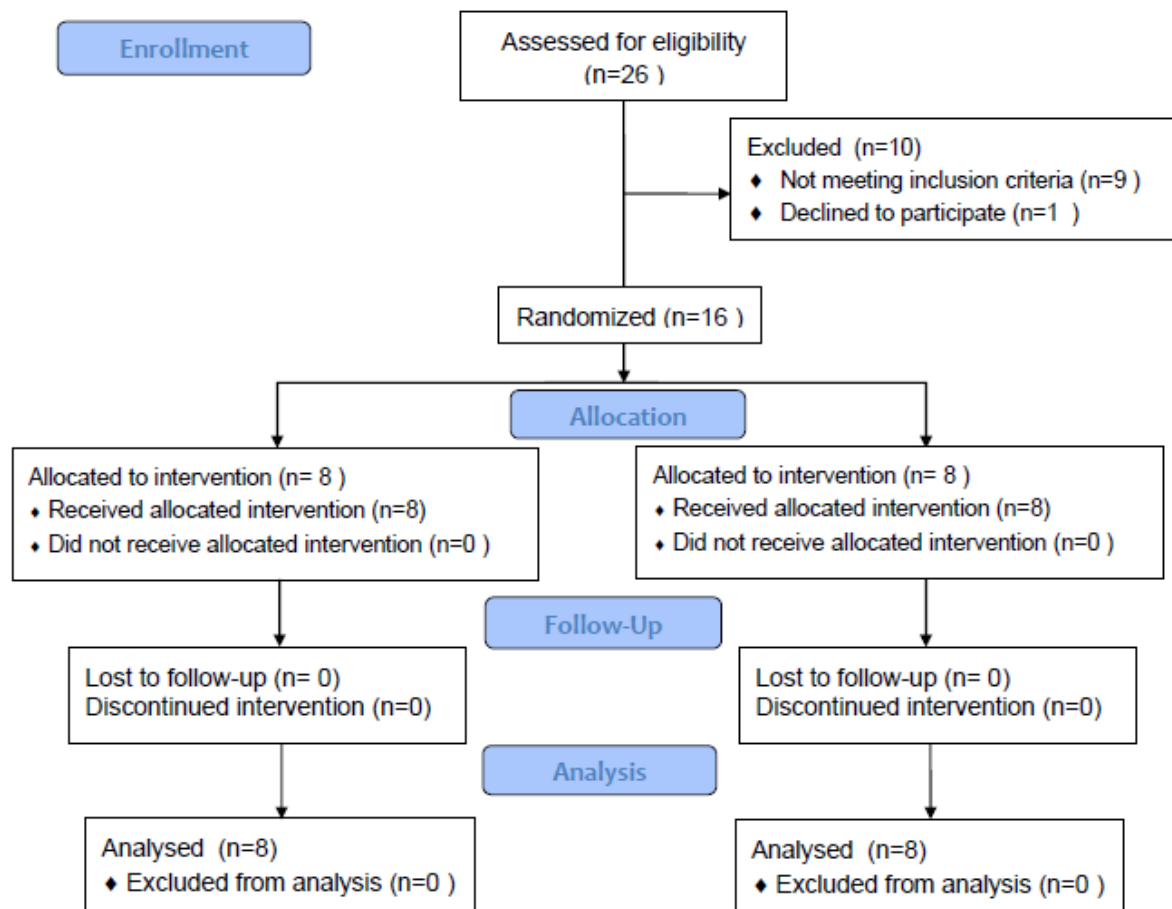


Fig. - CONSORT flow diagram of the study.

Outcomes

Bleeding on probing (BoP)

No significant difference was detected between the BoP scores of both groups at baseline ($p=0.95$) or at follow up ($p=0.64$). On the other hand, the mean difference of BoP –which represents the improvement of BoP– was a bit higher in the intervention group (HA+CHX) but not significantly different between the groups ($p=0.57$). However, Intragroup analysis revealed that each of the intervention and the control groups showed statistically significant difference in BoP before and after treatment ($p=0.014$ each) (table 1)

Table 1 - Clinical outcomes of bleeding on probing and plaque indices for the two study groups

BoP	BoP [mean(SD)]			
	Baseline	After 7 days	p-value†	Mean difference
HYL+CHX	0.48 (0.19)	0.31 (0.2)	0.014*	0.17 (0.1)
CHX	0.41 (0.15)	0.27 (0.18)	0.014*	0.14 (0.12)
p-value**	0.95	0.64		0.57
PI	PI [mean(SD)]			
	Baseline	After 7 days	p-value†	Mean difference
HYL+CHX	0.62 (0.19)	0.35 (0.16)	0.014*	0.26 (0.12)
CHX	0.63 (0.24)	0.34 (0.09)	0.014*	0.29 (0.25)
p-value**	0.96	0.79	-	0.96

Legend: *Significant at $p < 0.05$; ** Mann-Whitney U test; † Wilcoxon test.

Plaque index(PI)

Intergroup comparison at baseline and at follow up did not reveal statistically significant difference ($p=0.96$ and 0.79 respectively). Similarly, the change in PI was not significantly different between the groups ($p=0.96$). Nonetheless, each of the intervention and the control groups showed statistically significant improvement in PI after treatment ($p=0.014$ each) (table 1).

Patient-reported outcome

Responses of patients to the questionnaire of their experience regarding the mouthwash revealed statistically non-significant results (table 2).

Table 2 - Results [means (SDs)] of the questionnaire for the two groups

Patient-reported questionnaire results	HYL+CHX	CHX	p-value**
How was the taste of the product?	7.6 (2.5)	6.1 (3.1)	0.32
How long did the taste remain in the mouth after rinsing?	7.3 (1.4)	7 (1.7)	0.72
How was your taste of food and drinks affected?	7.25 (1.9)	7.25 (1.8)	0.79
Was the use of the mouthwash convenient?	8.12 (1.45)	8 (2.3)	0.72

What is your opinion about the rinsing time?	7.62 (1.9)	6.87 (2.2)	0.5
What was your perception of the plaque reduction?	8.4 (1.8)	7.5 (1.5)	0.23
Do you think the product affect the shade of your teeth?	8.5 (0.9)	8.4 (1.3)	0.95

Legend: *Significant at $p < 0.05$; ** Mann-Whitney U test.

Discussion

Gingivitis is one of the most common periodontal diseases which is crucially managed in order to prevent progress into periodontitis with further attachment destruction and ultimately tooth loss.⁽¹⁹⁾ Management takes place through mechanical as well as chemical plaque control. For chemical plaque control, CHX mouthwash is approved as the gold standard.⁽⁶⁾ Besides, HYL mouthwashes proved efficacy in comparison to CHX.^(8,9,10,11,12)

The adjunctive use of HYL with CHX has been previously tested for its impact on healing of implants⁽¹³⁾ and post-operative to periodontal flap surgeries.⁽¹²⁾ However, to the best of our knowledge, it was not previously investigated in managing gingivitis. Therefore, the current short-term pilot study aims to evaluate the impact of using HYL as an adjunct to CHX in managing gingivitis in comparison to the regular use of CHX alone.

In the present study, CHX mouthwash was utilized with concentration of 0.12% as the optimal concentration was proven to range between 0.1% and 0.2%; provided that the volume and duration of rinsing is standardized. Concentrations lower than 0.1% have low level of bacteriostatic effect; which is insufficient to minimize gingivitis. Furthermore, increasing the duration of rinsing for 30 to 60 seconds enhances the substantivity of CHX.^(20,21)

On the other hand, HYL is suggested as a promising adjunct to CHX owing to its anti-edematous, anti-inflammatory actions which assist in tissue regeneration and accelerated healing.⁽⁷⁾

Patients assigned to both groups were instructed to follow the oral hygiene measures and use the mouthwash. They were assessed after following this routine

for 7 days. This was based on the established success of the short-term use of mouthwashes (4-7 days) in controlling gingivitis.^(22,23,24)

Both arms of the study were assessed by clinical methods through BoP and PI. Besides, patient-reported outcomes were evaluated in the form of the patient's evaluation of the mouthwash used. Results of the current study revealed a significant improvement in clinical parameters of BoP and PI after using each of the two mouthwashes: HYL+CHX ($p=0.014$ each) and CHX alone ($p=0.014$ each).

However, comparing between both groups' mean differences of BoP and PI showed insignificant difference ($p=0.57$ and 0.96 respectively). Although insignificant, the mean difference of BoP was slightly higher in the intervention group; while PI improvement was slightly higher in the control group. BoP denotes the level of gingival inflammation; therefore, its superior results when HYL was added suggests the added positive action of HYL as a previously proven anti-inflammatory agent.⁽²⁵⁾ Besides, this is hypothesized to be attributed to the previous evidence in literature regarding the anti-bacterial, anti-adhesive and powerful tissue healing properties of HYL.⁽²⁶⁾ On the other hand, plaque index indicates the amount of accumulation of biofilm as the initiating factor of gingivitis. So, it is hypothesized that the reduced levels of PI in the group of CHX alone may be explained by the antibacterial and substantivity characteristics of CHX.⁽⁶⁾

The current study's significant results of intragroup analysis while insignificant results of intergroup analysis are in accordance with the previous studies that had the same study arms.^(12,13) In post-operative assessment after implant placement⁽¹³⁾ and after periodontal flap surgeries,⁽¹²⁾ CHX with and without HYL provided satisfying improvement of the clinical parameters. This is hypothesized to be ascribed to the powerful bacteriostatic effect of CHX enough to show significant results within seven days of regular rinsing.⁽²⁷⁾ Adding HYL to CHX provided better results that may have been more significant with a larger sample size.

Regarding the patient-reported outcome measures, patients answered a questionnaire to assess their experience with either mouthwashes. Recently, patient-reported outcomes draw special attention as they reflect the patient's actual

response and satisfaction to the received treatment; thereby, facilitating clinician-patient communication. By doing so, the treatment plan combines the clinician's expertise and the patient's perspective and feedback; enhancing the patient's quality of life.⁽²⁸⁾

In the present study, the patients assessed both mouthwashes as positive experiences. They evaluated the used mouthwash regarding its taste, after-taste, rinsing time and its impact on plaque reduction. In all the pre-stated criteria, the patients had more agreeable experience with the intervention group compared to the control group. However, the difference between the responses of both groups did not reach the level of statistical significance. These parameters are considered crucial; especially that altered taste is a well-documented side effect of CHX.⁽²⁹⁾ Yet, the results were not conclusive.

However, patients of both study groups responded similarly to the convenience of the mouthwash and its effect on the taste of food and drinks; and on teeth color. In all three parameters, the patients' experience was positive but was roughly the same.

Overall, the study had the novelty of being the first to test the efficacy of adding HYL to CHX in managing gingivitis. The current research not only evaluated the clinical parameters of gingival health; but also gathered the patient's perspective regarding the used treatments. However, the study faced a limitation; owing to its limited sample size as a short-term pilot study. Further studies with larger sample sizes and longer follow-up periods may achieve more significant results together with long-term effects and side effects of both mouthwashes.

Within the limitations of this short-term pilot randomized clinical trial, the study concluded that CHX with or without HYL mouthwash provide comparable short-term clinical and patient-reported outcomes.

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Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

Conceptualization: Heba Samir and Marwa Elsayed.

Investigation: Mohamed Osama, Mohamed Kamal, AbdElRahman AbdElAtty, Areej Ahmed, Amira Khaled, Doaa Abdelmonaim and Rania Ahmed.

Methodology: Heba Samir, Ayat Gamal-AbdelNaser and Marwa Elsayed.

Writing-original draft: Mohamed Osama, Mohamed Kamal, AbdElRahman AbdElAtty, Areej Ahmed, Amira Khaled, Doaa Abdelmonaim and Rania Ahmed.

Writing-review & editing: Heba Samir, Ayat Gamal-AbdelNaser and Marwa Elsayed.