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Comparative Evaluation of the Clinical Efficacy Between Hyaluronic Acid and Chlorhexidine Mouthwash on Dental Plaque and Gingival Inflammation in Adults - A Systematic Review

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Abstract: ***Background: This systematic review investigated the antiplaque and anti-inflammatory effects of CHX and HA mouthwashes. Aim: To compare the clinical efficacy between Hyaluronic acid & chlorhexidine mouth wash on dental plaque and gingival inflammation. Materials And Methods: A comprehensive search of the following search engine was performed, namely: PubMed, Cochrane, Google Scholar. A systematic search of PubMed was done. The keywords for the search included "chlorhexidine mouthwash" OR" AND "HA mouthwash" "gingivitis" "periodontitis". For Cochrane and google scholar similar strategy was used. All the search was limited to articles in English language. Results: 4 randomized controlled trails, double blinded which met the inclusion criteria covering 248 participants used chlorhexidine and hyaluronic acid mouthwash. 1 study was crossover clinical study. Conclusion: HA is as effective as CHX. In addition, based on its better acceptance by the participants, HA is potentially a good alternative to CHX, with higher effect of hyaluronic acid (HA) on plaque and gingival index.***

Keywords: Chlorhexidine, hyaluronic acid, gingivitis, periodontitis, plaque, gingival inflammation

1. Introduction

"Periodontal diseases" is a non-specific term referring to any disease or disease process affecting the periodontium. Most commonly it includes the inflammatory diseases of the periodontium which are mainly divided into gingivitis and periodontitis. Dental biofilm is, thus, recognized as the main local cause of periodontal diseases. Prevention and control of these conditions is primarily based on the self-performed plaque control and professional removal of microbial deposits at regular intervals. Mechanical plaque control methods such as the use of tooth brushes and interdentalcleaning aids are the most important and commonly used methods of removing biofilm and maintaining personal oral hygiene. However, mechanical means alonemay not be sufficient in controlling plaque and microbial deposits or preventing the reactivation of gingivitis. As a result the chemical plaque control agents were introduced. The chemical plaque control agents should be used as an adjunctive to the mechanical plaque control methods, as most of these chemical agents have proven to be effective only against the most external parts of the biofilm. Some agents such as chlorhexidine and essential oils, however, have demonstrated their efficacy in penetrating the biofilm.

CHX is the most widely used and most effective chemical agent used against oral biofilms. It has antimicrobial effects, plaque inhibitory effects, sustantivity. CHX mouthwash is the first-choice mouthwash due to its outstanding efficacy in inhibiting dental biofilm formation. However, it has a number of potential side effects, including staining, altered taste sensation. These side effects encourage the need to develop alternative mouthwashes with similar efficacy, but without these issues. Hyaluronic acid (HA) has gained wide attention because of its anti-inflammatory, bacteriostatic, anti adhesive and antioxidant properties. Therefore, this study aimed to determine the efficacy of two biologically active mouth rinses. The objective of this systematic review is to investigate the antiplaque and anti-inflammatory effects of CHX and HA mouthwashes.

2. Materials and Methods

The present systematic review was registered at the National Institute for Health Research PROSPERO International Prospective Register of Systematic Reviews. Registration number: CRD42024518009 The search protocol is designed based on the PRISMA (Preferred reporting Items for systematic Reviews and meta-analysis) guidelines 2009.

What is the difference between clinical efficacy of Chlorhexidine mouthwash and Hyaluronic acid mouthwash with regard to the dental plaque and gingival inflammation along with extrinsic staining.

S. No.	Category	Search items
1.	Population	Patients with gingivitis and/or periodontitis
2.	Intervention	Patients with gingivitis and/or periodontitis who are prescribed hyaluronic acid mouthwash.
3.	Comparator	Patients with gingivitis and/or periodontitis who are prescribedchlorhexidine mouthwash.
4.	Outcome	• Plaque Index - The amount of dental plaque visible on thevestibular and lingual surfaces of teeth. (measured after minimum 7 days) • Gingival Index - Recording the clinical severity of gingival • Inflammation. (measured after minimum 7 days) • Reduction of extrinsic staining - Discoloration of the oral mucosa and teeth measured by Tooth Staining Index

		(by Lobene, 1968) and MLSI, VAS scale, as well as clinical intraoral photographs recorded at baseline and after 14 days of usingthe mouthwash.
5.	Study design	Randomized controlled trials

Information Sources, Search Strategy and Study Selection-

A comprehensive search of the following search engine was performed, namely: PubMed, Cochrane, Google Scholar A systematic search of PubMed was done. The keywords for the search included "chlorhexidine mouthwash" OR" AND "HA mouthwash" "gingivitis" "periodontitis" For Cochrane and google scholar similar strategy was used. All the search was limited to articles in English language.

Risk of Bias/ Quality Assessment

This assessment was conducted by using the recommended approach for assessing risk of bias in studies included in Cochrane Reviews using the tool RevMan 5.4.1 We used the two-part tool to address the six specific domains (namely, sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other bias). Each domain includes one or more specific entries in a 'Risk of bias' table. Withineach entry, the first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry: either low risk, unclear risk or high risk.

Out of 4 studies, 2 studies showed low risk of bias and 2 studies showed some concerns in risk of bias.

Table: Risk of Bias Assessment

S. No	Author (Year)	Type of study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome	Incomplete outcome data	Selective reporting
1	Ali A. Abdulkareem et al 2020	Randomized Double- blind, parallel clinical trail	Yes	Yes	Yes	Not clear	Yes	Not clear
2	Santosh kumar Tadakamadla et al 2019	Double blind, three arm parallel, Randomised controlled clinical trial	Yes	Yes	Yes	Yes	No	Not clear
3	Begum Gizligoz et al 2019	Randomized, double blinded, crossover clinical study	Yes	Yes	Yes	Not clear	No	Not clear
4	Aryan A Sabri and Saeed Mohammed 2020	Comparative,randomized controlled study	Yes	Not clear	Yes	Not clear	Yes	No

3. Results

S. No	Author	Year	Country	Type of Study	Comparison Group	Control	Methodology	Conclusion
1	Ali A. Abdulkareem et al	2020	Iraq	Randomized Double-blind, parallel clinical trail	Hyaluronic acid and antioxidant mouthwash	CHX mouthwash	75 dental students with biofilm-induced gingivitis were included in the study. Clinical parameters (plaque index and bleeding on probing) and the staining effect were measured at baseline and after 7 days. In addition, a VAS-based assessment questionnaire was completed by the participants.	Significantly lowered plaque- and gingival index of control group, compared to comparison group. Both mouthwashes significantly reduced the total bleeding scores to <10% in 53% of the patients. based on its better acceptance by the participants, HA is potentially a good alternative to CHX.
2	Santosh Kumar Tadakamadla et al	2019	Australia	Double blind, three arm parallel, Randomised controlled clinical trial	Hyaluronic acid mouthwash and placebo mouthwash	CHX mouthwash	All the 75 subjects used the allocated mouthrinse twice daily for 21 days and were examined again at the end of the experimental period. Change in the score of clinical indices (oral malodour, extrinsic stains, calculus, gingivitis and plaque) was calculated and compared between the groups	There was a significant difference for change in plaque index scores between the groups. Teeth staining increased in the CHX and placebo groups but not in HA users. No significant differences were found between the three experimental groups for change in the gingival index.
3	Begum Gizligoz et al	2019	Turkey	Randomized, double blinded, crossover clinical study	Hyaluronic acid and distilled water	CHX mouthwash	33 subjects were randomly assigned into three mouthwashes. After prophylaxis they used mouthwashes on day 5, scoring of plaque index, gingival index , GCF volume	CHX showed statistically reduction in PI than HA. No statistically differences were detected between HA and CHX. HA was well accepted with better perceptions than CHX.

							were performed.	
4	Aryan A Sabri and Saeed Mohammed	2020	Iraq	Comparative, randomized controlled study	Hyaluronic acid mouthwash	CHX mouthwash	60 patients within 30-55 yrs participated in the study, divided randomly into 3groups (20 in each): 1st group received scaling and root planing followed by HA, and the 2nd group received scaling and root planing followed by CHX, and the 3rd group received scaling and root planing only. Plaque index (PI), gingival index (GI), probing pocket depth (PPD) and clinical attachment loss (CAL) were recorded at baseline and 2 months after periodontal therapy.	In all three groups a significant reduction in PI, GI, PPD and CAL were observed between base line and after two months of periodontal therapy. Use of hyaluronic acid (HA) and chlorhexidine (CHX) mouthwashes in conjunction with SRP has a significant beneficial effect on periodontal health in patients with chronic periodontitis with higher effect of hyaluronic acid (HA).

4. Discussion

Although CHX has a potent antiplaque effect and low toxicity after oral administration, unfortunately, its side effects, such as tooth staining and altered taste sensation, have been reported to discourage patient use. Tooth staining is the major side effect of rinsing with chlorhexidine mouthwash, also leading to a reduced patient compliance. . HA may offer an attractive alternative to CHX in patients where CHX can not be tolerated or is contraindicated. In addition, based on its better acceptance by the participants, HA is potentially a good alternative to CHX. This systematic review dwells upon the potential effects of HA mouthwash in reducing dental plaque and gingival inflammation. Furthermore, this evaluates extrinsic staining.

A summary of the main results is reported as primary and secondary outcomes. Primary outcome includes change in the plaque index and gingival index. Secondary or additional outcomes include reduction in the extrinsic staining on tooth surface.

The study done by Ali A. Abdulkareem et al did not evaluate the GI scores.At baseline, no significant difference (P > .05) was detected in mean PI, CHX = 1.08 ± 0.30, HA = 1.01 ± 0.21 or percent of bleeding sites among these groups. Analysis of the results showed that all interventions included in this study (CHX, Test 1, and Test 2) significantly reduced PI (P < .05) when compared to the baseline data. By contrast, HA mouthwash produced larger changes (P < .05) in PI (ΔPI = PI day1-PI day7) compared to the placebo. However, CHX showed a larger reduction in PI than did the HA mouthwash.

Santosh Kumar Tadakamadla et al stated that there was a significant difference for change in plaque index scores between the groups (estimated power 80%) with subjects in the placebo group experiencing higher levels of plaque accumulation (mean±SD: 0.047±0.05) than the test HA (0.015±0.02) and positive control CHX (0.01±0.02) groups. On post hoc comparisons after Bonferroni correction, no difference was observed between the CPC-HA and CHX groups (p=0.942). gingival inflammation increased in all the experimental groups (CPC-HA p=0.015, CHX p=0.015, but there was no differences for change in gingival index scores between the experimental groups (estimated power 70%).

In the study done by Begum Gizligoz, Both groups revealed increase in Pl values during the experimental periods. On day 5, the mean Pl values were 1.64 ± 0.31, 1.81 ± 0.21 for CHX, HA respectively. Intertreatment multiple comparisons of the mean Pl values showed a statistically significant difference (p = 0.000). Further comparisons in pairs revealed statistically significant differences between CHX and HA, CHX in favour of CHX and between HA. (p = 0.048, p = 0.001, p = 0.001, respectively). CHX showed statistically reduction in PI than HA.

Aryan a. Sabri and Saeed A. Mohammed did compared between the two groups, group A (HA mouthwash) and group B (CHX mouthwash) after two months of periodontal therapy the difference was significant P<0.005. Mean improvement of PI, GI were (1.57±0.18), (1.26 ± 0.17) respectively in group A, which was significantly (P< 0.005) higher than the mean improvement of PI, GI in group B (1.28±0.12), (0.99±0.15) respectively after two months of periodontal therapy. Hyaluronic acid (HA) and chlorhexidine (CHX) mouthwashes in conjunction with SRP has a significant beneficial effect on periodontal health in patients with chronic periodontitis with higher effect of hyaluronic acid (HA).

The extrinsic staining on tooth surface caused by chlorhexidine mouthwash & hyaluronic acid mouthwash in all the studies included in the systematic review except study done by Aryan A Sabri & Saeed Mohammed.

One of the many possible mechanisms of staining as per the manufacturer is, pertains to the protein denaturation property of CHX, which leads to the formation of organic yellow-brown ferric sulphides which in turn occurs through a combination reaction of hydrogen and sulphur with the iron that is present in saliva. The etiology of the extrinsic staining of teeth following the use of CHX is still not fully elucidated, and a number of theories have been proposed. However, the most accepted explanation is based on the interaction between adsorbed CHX and natural chromogenic components (including aldehydes and ketones) of food and beverages.

In this systematic review, the reduction of extrinsic staining is statistically significant in all the included studies except one. Study done by Ali A. Abdulkareem et al determined the staining effects by measuring shade changes, the mean shade

values recorded at the baseline were 3.77 ± 1.69 (CHX), 2.98 ± 1.03 (HA). The number of labial aspects of upper and lower anterior teeth that underwent shade changes at the end of the study was significantly higher ($P < .05$) in association with all interventions compared to their corresponding baseline data. Furthermore, the number of labial surfaces that showed a darker shade (higher shade-guide value) at the end of the study was significantly higher ($P < .05$) in the CHX and HA groups (57% and 43%, respectively). However short evaluation period & age ranges are limitations of this study, over the long-term; further studies are necessary to determine such an effect.

Study done by Santosh Kumar Tadakamadla et al there were few subjects with teeth staining. There was an increase in teeth staining in CHX (mean ± SD: 2.6 ± 3.0, $p < 0.001$) while such finding was not observed in CPC-HA users (0.16 ± 1.46, $P = 0.573$) after 21-days of mouthrinse use. Although there was a significant difference between these groups ($p = 0.004$; estimated power 75%) for change in teeth staining, no differences were observed between the pairs of groups on post-hoc comparisons.
tooth staining assessed by using Lobene stain index, which involves the examination of eight incisors (the nearest canine is examined when an incisor is missing. This was done on facial and lingual surfaces of all the incisors on two regions (tooth surface is divided into two regions; gingival area and the remaining tooth surface area called body of the tooth surface). Tooth staining was observed in both CHX and the placebo groups but not in CPC-HA group. Both placebo and CHX contained an edible colouring agent. Staining of the tongue was observed in 12% of CHX users.

By using VAS scores from questions of satisfaction questionnaire, Begum Gizligoz et al evaluated staining, favouring HA compared to CHX. Intertreatment comparison of mean VAS scores of CHX and HA mouthwash was statistically significant favoring HA.

5. Limitations

In this Systematic Review, one study has not evaluated the GI scores. the evaluation of staining effect was not done by following a standard criterion in all studies. short evaluation period & age ranges are limitations of these studies, over the long-term; further studies are necessary to determine staining effect. The duration of the experiments conducted by the included studies were not uniform. It ranges between 1 week to 9 weeks.

6. Conclusion

HA is as effective as CHX. In addition, based on its better acceptance by the participants, HA is potentially a good alternative to CHX, with higher effect of hyaluronic acid (HA) in patients with gingivitis /periodontitis.

Dental staining increased in CHX mouthrinse users but not in those using CPC-HA. Fewer subjects belonging to CPC-HA mouthrinse group reported adverse events compared to CHX, however this was not statistically significant.