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Article

Clinical efficacy of nanosilver and chlorhexidine in the treatment of plaque-induced gingivitis: a randomized controlled clinical trial.

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Abstract: Aim: The present study aimed to assess the clinical efficacy of nanosilver (NS) mouthwash and compared with chlorhexidine (CHX) mouthwash for the treatment of plaque-induced gingivitis. Materials and methods: Sixty-two (28 males and 34 females) plaque-induced gingivitis patients were allocated into two groups and asked to rinse with 10ml of NS or CHX, immediately after brushing, for 1 min, in the morning and evening. The plaque, gingival, and papilla bleeding indices were taken at baseline, two weeks, and finally at four weeks for each patient. The statistical analysis between and within groups were performed using Mann-Whitney U-test and Wilcoxon signed rank test respectively. Result: Intergroup comparison by Mann-Whitney U-test showed no statistically significant differences in the investigated groups at the baseline for all studied parameters. At 2 and 4 weeks follow up, the CHX group showed statistically significant lower plaque scores than the NS group ($p<0.05$). However, there is no statistically significant difference between NS and CHX groups for gingival and papilla bleeding scores ($p>0.05$). Both groups showed statistically significant reductions in plaque, gingival and papilla bleeding scores after 2 weeks and 4 weeks of product use when compared to baseline ($p<0.001$). Conclusion: Both mouthwashes decreased plaque, gingival and papilla bleeding scores, however the reduction in plaque scores was higher for the CHX group compared to the NS group.

Keywords: Dental plaque; gingivitis; antimicrobial mouthwash; nanosilver; chlorhexidine.

INTRODUCTION.

The oral cavity represents an environment for the coloniza¬tion and growth of many microorganisms, particularly bacteria.[1] There are more than 600 bacterial species that colonize the mouth at a concentration of 10^8–10^9 bacteria *per* ml of saliva or mg of dental plaque.[2]

It is widely accepted in dentistry that dental plaque is a key etiological factor that causes gingivitis and initiates periodontal disease.[3] Dental plaque is a dynamic complex oral biofilm consisting of bacterial toxin and carbohydrate matrices which adhere to each other and to dental surfaces.[4] Destruction of the gingival tissues is caused by interaction of a inflammatory process in the periodontal tissue and microorganisms in the dental plaque.[5]

The main objective of periodontal management is to establish

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adequate infection control through disruption of the biofilm and suppression of the inflammation. Mechanical plaque control is considered the cornerstone of plaque treatment.[6] However, mechanical plaque control requires motivation and skills. Therefore, chemical plaque control is required to overcome the insufficiency of mechanical plaque control. Consequently, antimicrobial agents have been used as adjuncts to daily oral care in the control of plaque and gingivitis.[7]

There are several types of antimicrobial agents available in the market today worldwide such as enzymes, bisbiguanides, phenolic compounds, quaternary ammonium compounds, Listerine®, cetylpyridinium chloride, delmopinol hydrochloride, triclosan, acidified sodium chlorate, salifluor, oxygenating agents, essential oils, fluoride, peroxide and chlorhexidine (CHX).[8] Ideally, it is required that any antimicrobial agent used should able to modify the oral environment by being precisely effective against pathogens without altering the normal flora. CHX in the form of a mouthwash, varnish or dentifrice gel is the most broadly used and has yielded beneficial results as a preventive strategy. CHX mouthwash has been the agent of choice as an antiplaque agent and is considered as the gold standard.[8] Nevertheless, despite its effectiveness in reducing the levels of microorganisms in the oral cavity, long-term use of CHX products is associated with local side effects such as tooth staining, impaired sense of taste on dorsum of tongue, increased formation of supragingival calculus, occasional irritation and desquamation of mucous membranes and bitter taste.[8,9] Thus, its acceptance by patients can be limited due to its side effects, particularly when a longer period of use is recommended. To overcome these side effects, the researchers continue searching for anti-plaque agents with less or free of side effects on gingival and gum tissues.

Nanotechnology is the science which deals with the production of functional materials and structures in the nanoscale using various physical and chemical methods. Nanosilver (NS) mouthwash was introduced into the market and preferred due to small size properties in antibacterial activity as surface area of nanoparticles size allow for more contact with the bacterial cells. This is due to the capability of nanoparticles to penetrate bacteria and other microorganisms and destroy them. NS mouthwash has shown potent anti-plaque and anti-gingivitis activity.[10]

Some authors have reported that the nanosilver has higher antimicrobial effect than chlorhexidine,[10,11] however other investigators found that the antimicrobial effect of nanosilver was lower than chlorhexidine.[12-14] Therefore, there is no agreement on the ideal mouthwash with excellent antimicrobial effects. Furthermore, nanosilver mouthwash has not yet been investigated clinically, and information is lacking as to when and how to use these agents for maximum benefit. As such, practitioner decision regarding the selection of the proper mouthwash is made difficult by the number of existing options. Therefore, the current study was carried out, which aimed to assess the clinical efficacy of a NS mouthwash compared with a CHX mouthwash as the treatment of plaque-induced gingivitis.

The null hypothesis was that there is no difference between NS and CHX mouthwashes in the clinical efficacy of treatment of plaque-induced gingivitis.

MATERIALS AND METHODS.

Study Design

This study was a triple-blinded randomized controlled comparative trial of four weeks duration, conducted in the Dental Polyclinics of the Dental College at University of Science and Technology (UST), Sana'a, Yemen. The trial was registered and allocated at the ACTRN (the number in ANZCTR: ACTRN12618001265268).

Bioethical considerations

All patients signed an informed consent form. Ethical approval was obtained from the Faculty of Medicine and Health Sciences at UST (MECA No. 2016/22).

Study Population

The sample of the present study consisted of patients with an average age of 23 years referred for treatment to the Dental Polyclinics of the Dental College at UST. The subjects were enrolled between January and November 2017. The inclusion criteria comprised good general health, availability for the 4 weeks of study duration, evidence of plaque-induced gingivitis without periodontitis, and a minimum of 20 natural teeth, excluding third molars. Subjects were excluded from the study if they had any of the following conditions: orthodontic bands; partial

removable dentures; were pregnant or breast feeding; systemic disorders or on medications that might influence the periodontium; a history of allergy to oral consumer products; who smoked; periodontal treatment or antibiotic therapy any time during the previous month; tumor(s) or a significant pathology in the soft or hard tissues of the oral cavity; five or more carious lesions needing immediate care; subjects who had received dental prophylaxis in the two weeks prior to the baseline examination.

Participants were randomly selected using the fishbowl technique (with or without replacement), in which any subject who enters to the dental polyclinics of the dental college at the UST was selected after a screening examination, and chosen according to the inclusion/exclusion criteria. The UST was selected as it is oldest university in Yemen and its service offered in the dental polyclinics attracts many patients who can get access to free dental care. Those patients come from Sana'a city and its surrounding neighborhoods. This city is the largest in Yemen, with a population of about 3 million people. Moreover, the majority of the residents are migrants from all over the country.

After a screening examination that included a full medical and dental history and intraoral examination, the final sample size in the study consisted of 68 patients with plaque-induced gingivitis according to the inclusion/exclusion criteria.

The subjects were then randomly divided into two groups as shown in Figure 1:

The control group that consisted of 34 patients who rinsed with 0.12% chlorhexidine mouthwash (Shiba Pharma co., Yemen), 10ml for one minute twice daily. The experimental group included 34 patients who rinsed with a nanosilver mouthwash (Nanogist co., Korea), 10 ml for one minute twice daily.

Experimental Design

All patients received a complete dental prophylaxis to remove all plaque, calculus and extrinsic stain before entering the study.[15] The participants were motivated on regular intervals by personal and phone contact, to use tooth brush and mouthwash on regular basis. The patients were instructed to use a soft tooth brush, brush only with the same toothpaste (Colgate® Cavity Protection fluoride toothpaste) and to brush their teeth twice daily, once in the morning after breakfast and once in the evening before bedtime, for a minimum of three minutes. They also were instructed on the Bass brushing technique, and to rinse their mouth with mouth wash at least half an hour after tooth brushing and not to ingest any liquid or food for at least 30 minutes afterwards, to avoid decreasing the efficacy of the mouth wash, and to diminish the side effects of CHX like staining and bad taste.[8]

All mouth rinses were packaged by an assistant in opaque bottles containing the codes A and B. The assistant added a new patient to a list of randomly assigned letters (A and B), and the patient was given the medication assigned that letter. Thus, this way the triple blinding of the examiner (AA), the supervisor (WA) and the subjects was achieved.

In the present study six teeth were chosen, which represent the six segments of the jaw as proposed in Löe and Silness.[16] Thus the clinical parameters were assessed in the following selected teeth (maxillary right 1st molar, maxillary right lateral incisor, maxillary 1st first bicuspid, mandibular left 1st molar, mandibular left lateral incisor and mandibular right 1st bicuspid).[12] The clinical parameters (plaque, gingival, papilla bleeding indices) were taken at baseline, two weeks, and finally at four weeks for each patient. Indices were measured from four surfaces for each index tooth, then the mean value was calculated for each tooth and finally for each participant. The calibration performed for this step resulted in high intra-examiner agreement. (Kappa =0.90)

Statistical Analysis

The analysis of the data was performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA). The Mann-Whitney U-test was used to determine statistical significance between groups (intergroup analysis). The clinical parameters within the groups were evaluated using the Wilcoxon signed rank test (intragroup analysis). The significance level was set at $p< 0.05$.

RESULTS.

At the onset of the study, there were 68 participants. Six participants dropped out, 2 from NS group, and 4 from CHX group, thus at the end of the study, 62 participants were present (CHX=30, and NS=32). Dropping out was due to failure in following the study protocol.

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Figure 1. Study design flowchart showing participants' studied parameters, allocation, follow-up, and analysis.

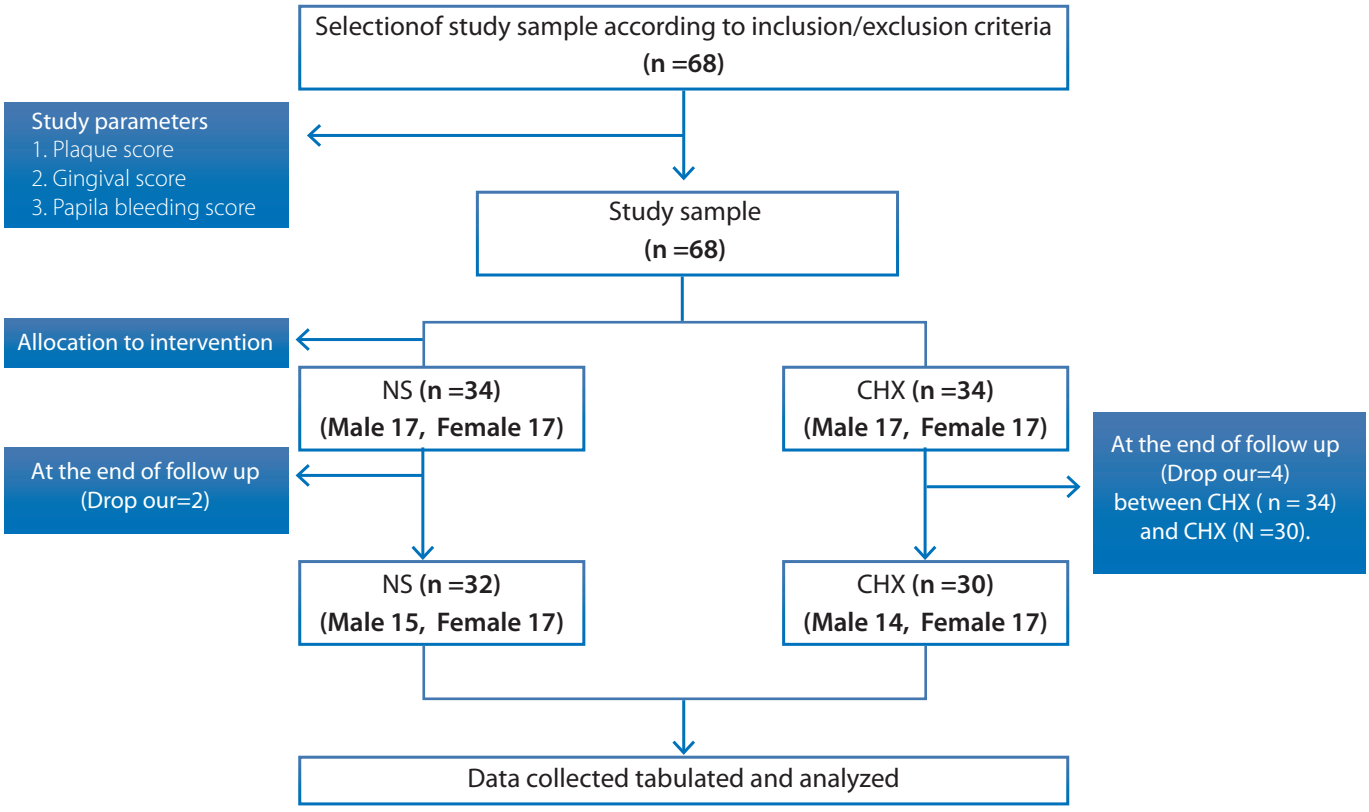

Table 1. Means (SD) and medians of studied clinical parameters on baseline, second and third visits for treatment groups.

	Baseline		Two week		Four week	
Plaque index score	M±SD	Median	M±SD	Median	M±SD	Median
NS	1.51± 0.39	1.58	0.70± 0.31	0.63	0.55± 0.26	0.54
CHX	1.51± 0.41	1.62	0.39± 0.14	0.37	0.25± 0.14	0.25
Gingival index scores						
NS	1.92± 0.16	1.95	1.16± 0.31	1.12	0.74± 0.30	0.75
CHX	1.90± 0.09	1.91	1.23± 0.31	1.25	0.76± 0.29	0.75
Papilla bleeding scores						
NS	2.39± 0.48	2.50	0.86±0.43	0.91	0.39± 0.28	0.33
CHX	2.47± 0.28	2.54	0.89±0.41	0.83	0.42± 0.32	0.29

M = Mean. **SD** = Standard deviation.
a. Intergroup analysis showed significant differences between groups in two weeks and four weeks for plaque index score ($p< 0.05$). However other clinical parameters did not show significant differences between NS and CHX ($p >0.05$).
b. Intragroup analysis showed significant differences within the groups from baseline to 3rd visits (at 4 weeks), from baseline to 2nd visits (at two weeks), and from 2nd to 3rd visits for clinical parameters ($p< 0.001$).

The mean (SD) and median values of plaque, gingival, and papilla bleeding scores of both NS and CHX groups are shown in Table 1. Intergroup comparison by Mann-Whitney U-test showed no statistically significant differences between the groups at baseline for all studied parameters. At two and four weeks follow up, the CHX group showed statistically significant lower plaque scores compared to the NS group (p<0.05). However, there is no statistically significant difference between NS and CHX groups for gingival and papilla bleeding scores at 2 and 4 weeks follow up as shown in Table 1. When the amount of reduction in plaque scores was compared, the CHX group showed a significant reduction in plaque scores compared to the NS group from baseline to 2 and four weeks of product use (p<0.05). However there was no statistical significant difference on the amount of plaque, gingival and papilla bleeding scores reduction from two to four weeks between the NS and CHX groups (p>0.05). Also, there was no statistically significant difference between both groups regarding the amount of reduction in gingival and papilla bleeding from baseline to two and four weeks (p>0.05).

Intragroup comparison by Wilcoxon signed rank test showed a statistically significant reductions in plaque, gingival and papilla bleeding scores after two and four weeks of product use when compared to baseline (p<0. 001) as shown in Table 1. Also there a statistically significant reduction (p<0.001) in plaque, gingival, papilla and bleeding scores for both mouthwash groups (NS, and CHX) comparing two and four weeks of product use.

DISCUSSION.

Dental plaque has long been considered to be the main etiological agent in gingivitis, and periodontal disease. Therefore, suitable plaque control is vital to prevent the incidence of the aforementioned conditions.[17] Plaque control can be accomplished by mechanical or chemical means, or by a combination of both. Mouthwash is a chemical plaque control that should be used alongside mechanical hygiene.[12,18] It has been recommended as a regular adjunct to mechanical therapy to maintain oral health.[19]

CHX has ben used for many years as part of a periodontal treatment regimen and is considered the gold standard.[8] However, CHX is known to have various side effects,[8,9,20] therefore its use as long-term therapy has been limited or not actively recommended.[20] Considering the drawbacks of CHX mouthwash, alternative antiplaque agents have been developed in the recent years. These alternative antiplaque agents do not the same negative effects of CHX, but none has been successful in providing similar antiplaque and anti-gingivitis effect.[8,9,20] In recent time, NS mouthwash has gained attention for its antimicrobial properties.[21] This is due to the smaller size of these particles (nanoparticles), which have the potential to penetrate and kill microorganisms. Thus, the present study was conducted to compare the effects of NS and CHX on the treatment of patients with plaque-induced gingivitis using clinical parameters.

Assessment of the gingival health was determined using three indices. Plaque index (PLI) is the most sensitive indicator for dental deposits. Papilla bleeding index (PBI) is the most sensitive indicator for gingival health, marginal periodontitis and interproximal alveolar bone loss and the effectiveness of preventive procedures is more easily related to the presence or absence of interdental plaque. Gingival index (GI) is one of the most commonly used indices for assessing the gingival health status. A combination of these indices provides a reliable assessment for superiority or equivalence of antiplaque and antiseptic agents.[12,15,18,22]

In this study, there was no significant difference between the baseline data of both groups. Generally, both groups showed a highly significant reduction in PLI, GI and BPI at two and four weeks. There was no statistical difference between both groups, except that CHX demonstrated more reduction in mean PLI with a significant difference compared to NS. The findings of the present study are consistent with previous studies.[22-27] Jain *et al.,*[22] noticed that there was a significant decrease in plaque score in CHX group at 15 days and 30 days. In this study, a significant reduction in PLI, GI and BPI at two and four weeks was found after using CHX mouthwash. The findings of the current study concur with those of Chandrasekaran *et al.,*[15] who showed that rinsing with CHX caused a significant decrease in the mean of PLI and GI at the 3rd follow-up visit. The results of this study are also in agreement with a study conducted by Halkai

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et al.,[24] who reported NS antibacterial activity against *Porphyromonas gingivalis* Shawky *et al.,*[25] showed that NS resulted in a pronounced improvement in clinical parameters and reduction of microbial infections. Lu *et al.,*[26] showed that NS had apparent antibacterial effects against five anaerobic oral pathogenic bacteria and aerobic bacteria. Freire *et al.,*[27] also showed that NS significantly reduced the CFUs four fold in 24 hours. Sadeghi *et al.,*[28] reported that NS had bactericidal effects against S*treptococcus mutans* comparable to CHX.

In contradiction to the current study Esfahanian *et al.,*[12] showed that CHX mouthwash had a significant statistical superiority to NS mouthwash. Differences in results could be due to differences in the composition of the NS (hydrogen peroxide formulation that contains few silver ions), a different concentration of CHX (0.2%) and also due to differences in methodology. The present study were used the mouth wash as irrigation in the mouth *in vivo* not in an *in vitro* laboratory setting, and presence of the biofilm in the mouth may cause differences in the results.

Besinis *et al.,*[11] showed that NS had the strongest antibacterial activity of all tested nanoparticles, with bacterial growth lower than that in the CHX group. Mozayeni *et al.,*[13] indicated that NS gel had lower activity against *Candida albicans* than CHX gel. Disagreement with the results of this study may be attributed to differences in product formulation and the targets of study, as they focused on antifungal activity.

There are some limitations of this study that should be considered. The number of plaque-induced gingivitis studied was limited; further study with a larger sample number should be performed to confirm the results. Moreover, this study was performed in young patients, and the microbiota in adult patients may differ and could yield different results in other populations. In addition, no objective sample calculation was performed. Also, the samples were not objectively randomized according to Consort 2010. Lastly, the follow-up period was only four weeks; further studies with a longer follow-up period should be considered.

CONCLUSION.

Within the limitations of the present study, it can be concluded that the NS mouthwash was comparable to the CHX mouthwash in reducing plaque, gingival and papilla bleeding scores, however CHX was better in decreasing plaque scores than NS.

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