EFFECT OF SUBGINGIVAL IRRIGATION WITH SILVER NANOCOLLOID ON CLINICAL PERIODONTAL PARAMETERS AS AN ADJUNCT TO SUBGINGIVAL ROOT DEBRIDEMENT: A RANDOMIZED, SPLIT MOUTH CONTROLLED TRIAL

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Abstract

Local delivery of antimicrobials has been investigated as an adjunct to conventional therapy. This study aimed to determine the efficacy and clinical outcomes of silver nanocolloid irrigation as an adjunct to mechanical root debridement in the management of periodontitis. Fifty one (51) patients with the presence of at least 1 pocketing site of ≥ 6mm in both contralateral half mouth after periodontal assessment were enrolled. In this split mouth design study, pocketing sites of ≥ 6mm were treated with subgingival root debridement in combination with either silver nanocolloid or saline subgingival irrigation. Bleeding score showed a significant reduction over the observation period in control group (p = 0.034). The probing pocket depths were reduced for both groups, with a significant treatment effect (p < 0.001) from baseline to 6-week review. Also, there was a notable reduction in overall median pocket depth in both genders. In conclusion, within the limitations of the study, no additional benefits were observed with the use of silver nanocolloid irrigation following mechanical debridement.

Keywords: Colloid, Nanoparticles, Silver Nanocolloid, Periodontitis

Introduction

Periodontitis is a multi-factorial chronic inflammatory condition that causes the destruction of tooth supporting tissues. If left untreated, it will ultimately result in tooth loss (1). The bacterial plaque in the periodontal pockets drives the localized inflammatory responses and plays a significant role not only the initiation but the progression of the periodontal disease (2). With the better understanding of the association and interaction of the pathogenic microorganism and periodontal disease has led to considerable research interest in investigating the use of chemotherapeutic agents including antiseptic and antimicrobial agents particularly as an adjunct to mechanical therapy. Antimicrobial agents have been used in periodontal managements to modulate the inflammatory response, eliminate or suppress the pathogenic bacteria at the target diseased site and they have shown to have considerable benefits (3).

Periodontal pockets provide an ideal environment for the use of local drug administration and allow controlled, sustained release of a drug over a period of time (4). On the other hand, systemic antimicrobials have numerous disadvantages especially concerning to the bacterial resistance (5). Local drug delivery can overcome some of the drawbacks associated with systemic administration by limiting the dosage of a drug to a specific site and a high concentration of drug can be maintained in the gingival crevicular fluid (GCF) for a sufficient duration with minimal or no systemic effects (4). Therefore, unwanted effects could be potentially minimised. Difficulties in accessing deep pocketing sites due to anatomical boundaries may limit the efficacy of the conventional periodontal treatment (3) . Hence, antimicrobial agents are used as an adjunct to mechanical instrumentation and several previous studies have evaluated its efficacy. The available evidence supporting the use of subgingival irrigation as a monotherapy or as an adjunct to subgingival root debridment remains controversial (6). However, a systematic review demonstrated favourable periodontal outcomes with the adjunctive use of local antimicrobial agent to subgingival debridement in periodontal therapy. The most promising results were reported with tetracycline, minocycline, metronidazole and chlorhexidine. The positive

effect of adjunctive treatment was greatest with advanced periodontal diseases (7). Similarly, another systemic review also reported that the adjunctive use of local subgingival application of antimicrobial agent to debridement has demonstrated additional clinical benefits especially in probing depth reductions. They have also reported that the occurrence of adverse events with local use of antimicrobials was minimal (8).

To date there has been no one ideal chemotherapeutic agent available. Chlorhexidine has long been used as chemical plaque control which is safe and among the most widely investigated antiseptic agent for plaque control. Studies have demonstrated that short term therapeutic effect by reduction in gingival inflammation and periodontal pathogens with the application of chlorhexidine (9). However, local side effects from prolonged use of chlorhexidine such as extrinsic tooth staining and unpleasant taste remained as a concern to many users (10). Alternatively, normal saline is routinely used to flush out any debris present subgingivally and it is financially sustainable. Other irrigating agents have been selectively used on case to case basis considering its cost-effectiveness.

Silver nanocolloid is composed of silver nanoparticles, suspended in a liquid solution. Several studies have demonstrated its effectiveness against virus and fungus with useful anti-inflammatory properties in addition to its known antibacterial properties (11). Hence, it is accepted as an antiseptic agent. It was proposed that the silver nanoparticles attack the biological pathways in pathogens by causing alterations to the structure and function of bacterial cell membrane and also inhibit the expression of proteins associated with adenosine triphosphate metabolism (12). These actions kill the pathogens and make it impossible for the pathogens to survive and thereby inhibiting bacterial growth. However, the antibacterial mechanism involved is not fully understood. Silver is effective at preventing and treating infections and it has been used extensively in medical treatments such as wound dressings, treatment for burns and scalds, acne and eye infections (13).

Silver nanocolloid (Perioflush, Dental Life Sciences (Mfg) Ltd., Ince, Manchester, United Kingdom) is a potential alternative anti-microbial irrigating solution in addition, it is not an antibiotic. The manufacturer claimed that it is non-toxic, does not stain the teeth or causing any development of bacterial resistance. There were also no known untoward reactions, or interactions reported with the use of this solution. Silver nanocolloid shows high penetration capabilities in deep periodontal pockets due to its small particle size (14). When applied locally in the periodontal pockets as an adjunct to mechanical debridement it has demonstrated greater pocket depth reduction, decreased bacterial counts and better clinical attachment gain when compared to mechanical debridement alone or locally applied tetracycline films (15).

To the best of our knowledge, the use of silver nanocolloid irrigation as an adjunctive treatment for periodontal therapy has rarely been investigated. The current available evidence on the effect of subgingival irrigations is limited and conflicting. In this study, we aimed to compare the efficacy of silver nanocolloid by evaluating the clinical parameters of subgingival root debridement with saline irrigation or silver nanocolloid as intracrevicular irrigation, as an adjunct to subgingival debridement in the management of periodontitis. The null hypothesis of this study was that the use of silver nanocolloid in conjunction with subgingival root debridement has no additional effect when compared to saline irrigation.

Materials and Methods

Sampling Method

Convenient sampling was adopted and subjects were selected following screening procedures which includes a complete medical history questionnaire, clinical examinations and periodontal assessments to obtain the appropriate periodontal diagnosis.

Adult subjects with moderate to severe periodontitis who was planned for non-surgical periodontal therapy and fulfilled the inclusion criteria were recruited. Random permuted blocks of sizes 4 or 6 were used in randomization of sites to either treatment. Random permuted blocks are blocks of different sizes, where the size of the next block was randomly chosen from the available block sizes. A computer generated randomization by a non-investigator was used for treatment allocation, with “A” indicating the subgingival irrigation with silver nanocolloid at the eligible site(s) at right side of the dentition following subgingival debridement whereas normal saline at eligible site(s) at left side of the dentition and vice versa for “B”. Allocation concealment was performed by a non-investigator using sealed envelopes to be opened after subgingival debridement. This method ensures that the investigators were blinded throughout subjects allocation.

To the best of knowledge of the investigators, to date, no similar studies comparing silver nanocolloid (Perioflush, Dental Life Sciences (Mfg) Ltd., Ince, Manchester, United Kingdom) and saline (Ain Medicare Sdn. Bhd., Kota Bharu, Kelantan, Malaysia) as irrigation material in subgingival root debridement. Unplublished data showed that nanocolloid silver and honey have similar efficacy in reducing probing pocket depth after six to eight weeks, when being used as irrigation agent in periodontal therapy. Due to the limited available data advocated to silver nanocolloid, the sample size calculations was based on the study conducted by Sanghani NN et al. which was related to honey as irrigation agent (16). The minimum sample size required was 86 sites per 43 subjects. This was computed using PS software version 3.1, at 0.05 significance level, power at 0.9, mean difference at 0.4 and SD (largest SD) at 0.79.

To account for the drop out rate of 15%, a total of 51 patients were required. There will be two irrigation sites per patient, 102 sites will be achieved.

Systemically healthy individuals diagnosed with moderate to severe chronic periodontitis were enrolled in the study if they aged between 21 to 85 years and have at least one site whereby probing pocket depth ≥ 6mm, that bleeds on probing, in both contralateral half of the mouth.

Subjects were excluded if they have any systemic condition known to exacerbate or modulate periodontal disease (e.g. diabetes mellitus, immunocompromised), have taken antibiotics in the past three months, taking any anti-inflammatory drugs or other medications (e.g. steroid) regularly which was likely to affect the periodontal tissue. Smokers, pregnant female and subjects with a known allergy to the silver nanocolloid agent were excluded.

Recruitment and screening

This is a split mouth study design in which the mouth of the same patient will be divided into test and control sites. Volunteers with the presence of at least one pocketing site of ≥ 6mm in both contralateral half mouth after periodontal assessment will be enrolled.

Recruited subjects were given oral hygiene instructions and prophylaxis. Once optimal oral hygiene was achieved, the pocketing sites of ≥ 6mm were treated with subgingival root debridment in combination with either silver nanocolloid (Perioflush, Dental Life Sciences (Mfg) Ltd., Ince, Manchester, United Kingdom) or saline subgingival irrigation.

Periodontal sites in both contralateral half mouth with clinical probing depth of ≥ 6mm were randomly irrigated with a single dose (1 – 2cc) of either normal saline or silver nanocolloid solution. The test and control sites were randomized which represent either the right or left sites of the mouth.

The silver nanocolloid solution was supplied in a syringe applicator and a fine, bent tip. The bent tip was inserted into the base of the periodontal pocket and slowly moving it along the surface of the tooth during irrigation. A high evacuation suction was placed close to the periodontal pocket to effectively evacuate the residual irrigating solution avoiding any contamination to the other sites of the mouth. The same technique was applied when irrigating the periodontal pockets with saline on the contralateral (other) site of the mouth. Normal oral hygiene practices were allowed except for the use of chemotherapeutic mouth rinses and oral irrigation devices. Subjects were advised to continue their normal lifestyles.

Baseline and post-treatment (6 – 8 weeks) clinical assessments of the target teeth included probing pocket depth (PPD), full mouth plaque score (FMPS) and full mouth bleeding score (FMBS) were recorded.

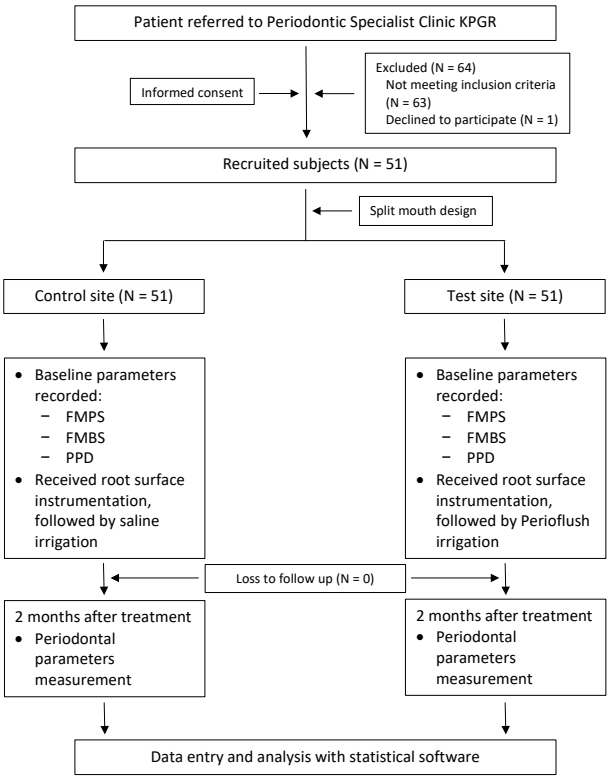

Figure 1: Flowchart of methodology

Two investigators were involved in the periodontal assessment and performing the periodontal interventions for both test and control sites at baseline and post-treatment. Both investigators were blinded to the treatment allocations of the subjects and delivered subgingival irrigation with silver nanocolloid at test site and normal saline at control site as indicated inside the envelope following subgingival debridement. Both investigators involved in the study underwent training and calibration for at least six months at investigator site.

Results

Clinical data was available from 51 subjects who completed both the baseline and post treatment (6 – 8 weeks) review visits. Table 1 shows the baseline characteristics of study participants.

Table 1: Subject characteristics

Variables	N
Age in year (Mean, SD)	49.7, 10.4
Gender	
Male	13 (25.5%)
Female	38 (74.5%)

All subjects turned up during the post treatment evaluation stage, translating to a zero drop out. None of them reported any pain, allergic reactions to silver nanocolloid irrigation, nor experienced any complications after the procedure. FMPS and FMBS at post treatment review revealed a statistically insignificant improvements ($p = 0.072$ and $p = 0.167$ respectively) from baseline data (Table 2).

Table 2: Periodontal parameters at baseline and post treatment review

Variables	N	Baseline	Review	p value*
Full mouth plaque score in % (Median, IQR)	51	19.0 (11.0)	15.0 (12.0)	0.072
Full mouth bleeding score in % (Median, IQR)	51	14.0 (8.0)	12.0 (12.0)	0.167

* Wilcoxon signed-rank test, significance level set at 0.05

Comparing the intra-group median plaque score, there was no significant difference when compared to baseline values ($p > 0.05$). However, bleeding score showed a significant reduction over the observation period in control group ($p = 0.034$) but not in the test group ($p = 0.139$). The PPDs were reduced for both test and control group, with a significant treatment effect ($p < 0.001$) from baseline to post treatment review.

Improvements of periodontal parameters did not confer on either gender (Table 4). Plaque score and bleeding score from baseline to review showed trivial improvement in both males and females. On the contrary, there was a notable reduction in PPD in both genders, with an improvement of the overall median depth from 6.5 mm to 4.9 mm in males ($p < 0.001$) and 6.5 mm to 5.0 mm in females ($p < 0.001$).

Intergroup comparison showed no statistically significant differences between the groups at baseline for all studied parameters. When comparing the plaque and bleeding scores and PPD between test group and control group at post treatment review, there were insignificant differences

Table 3: Comparison of within group baseline and review parameters

Variables	Test Group		*p* value*	Control Group		*p* value*
	Baseline	Review		Baseline	Review	
Plaque score in % (Median, IQR)	25.0 (22.2)	22.2 (16.6)	0.754	25.0 (25.6)	20.8 (20.0)	0.444
Bleeding score in % (Median, IQR)	25.0 (20.8)	16.7 (25.0)	0.139	27.8 (21.6)	16.7 (25.0)	0.034
PPD in mm (Median, IQR)	6.5 (1.0)	5.0 (1.1)	< 0.001	6.5 (0.9)	5.0 (1.9)	< 0.001

* Wilcoxon signed-rank test

Table 4: Comparison of periodontal parameters between gender

Variables	Male		*p* value*	Female		*p* value*
	Baseline	Review		Baseline	Review	
Plaque score in % (Median, IQR)	25.0 (20.3)	22.2 (16.6)	0.627	25.5 (21.7)	21.5 (16.6)	0.907
Bleeding score in % (Median, IQR)	19.8 (18.8)	16.7 (21.9)	0.184	26.4 (16.6)	16.7 (25.0)	0.038
PPD in mm (Median, IQR)	6.5 (0.4)	4.9 (1.7)	< 0.001	6.5 (1.0)	5.0 (1.3)	< 0.001

* Wilcoxon signed-rank test

Table 5: Intergroup comparison of periodontal parameters at baseline and post treatment between test and control sites

Parameters	Baseline		*p* value*	Review		*p* value*
	Test	Control		Test	Control	
Plaque score in % (Median, IQR)	25.0 (22.2)	25.0 (25.6)	0.768	22.2 (16.6)	20.8 (20.0)	0.775
Bleeding score in % (Median, IQR)	25.0 (20.8)	27.8 (21.6)	0.224	16.7 (25.0)	16.7 (25.0)	0.652
PPD in mm (Median, IQR)	6.5 (1.0)	6.5 (0.9)	0.903	5.0 (1.1)	5.0 (1.9)	0.665

*Mann-Whitney U test

between them as well (Table 5). The reduction of median plaque score, bleeding score and pocket reduction in both groups was not significantly different.

Discussion

Intrapocket delivery of antiseptics and antibiotics had been used as an adjunct to subgingival root debridement to reduce subgingival microbiota and thereby improve the overall clinical outcome. In recent years, the focus has been placed upon the medical and chemical applications of silver nanoparticles due to their antimicrobial, anti-inflammatory and antitumor activity, apart from being a potential carrier in sustained drug delivery (17). It has been utilized for burn wound treatment, dental work, catheters, and bacterial infection control (13). Indeed, silver nanoparticles exhibit various applications in dentistry. They are used in restorative dentistry, where the silver nanoparticles were incorporated into nano-composites of quaternary ammonium dimethacrylate and calcium phosphate (18), tissue conditioners for patients using dental prosthesis (19) as well as in the coating of titanium implants (20). Besides, silver nanoparticles have also been used with endodontic retrofill cements owing to their antimicrobial effects (21).

The human use level of silver has been reported to be 0.4 – 27 µg/day, which is equivalent to 0.007 – 0.5 µg/kg of bw/day (22). The current data available with regards to average human dietary exposure and toxicity of silver, a margin of safety calculation has indicated at least a factor of five as a level of concern to the population (23). Silver nanocolloid solution employed in this study (Perioflush, Dental Life Sciences (Mfg) Ltd., Ince, Manchester, United Kingdom) has been tested and is proven to be safe for intraoral use. It is commercially available in the market and was used only as an irrigating solution. The risk of ingestion is low. Additionally, the amount of silver nanocolloid solution used for irrigation per site is very minimal and thus, it does not exceed the tolerable limits.

The purpose of the present investigation was to determine the efficacy and clinical outcome of silver nanocolloid irrigation as an adjunct to subgingival root debridement in the management of periodontitis. In the current study, there were no significant differences observed between both groups irrespective of plaque score, bleeding score or initial PPD at baseline. All subjects had an approximately equal level of oral hygiene, degree of gingival inflammation and disease severity at baseline.

Periodontitis site treated with silver nanocolloid irrigation as adjunct to mechanical therapy did not result in statistically significant plaque reduction. However, there was statistically significant reduction of inflammatory parameters in control group, but not in test group. This is consistent with a study which revealed the level of gingival inflammation measured by papillary bleeding index and gingival index in the scaling and root planning with silver nanoparticles application group denoted insignificant reduction at 1-month and 3-month review (15).

In the present work, control group was equally efficient to silver nanocolloid irrigation in reducing PPD. Both treatment groups showed a significant reduction of median PPD of 6.5mm at baseline to 5.0 mm at 6-week re-evaluation. According to Shawky et al. (15), treatment group with silver nanoparticles application group demonstrated reduction of median probing depth of 5.0 mm at baseline to 3.5 mm at 1-month review and 2.0 mm at 3-month review. More significant reduction of probing depth appreciated by third month compared to baseline reading.

Both test and control groups did not show any statistically significant reduction in plaque score, bleeding score and PPD at post treatment review when compared between groups. This suggested that improvement of the PPD in test group resulted from remission of inflammation following subgingival instrumentation and no superiority of silver nanocolloid irrigation was appreciated. A literature review observed additional benefits following subgingival root debridement with multiple professional irrigation visits or regular irrigation by the patient themselves (24). However, in our study only single flushing with silver nanocolloid irrigation was performed.

The lack of significant reduction in median plaque score in both test group and control group compared to baseline may in partly be due to the lack of patients' motivation and unwillingness to perform effective oral self-care. Lack of knowledge, attitudes towards oral hygiene care, regret about past negligence, dentist-patient relationship cultural beliefs and affordability were identified as factors contributing to the patients' adherence to oral hygiene

care (25). However, the crux of a successful treatment of periodontitis and/or in maintaining periodontal health is still optimum plaque management (26). Thus, oral hygiene reinforcement and patient motivation are crucial to reduce plaque accumulation.

Despite the insignificant reduction of plaque score in both treatment groups, the control group in our study yielded a greater degree reduction of bleeding on probing at sixth week even though the intergroup differences were not significant. Instead, a collective literature review anticipates that non-surgical periodontal therapy will predictably reduce the inflammatory levels. These studies indicated a 6 – 64% reduction in bleeding on probing at 1-month post-therapy, 10 – 80% at 3 months, and 12 – 87% at 6 months (27). The insignificant reduction in bleeding score in test group maybe due to the short period of contact time of the irrigant subgingivally or delivery of the irrigant not to the bottom of deeper pockets. The effect of an antimicrobial drug depends on its concentration and contact time (28). Indeed most studies revealed in both single and multirooted teeth, irrigation techniques failed to penetrate the entire pocket depth predictably and consistently in shallow or deep pockets (29). Even if full penetrability was achieved, the effects of subgingival irrigation may have been restricted by the stimulation of crevicular fluid flow, resulting in rapid clearance of the irrigant, thus exerting limited effect of the local irrigation on the subgingival microflora (28).

A systematic review demonstrated that non-surgical mechanical subgingival instrumentation is efficacious in reducing inflammation, probing pocket depth and the number of disease sites in periodontitis patients (30). At shallow sites (4 – 6 mm), a mean reduction of PPD of 1.5 mm can be expected at 6 or 8 months, whereas at deeper sites (≥ 7mm) the mean PPD reduction was estimated at 2.6 mm.

Cobb (27) concluded that evaluation of the response of the periodontium to scaling and subgingival debridement should not be performed earlier than four weeks following treatment. Thus in our study, we reviewed all our subjects at six weeks following subgingival debridement.

Changes in plaque score and bleeding score in both male and female were modest in both test and control group. However, both genders exhibited statistically significant decrease in PPD, with male has slightly greater reduction in PPD. National Health and Nutrition Examination Survey (NHANES) III, which was conducted between year 1988 and 1994 showed males scored more poorly on the measures of oral hygiene. In contrast to that, both genders in our study maintained their oral hygiene throughout the study. There is no documented report suggesting gender-dependent effects on PPD reduction.

The current study is limited by the relatively short follow-up time. Typically, a tooth with deep pocket that responds poorly to initial therapy would be further treated by another non surgical periodontal therapy or surgical periodontal therapy. Additionally, microbiologic analysis was not studied to determine impact of subgingival irrigation of silver nanocolloid on periodontal pathogens within the periodontal pocket.

Conclusion

Within the limitation of this study, no additional benefits were observed with the use of silver nanocolloid irrigation following mechanical debridement. To advocate the use of silver nanocolloid irrigation, it is necessary to carry out a long-term study on a larger sample using clinical and microbiologic parameters to determine its efficacy as an antiplaque and anti-inflammatory agent.

Acknowledgement

The authors would like to express their appreciation to Clinical Research Centre Ipoh, Oral Health Programme, Ministry of Health Malaysia, State Deputy Director of Oral Health Perak, and Dr Yap Hsiao Fern who had been involved directly in conducting this research.

Competing interests

The authors declare that they have no competing interests.

Ethical Clearance

This study has been approved by Medical Research and Ethics Committee on the 20th July 2017. (Ref. No: NMRR-17-759-35724 (IIR)).

Informed Consent

Informed consent was obtained from all participants included in the article.

Financial support

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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