Title

Evaluating efficacy of a novel dentifrice in reducing probing depths in Stage I and II periodontitis maintenance patients: A randomized, double-blind, positive controlled clinical trial

Journal

Journal of Periodontology, 92(9)

ISSN

0022-3492

Authors

Kaur, Maninder
Geurs, Nicolaas C
Cobb, Charles M
et al.

Publication Date

2021-09-01

DOI

10.1002/jper.20-0721

Peer reviewed

Received: 13 October 2020 | Revised: 5 December 2020 | Accepted: 6 December 2020

DOI: 10.1002/JPER.20-0721

JOURNAL OF Periodontology

HUMAN RANDOMIZED CONTROLLED TRIAL

Evaluating efficacy of a novel dentifrice in reducing probing depths in stage I and II periodontitis maintenance patients: A randomized, double-blind, positive controlled clinical trial

Maninder Kaur[1] | **Nicolaas C. Geurs**[1] | **Charles M. Cobb**[2] | **Joan Otomo-Corgel**[3] | **Thair Takesh**[4] | **June H. Lee**[4] | **Tracie M. Lam**[4] | **Kairong Lin**[4] | **Audrey Nguyen**[4] | **Brian L. Nguyen**[4] | **Petra Wilder-Smith**[4]

[1] School of Dentistry, Department of Periodontology, University of Alabama at Birmingham, Birmingham, Alabama, USA

[2] School of Dentistry, Department of Periodontology, University of Missouri-Kansas City, Kansas, Missouri, USA

[3] School of Dentistry, Department of Periodontology, University of California at Los Angles, Los Angeles, California, USA

[4] Beckman Laser Institute and Medical Clinic, Department of Dentistry, University of California at Irvine, Irvine, California, USA

Correspondence
Maninder Kaur, BDS, MPH, MS, University of Alabama at Birmingham, School of Dentistry, Department of Periodontology, 1919, 7th Avenue South, SDB 412, Birmingham, AL 35294-007, USA
Email: maninder@uab.edu

Abstract

Background: Compliance to periodontal maintenance therapy (PMT) is essential for long-term periodontal health. Between PMT visits, patients must maintain good oral hygiene. A dentifrice with demonstrable clinical benefits for use between PMT visits would be highly desirable. The aim of this clinical study was to investigate the effect of a novel dental gel on probing depths (PD) and inflammation when used as a home care dentifrice in Stage I and II periodontitis patients.

Methods: This double-blind clinical study randomized 65 subjects with Stage I and II periodontitis to the novel dental gel containing 2.6% EDTA, and a commercially available anti-gingivitis dentifrice with 0.454% stannous fluoride. Primary endpoint was PD at 6 months for those sites with baseline PD $\geq$ 4 mm and secondary endpoints included whole mouth mean scores of modified gingival index (MGI), modified sulcus bleeding index (mSBI) and plaque index (PI). No SRP was performed at baseline.

Results: Subjects using the novel dentifrice showed significant PD reductions of 1.18 mm (from 4.27 mm at baseline to 3.09 mm at 6 months) compared to 0.93 mm (from 4.23 mm at baseline to 3.30 mm at 6 months) shown for those using the positive control dentifrice. Difference between treatments at 6 months was 0.21 mm with P-value = 0.0126. Significant improvements in MGI (P = 0.0000), mSBI (P = 0.0000), and PI (P = 0.0102) were also observed in 6 months.

Conclusion: The novel dentifrice showed significant reductions in PD and gingival inflammation over 6 months solely as a home care dentifrice without baseline SRP in Stage I and II periodontitis maintenance patients.

KEYWORDS
anti-inflammatory agents, oral hygiene, periodontitis, plaque control, tooth brushing

1 | INTRODUCTION

Periodontal disease includes a group of inflammatory conditions, typically initiated by the community of microorganisms embedded in an extracellular polysaccharide matrix of the oral biofilm that develops on all surfaces in the oral cavity including the tooth surface, gingival margin and subgingival environment.[1] If this oral biofilm is left undisturbed, it can lead to formation of dental calculus, periodontal disease, dental demineralization, and caries.[2,3] Periodontal diseases include gingivitis,[4] reversible inflammation contained within the gingiva, and periodontitis, a chronic multifactorial inflammatory disease associated with dysbiotic biofilms and characterized by progressive destruction of the tooth-supporting apparatus.[5] In addition, recent evidence indicates that periodontal inflammation may increase the risk of systemic diseases, such as diabetes mellitus, cardiovascular diseases, rheumatoid arthritis, and adverse pregnancy outcomes.[6–9]

The cornerstone of success of all therapies implemented for treatment of inflammatory periodontal disease is in the removal of the biofilm and reduction of periodontal pathogens associated with the tooth surfaces, periodontal tissues, and other niches within the oral cavity.[10] This highlights the importance of an individual to be a co-therapist for the establishment of optimal oral hygiene and to perform effective daily plaque control to prevent periodontal disease and to improve gingival health.[11–13] Although heightened awareness, concerted public health measures, and use of home care products to facilitate mechanical and chemical methods of plaque control have contributed to an overall improvement in oral cleanliness, the prevalence of periodontal disease, especially severe periodontitis, has continued to remain high in developed countries.[14] Several epidemiological studies have revealed that plaque-induced gingivitis is prevalent among all ages of dentate individuals.[15,16] Also, based on data collected as part of CDC's 2009-2014 National Health and Nutrition Examination Survey (NHANES), 42.2% of adults aged 30-years and older in the U.S have some form of periodontitis.[17]

Thus, different chemotherapeutic agents have been studied and incorporated into dentifrice formulations for daily use to remove oral biofilm and prevent its re-accumulation. Numerous side-effects of such existing anti-plaque formulations including taste alteration, staining of teeth, dental abrasion, sensitivity, and gingival lesions have been reported.[18] A new novel dental gel containing 2.6% ethylenediamine tetra acetic acid (EDTA) has been studied to improve plaque control and alleviate symptoms of gingivitis while minimizing the side effects experienced with some of other dentifrices as published in several studies that have demonstrated its superior anti-gingivitis and anti-biofilm efficacies.[19–21] Other studies have also been published to show no observation of tooth surface degradation and no significant difference in microhardness when comparing the novel dental gel without fluoride to standard fluoride toothpastes.[22–23] Interim analysis in early to moderate periodontitis patients has also been reported recently with promising results.[24]

The overall aim of this study was to evaluate the safety and effectiveness of the novel dental gel containing 2.6% EDTA as a home care dentifrice compared to a positive control dentifrice on clinical periodontal parameters in Stage I and II periodontitis patients, using a reduction in PD as the primary efficacy endpoint. All study subjects were between PMT visits, so additional SRP was not performed at baseline or during the relatively short study duration of 6 months.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This single center randomized active-controlled clinical study was designed as a prospective, double-blind study in maintenance patients with Stage I and II periodontitis and conducted at University of California at Irvine.[25,26] It was approved by the University of California at Irvine, IRB protocol #2013-9778 and all clinical procedures were conducted in accordance with the Helsinki Declaration of 1975, as updated in 2013.[27] This clinical study was registered on clinicaltrials.gov, with registration number NCT02271815. No significant changes were made in the study design after commencement of the study.

Subjects in this clinical study were between their PMT visits at local community dental clinics and were referred to the university study center for potential participation in this clinical study. Males and females aged ≥ 30 years with a minimum of 20 natural teeth were included in this study. Key inclusion criteria included subjects having 1) Plaque Index ≥ 2.0, Modified Gingival Index[26] ≥ 1.5, and Modified Sulcus Bleeding Index[27] ≥ 1.0, 2) Stage I or II periodontitis,[24] 3) at least 3 teeth with periodontal pocket depth ≥ 4 mm, and 4) bleeding on probing > 50% of teeth as determined by single-pass probing depth measurements. Key exclusion criteria included (1) pregnant female, (2) tobacco use, (3) participation in a clinical trial within 30 days of the start of the study, (4) history of significant adverse effects, including allergies following use of oral hygiene products, (5) any quadrant or maintenance scaling, and root planing; or periodontal surgical therapy within the 6 months prior to baseline, (6) subjects who have been diagnosed with Sjögren's disease, or immune deficiency diseases (i.e., HIV or AIDS, poorly controlled diabetes), or (7) anti TNF-alpha medication

for rheumatoid arthritis, systemic antibiotics in the last 3 months, or anti-inflammatory drugs, or immune suppressants. After eligibility was determined based on the inclusion and exclusion criteria, and after obtaining informed written consent, the participants were randomly assigned in a 1:1 ratio to the treatment with either the test dentifrice or the positive control dentifrice. The rolling recruitment through advertisements was initiated in September 2017 and all the study visits were completed by a single examiner by March 2020.

2.2 | Study products and interventions

Both the participants and the study examiner were kept blinded on the randomization and throughout the study. The oral hygiene of the subjects was standardized by rigorous uniform instructions and training. Subjects were provided with a new standard toothbrush[*] and trained using the tell-show-do method in the standard sulcular brushing technique by the study examiner with over 10 years of clinical experience as a periodontist.

2.3 | Study products included

1. **Test dental gel**: a commercially available dentifrice formulated with 2.6% EDTA[†]; and
2. **Positive control dentifrice**: a commercially available dentifrice formulated with 0.454% stannous fluoride[‡].

Participants were instructed to brush with the study material twice a day (in the morning and evening) for 2 minutes and to use a pea size amount of the dentifrice provided. They were required to bring back the empty and partially empty dentifrice tubes at each visit and each tube returned was weighed to measure compliance. Subjects were provided with de-identified plain white, numbered tubes of toothpaste and new toothbrushes at each study visit. They were also asked not to use any other oral hygiene products including interproximal cleaning devices throughout the study duration. No prophylaxis or SRP was performed in this study.

2.4 | Outcomes

The first brushing occurred during the baseline (day 0) visit. Study duration was 6 months (180 days); subjects were evaluated at Visit 1–(day 0 or baseline), Visit 2 (day 90 ± 3 or 3-month), and Visit 3 (day 180 ± 3 or 6-month). Following clinical variables were recorded at these 3 visits by the same blinded, pre-standardized, experienced study periodontist (who was being calibrated for measuring these clinical variables on a quarterly basis by the IRB with a minimum of 90% accuracy):

1. Probing Depths (PD) measured as the distance between gingival margin and base of the pocket.
2. Clinical Attachment Loss (CAL) calculated as the distance between the cementoenamel junction (CEJ) and base of the pocket based on the measured PD and free gingival margin (FGM).
3. Modified Gingival Index (MGI): Same as Löe and Silness Gingival Index but without the bleeding on probing component.[28]
4. Modified Sulcus Bleeding Index (mSBI).[29]
5. Plaque Index (PI): Quigley Hein Index with Turesky modification.[28]

PD and CAL was were recorded at six sites (buccal, lingual, mesiobuccal, distobuccal, mesiolingual, distolingual) per tooth. The examiner used a calibrated technique to obtain PD and CAL measurements which were rounded to the nearest millimeter with a standard manual UNC probe. MGI and mSBI scores were recorded at four sites (mesiobuccal, distobuccal, mesiolingual, distolingual) per tooth whereas PI scores were recorded on the buccal and lingual sites per tooth. PI was measured using a commercially available disclosing solution[§] before recording the other periodontal variables.

The primary efficacy endpoint was mean PD at 6 months for those sites that measured PD ≥ 4 mm (defined as disease sites) at baseline. Mean clinical attachment loss (CAL) at 6 months was included as a safety outcome in order to ascertain that PD reduction did not occur at the expense of CAL worsening. Secondary efficacy endpoints included the improvement in clinical indices such as MGI, mSBI and PI. Safety was monitored throughout the study by assessing the incidence, timing, and severity of adverse events (AEs) as well as by examining overall oral health of the subjects by the examiner at the time of scheduled visits. Subjects were also provided with a direct telephone number to contact in case of any AEs.

2.5 | Sample size and data analysis

This was the first randomized double-blind study evaluating the test dentifrice for the improvement in PD as

[*] Oral-B Pro-Flex, Procter & Gamble, Cincinnati, OH.
[†] LivFresh Dental Gel, Livionex Inc., Los Gatos, CA.
[‡] Crest ProHealth, Procter & Gamble, Cincinnati, OH.
[§] GUM Butler Red-Cote, Sunstar Americas Inc., Schaumburg, IL.

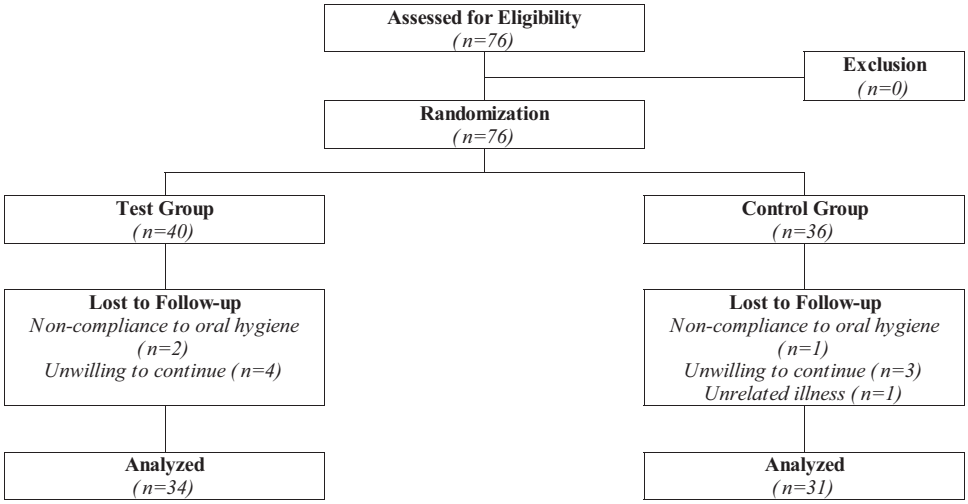

FIGURE 1 Flowchart of patients throughout the study

a primary outcome. A minimum sample size of 60 subjects (30 subjects in each group) was determined based on prior studies including case studies in periodontal patients and gingival inflammation/bleeding studies in gingivitis patients, and to provide at least 80% power with an alpha of 0.05 to detect a between-treatment difference of 0.2 mm in PD, assuming a standard deviation of 0.25 mm. Accordingly, 76 subjects (38 subjects in each group) were recruited to compensate for possible dropouts during the study period. An interim analysis was performed with 33 subjects (14 in the test group and 19 in the control group) who had completed their 6-month visit as of December 2018 in order to ensure that the test dental gel has no deleterious effect on periodontal health, whereas the study examiner continued to be blinded, therefore there is no impact on the current data analysis.

Randomization was based on a block randomization scheme with a fixed block size of four in order to ensure a balance in sample size across groups over time. To ensure allocation concealment, each qualified subject was assigned a randomization number generated by a random number generator by an independent statistician. The unique randomization number determined the treatment assignment for that subject.

Site-specific measurements were averaged to calculate a patient-specific mean value for each clinical parameter. Primary and secondary efficacy endpoints were assessed and compared between treatments using analysis of covariance (ANCOVA) with treatment as a factor and the corresponding baseline values as a covariate. Clinical response (in terms of the number of measurement sites showing a decrease, no change, or increase in PD in 6 months) was also assessed and compared between treatments using Pearson's Chi squared test. Two-tailed statistical significance was determined by a $P < 0.05$.

3 | RESULTS

Efficacy was analyzed based on the full analysis set (FAS) following the Intent-to-Treat principle, defined as all randomized subjects who had completed at least through the follow-up visit at 3 months. A total of 65 such subjects (34 in the test group and 31 in the control group) were analyzed in this study. All 65 subjects were in compliance with their usage of the assigned dentifrice. The flowchart of patients throughout this clinical study is illustrated in Figure 1.

Participants in the test group ranged in age from 39 to 79 years old, mean 60 years, and in the control group 40 to 76 years, mean 57-years old. Majority of the participants in both groups were Asians. There were no statistically significant differences between the test group and the control group in terms of demographics and baseline clinical characteristics.

In the disease sites with baseline PD $\geq$ 4 mm, the test group demonstrated greater improvements in PD at 6 months compared to the control group as presented in Table 1. Mean PD values were 3.09 mm in the test group and 3.30 mm in the control group at 6 months with the mean difference between treatments of 0.21 mm ($P = 0.0126$). Mean PD reductions from baseline to 6 months were 1.18 mm in the test group and 0.93 mm in the control group. These PD improvements were accompanied by the corresponding CAL gains in both groups but there was no statistically significant difference in CAL gains between groups. As summarized in Table 2, the mean PD reductions were greater for deeper sites as compared to shallower sites.

A total of 10,320 periodontal pockets sites (5382 in the test group and 4938 sites in the control group) were measured for PD in this clinical study. Of these measured sites,

TABLE 1 Comparison of PD and CAL with baseline PD ≥ 4 mm

Outcome	Test Group ($n = 34$)				Control Group ($n = 31$)			
	Mean		Change		Mean		Change	
	Mm	SD	Mm	%	Mm	SD	mm	%
PD								
BL	4.27	0.21	N/A	N/A	4.23	0.21	N/A	N/A
3 M	3.23	0.36	1.05	24.5%	3.43	0.36	0.80	18.9%
6 M	3.09 *	0.33	1.18	27.6%	3.30 *	0.33	0.93	21.9%
Difference between treatments (95% confidence interval) at 6 M = 0.21 mm (0.05 mm, 0.38 mm) with $P = 0.0126$.								
CAL								
BL	4.19	0.51	N/A	N/A	4.03	0.31	N/A	N/A
3 M	3.21	0.41	0.98	23.4%	3.32	0.41	0.71	17.7%
6 M	3.10	0.38	1.09	26.0%	3.21	0.38	0.82	20.4%

BL, baseline; SD, standard deviation; SE, standard error

Difference between treatments (95% confidence interval) at 6 M = 0.11 mm (-0.08 mm, 0.30 mm) with p = 0.2535.

BL values presented in mean ± SD, and 3 M and 6 M values presented in adjusted mean ± SE based on ANCOVA model. *P*-values were calculated based on ANCOVA model with term for treatment and baseline as covariate.

3 M, 3 months; 6 M, 6 Months.

*$P < 0.05$.

TABLE 2 PD changes at 6 M for PD categorized by baseline PD

Study Arm	Baseline PD						
	≤ 1 mm	2 mm	3 mm	4 mm	5 mm	> 5 mm	All sites
Test Group	0.28	(0.06)	(0.51)	(1.02)	(1.46)	(2.03)	(2.03)
Control Group	0.44	0.03	(0.32)	(0.82)	(1.47)	(1.94)	(1.94)

1472 sites (739 sites in the test group and 733 sites in the control group) were PD ≥ 4 mm at baseline. Clinical response was assessed by categorizing these sites based upon if the PD decreased, remained unchanged or increased over a period of 6 months as shown in Table 3. 80.9% of the test sites and 76.1% of the control sites responded well to the respective treatment and showed PD reductions whereas 2.3% of the test sites and 3.8% of the control sites did not respond well and showed increases in PD over the 6-month duration of this study ($P = 0.0497$). There were also statistically and clinically significant reductions in the number of sites with PD ≥ 4 mm and PD ≥ 5 mm as summarized in Table 4. The number of the sites with PD ≥ 4 mm was reduced from 739 at baseline to 309 at 6 months (by 58.2%) for the test group and from 733 to 371 (49.4%) in the control group.

Full mouth scores of all the clinical periodontal indices (MGI, mSBI, PI) with mean value and standard deviation (SD) at baseline, 3 months and 6 months are summarized in Table 5. The test group demonstrated statistically significant improvements at 3 months in MGI ($P < 0.0008$), mSBI ($P < 0.0002$), and PI ($P = 0.0131$) and further improvements at 6 months in MGI ($P < 0.0000$), mSBI ($P < 0.0000$), and PI ($P = 0.0102$) compared to the control group. No adverse events were reported during the study.

4 | DISCUSSION

Several studies have been conducted to assess the effect of the novel formulation of dental gel that contains 2.6% EDTA on oral biofilm and gingivitis.[19–21,24,31] Previous studies have demonstrated enhanced plaque removal, improved gingival health, and prevention of biofilm re-accumulation with the use of the test dental gel than a positive control dentifrice in patients with gingivitis.[19,31] In a study utilizing high-resolution in vivo multiphoton microscopy and digital imaging, it was concluded that reduced biofilm levels of using the test dental gel were associated with a macroscopic break-up of the dental plaque layer, and smaller, fragmented residual deposits with no apparent changes in the pellicle and significantly more reduction in clinical indices was reported in the test group versus the control group.[20] An unpublished in vitro study (available on request) showed that the test dental gel makes the zeta potential (a measure of electrical charge) on hydroxyapatite spheres more negative, thus resulting in a larger repulsive force between the tooth surface and negatively charged bacteria. This repulsion makes it easier to remove bacterial plaque while brushing and harder for the bacteria to attach (or re-attach) to tooth surface.

TABLE 3 Number of sites with baseline PD ≥ 4 mm, stratified as per 6 M change

	Decrease		No change		Increase		Total		
Study Arm	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	***P*-value**
Test Group	598	80.9%	124	16.8%	17	2.3%	739	100.0%	0.0497
Control Group	558	76.1%	147	20.1%	28	3.8%	733	100.0%	

P-value was calculated based on Pearson's chi squared test.

TABLE 4 Number of sites with PD ≥ 4 mm and PD ≥ 5 mm at BL and 6 M

	PD ≥ 4 mm			PD ≥ 5 mm		
Study Arm	**BL**	**6 M**	***P*-value**	**BL**	**6 M**	***P*-value**
Test Group	739	309	0.0399	229	65	0.0345
Control Group	733	371		177	76	

P-values were calculated based on Pearson's chi squared test.

All previous clinical studies conducted in gingivitis patients have demonstrated that the test dental gel is a safe and effective tool for plaque removal and improving gingival health.[19–21,31] This investigation is the first controlled study to assess this novel dental gel in the therapy of periodontitis patients. Thus, this randomized control double-blind clinical study is the first in the series to evaluate and compare the efficacy of this novel dentifrice with 2.6% EDTA on periodontal health of patients with Stage I and II periodontitis. Interim data from this clinical study was reported in which the test dental gel was found to improve periodontal pocket depths as well as gingival inflammation and bleeding significantly better than the positive control dentifrice in the periodontitis patient population.[24]

Periodontal health (as reported in PD and CAL in this study) is evaluated using the data for those disease sites with baseline PD ≥ 4 mm. Mean PD reduction achieved by the test group during the study duration of 6 months was 1.18 mm (Table 1). It is useful to compare these reductions in PD without prophylaxis to other clinical trials for

TABLE 5 Comparison of full mouth clinical indices

	Test group ($n = 34$)				Control group ($n = 31$)			
	Mean		Change		Mean		Change	
Outcome	**Score**	**SD**	**Score**	**%**	**Score**	**SD**	**Score**	**%**
MGI								
BL	2.56	0.22	N/A	N/A	2.54	0.22	N/A	N/A
3 M	2.23[a]	0.17	0.33	12.9%	2.38 [a]	0.17	0.16	6.2%
6 M	2.08[a]	0.20	0.48	18.9%	2.35 [a]	0.20	0.19	7.6%
Difference between treatments (95% confidence interval) at 6 M = 0.27 (0.17, 0.37) with $P = 0.0000$.								
mSBI								
BL	2.58	0.21	N/A	N/A	2.53	0.24	N/A	N/A
3 M	2.25 [a]	0.17	0.34	13.0%	2.42 [a]	0.17	0.11	4.2%
6 M	2.13 [a]	0.19	0.45	17.6%	2.37 [a]	0.19	0.16	6.4%
Difference between treatments (95% confidence interval) at 6 M = 0.24 (0.14, 0.33) with $P = 0.0000$.								
PI								
BL	2.18	0.38	N/A	N/A	2.26	0.46	N/A	N/A
3 M	1.69 [b]	0.24	0.49	22.4%	1.85 [b]	0.24	0.41	18.3%
6 M	1.51 [b]	0.28	0.67	30.7%	1.70 [b]	0.28	0.56	24.8%

BL, baseline; SD, standard deviation; SE, standard error.

Difference between treatments (95% confidence interval) at 6 M = 0.19 (0.05, 0.33) with $P = 0.0102$.

BL values presented in mean ± SD and 3 M and 6 M values presented in adjusted mean ± SE based on ANCOVA model. *P*-values were calculated based on ANCOVA model with term for treatment and baseline as covariate.

3 M, 3 months; 6 M, 6 Months.

[a] $P < 0.0001$.

[b] $P < 0.05$.

FDA approved locally administered antimicrobial therapies adjunctive to SRP in (moderate to severe) periodontitis patients.[32] Arestin (a locally administered minocycline) as an adjunct to SRP has shown PD reductions of 1.32 mm (compared to 1.08 mm for SRP alone) and 1.63 mm in its 9-month randomized controlled clinical trial (n = 748) and Perio Chip (a locally administered chlorhexidine) also as an adjunct to SRP has shown the combined average of 0.95 mm (compared to 0.65 mm for SRP alone) in its two 9-month randomized controlled clinical trials (n = 447).[33,34] Baseline PD values are also important to consider because nonsurgical periodontitis treatments generally have a greater impact in deeper periodontal pockets, because there is more room for reduction in PD values. The baseline means PD for Arestin and Perio Chip studies was ≈5.80 mm versus 4.27 mm in this study. It should be noted that potential adverse effects (such as gingival discomfort, teeth sensitivity, and antimicrobial-resistant bacteria) must also be taken into account when assessing the benefit of these antimicrobial adjunctive therapies.

A comprehensive systemic review article found the PD reductions for the SRP (which is the gold standard for nonsurgical periodontal treatment) have a weighted average PD reduction of 1.40 mm for those sites with baseline PD of 4 to 6 mm.[35] In contrast, this clinical study was based solely on home care without SRP or prophylaxis. Another unpublished randomized double-blind clinical study (available on request) has demonstrated that as an adjunct to professional prophylaxis (scaling and polishing) at baseline, the test dental gel was able to achieve statistically and clinically significant PD reductions of 0.81 mm in just 30 days. It is plausible to expect even greater PD reductions for the test dental gel when used as an adjunct to SRP in future studies.

Good oral hygiene alone (without professional periodontal therapy) is not sufficient in healing periodontal pockets (i.e., reducing PD) in periodontitis patients but the test dental gel was able to demonstrate clinically significant PD reductions as a home care dentifrice product in this controlled clinical study.[36] The findings are clinically significant particularly for Stage I and II periodontitis patients who can accelerate healing time and/or extend time interval of their professional periodontal therapy including SRP and other (non-invasive and/or invasive) interventions.

Significant mean PD reductions were also supported by the statistically and clinically significant response rates (Table 2) and the decrease in the number of the disease sites (Table 3) as well as the overall improvements in gingival health (gingival inflammation and bleeding) and plaque control (Table 5) in the test group.

It is well understood that deeper periodontal pockets (comparing to shallow periodontal pockets) experience greater clinical improvements after nonsurgical periodontal treatments.[37] The data from this study also demonstrated that greater PD reductions were achieved in periodontal pockets that were deeper at baseline. Mean PD changes in all baseline PD categories are greater for the test group than the control group as summarized in Table 4.

Smaller CAL gains and resulting lack of statistical significance as compared to PD reductions were likely because of a) CAL measurements having greater variability than PD measurements and b) the impact of gingival recession not being a part of the CAL measurements. Therefore, CAL is more difficult to show a significant difference because it does not take into account (unlike PD) the amount of gingival recession because of decreased inflammation. The test group has shown improvements in PD of 1.18 mm and in CAL of 1.09 mm at 6 months, the difference of 0.09 mm representing the amount of gingival recession (or the change in FGM) in 6 months. On average in the test group, the gingival margin moved apically from 0.08 mm above CEJ to 0.06 mm below the CEJ in 6 months because of reduced gingival inflammation.

Clinically and statistically significant improvements in full mouth MGI, mSBI, and PI scores are noted for the test group compared to the positive control group in this study (Table 5). However, these improvements in clinical indices are smaller than the results reported in previous clinical studies for the test dental gel in gingivitis patients.[19–21] This probably reflects the fact that the patient population recruited for this study was characterized by poor plaque control and generalized severe inflammation in both groups at baseline and (unlike PD or CAL) these indices have inherent limitations in capturing the degree of severity in the high score range especially in a population with poor oral hygiene. The inflammatory data in Table 5 might indicate a poorly controlled group of patients. However, it is interesting to note that the test dental gel and oral hygiene still resulted in a significant PD reduction, in spite of the persistent level of inflammation. This may suggest that the impact of the test dental gel on PD might yield an even greater clinical benefit when used in patients with less inflammation at baseline.

Both groups showed significant improvement in the periodontal clinical parameters in patients with Stage I and II periodontitis; this may be attributed to the mechanical disruption of the plaque biofilm and as well as the anti-plaque and anti-gingivitis properties of the active ingredients in the positive control group.[38,39] Despite these established properties of the positive control dentifrice, the test dental gel had significantly superior efficacy. It should be noted that the test dental gel does not contain abrasives or antimicrobial (bactericidal) active ingredients typically formulated in commercially available anti-plaque and anti-gingivitis toothpastes.

5 | CONCLUSION

The results of this clinical study show that Stage I and II periodontitis patients can achieve significant PD reductions, reduce the level of inflammation and improve their periodontal health by using the test dental gel as a home care dentifrice during PMT and/or between scheduled PMT visits. The study population had previously been diagnosed and treated in community dental clinics for Stage I and II periodontitis prior to referral as potential study participants. This level of disease may have inherently limited the amount of PD reductions that was achieved. Future studies should evaluate the efficacy of the test dental gel as an adjunct to SRP. If future studies show the test dental gel has an adjunctive therapeutic benefit to SRP, it would support potential inclusion as a therapeutic component in nonsurgical periodontal therapy to extend the benefit of SRP and delay and/or prevent relapse of periodontal disease.

ACKNOWLEDGMENTS

This study was supported by: LAMMP NIH/NIBIB P41EB05890; NIH/NCI P30CA062203; AFOSR FA9550-17-1-0193 and AFOSR FA9550-20-1-0052; the Arnold and Mabel Beckman Foundation through University of California, Irvine; NIH/NIBIB UH2EB022623 through University of Arizona; and Livionex Inc., Los Gatos, CA. We confirm that none of the authors of this paper have any perceived or actual funding conflicts. The views expressed in this paper are those of the authors and do not necessarily represent the official position or policy of the U.S. Government, the Department of Defense, or the Department of the Air Force. The authors report no conflicts of interest related to this study.

AUTHOR CONTRIBUTIONS

M. Kaur contributed to data interpretation, drafted and critically revised the manuscript; N.C. Geurs, C.M. Cobb and J. Otomo-Corgel contributed to study conception, design, data interpretation, and drafted and critically revised the manuscript; T. Takesh contributed to data collection, statistical design, data analysis and data interpretation; J.H. Lee and T.M. Lam contributed to data collection and data analysis; K. Lin, A. Nguyen, B.L. Nguyen contributed to clinical observation, execution and data collection; P. Wilder-Smith contributed to study conception, design, execution, data interpretation, and drafted and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

REFERENCES

1. Haffajee AD, Socransky SS. Microbial etiological agents of destructive periodontal diseases. *Periodontol 2000*. 1994;5:78-111.
2. Jeon JG, Rosalen PL, Falsetta ML, Koo H. Natural products in caries research: current (limited) knowledge, challenges and future perspective. *Caries Res*. 2011;45:243-263.
3. Axelsson P, Lindhe J. The significance of maintenance care in the treatment of periodontal disease. *J Clin Periodontol*. 1981;8:281-294.
4. Chapple ILC, Mealey BL, Van Dyke TE, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: consensus report of workgroup 1 of the 2017 World Workshop on the classification of periodontal and peri-implant diseases and conditions. *J Periodontol*. 2018;89(Suppl 1):S74-S84.
5. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: consensus report of workgroup 2 of the 2017 World Workshop on the classification of periodontal and peri-implant diseases and conditions. *J Periodontol*. 2018;89(Suppl 1):S173-S182.
6. Pritchard AB, Crean S, Olsen I, Shinghrao SK. Periodontitis, microbiomes and their role in Alzheimer's disease. *Front Aging Neurosci*. 2017;9:336.
7. Leira Y, Seoane J, Blanco M, et al. Association between periodontitis and ischemic stroke: a systematic review and meta-analysis. *Eur J Epidemiol*. 2017;32:43-53.
8. Khumaedi AI, Purnamasari D, Wijaya IP, Soeroso Y. The relationship of diabetes, periodontitis and cardiovascular disease. *Diabetes Metab Syndr*. 2019;13:1675-1678.
9. Tang Q, Fu H, Qin B, et al. A possible link between rheumatoid arthritis and periodontitis: a systematic review and meta-analysis. *Int J Periodontics Restorative Dent*. 2017;37:79-86.
10. Slots J. Subgingival microflora and periodontal disease. *J Clin Periodontol*. 1979;6:351-382.
11. Van der Weijden GA, Hioe KP. A systematic review of the effectiveness of self-performed mechanical plaque removal in adults with gingivitis using a manual toothbrush. *J Clin Periodontol*. 2005;32(Suppl 6):214-228.
12. Axelsson P, Lindhe J. The significance of maintenance care in the treatment of periodontal disease. *J Clin Periodontol*. 1981;8:281-294.
13. Lippert F, Arrageg MA, Eckert GJ, Hara AT. Interaction between tooth- paste abrasivity and toothbrush filament stiffness on the development of erosive/abrasive lesions in vitro. *Int Dent J*. 2017;67:344-350.
14. Tonetti MS, Eickholz P, Loos BG, et al. Principles in prevention of periodontal diseases: consensus report of group 1 of the 11th European Workshop on Periodontology on effective prevention of periodontal and peri-implant diseases. *J Clin Periodontol*. 2015;42(Suppl.16):S5-S11.
15. Li Y, Lee S, Hujoel P, et al. Prevalence and severity of gingivitis in American adults. *Am J Dent*. 2010;23:9-13.
16. Coventry J, Griffiths G, Scully C, Tonetti M. ABC of oral health: periodontal disease. *BMJ*. 2000;321(7252):36-39.
17. Eke PI, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA, Genco RJ. Periodontitis in US adults: national Health and Nutrition Examination Survey 2009-2014. *J Am Dent Assoc*. 2018;149:576-588.

18. Gunsolley JC. A meta-analysis of six-month studies of antiplaque and antigingivitis agents. *J Am Dent Assoc*. 2006;137:1649-1657.
19. Dadkhah M, Chung NE, Ajdaharian J, Wink C, Klokkevold P, Wilder-Smith P. Effects of a novel dental gel on plaque and gingivitis: a comparative study. *Dentistry*. 2014;4(6):239.
20. Ajdaharian J, Dadkhah M, Sabokpey S, et al. Multimodality imaging of the effects of a novel dentifrice on oral biofilm. *Lasers Surg Med*. 2014;46:546-552.
21. Anbarani AG, Wink C, Ho J, et al. Dental plaque removal and re-accumulation: a clinical randomized pilot study evaluating a gel dentifrice containing 2.6% Edathamil. *J Clin Dent*. 2018;29:40-44.
22. Anbarani AG, Ho J, Vu TH, et al. A double-blinded, randomized study evaluating the in vivo effects of a novel dental gel on enamel surface microstructure and microhardness. *J Clin Dent*. 2017;28:49-55.
23. Lam T, Ho J, Anbarani AG, et al. Effects of a novel dental gel on enamel surface recovery from acid challenge. *Dentistry*. 2016;6:397.
24. Lin K, Takesh T, Lee JH, et al. Effects of a dental gel over 6 months on periodontal health in subjects with stage II and III (Mild and Moderate) periodontitis. *J Dent Oral Sci*. 2019;1(3):10.37191.
25. Armitage GC. Development of a classification system for periodontal diseases and conditions. *Ann Periodontol*. 1999;4:1-6.
26. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: framework and proposal of a new classification and case definition. *J Clin Periodontol*. 2018;45(Suppl 20):S149-S161.
27. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Med Assoc*. 2013;310: 2191-2194.
28. Trombelli L, Tatakis DN, Scapoli C, Bottega S, Orlandini E, Tosi M. Modulation of clinical expression of plaque-induced gingivitis. II. Identification of "high-responder" and "low-responder" subjects. *J Clin Periodontol*. 2004;31:239-252.
29. Newbrun E. Indices to measure gingival bleeding. *J Periodontol*. 1996;67:555-561.
30. Turesky S, Gilmore ND, Glickman I. Reduced plaque formation by the chloromethyl analogue of vitamin C. *J Periodontol*. 1970;41:41-43.
31. Nayudu A, Lam T, Ho J, et al. Plaque removal and gingival health after use of a novel dental gel: a clinical study. *Dentistry*. 2016(10):396. .
32. Smiley CJ, Tracy SL, Abt E, et al. Evidence-based clinical practice guideline on the nonsurgical treatment of chronic periodontitis by means of scaling and root planing with or without adjuncts. *J Am Dent Assoc*. 2015;146:525-535.
33. Williams RC, Paquette DW, Offenbacher S, et al. Treatment of periodontitis by local administration of minocycline microspheres: a controlled trial. *J Periodontol*. 2001;72:1535-1544.
34. Jeffcoat MK, Bray KS, Ciancio SG, et al. Adjunctive use of a subgingival controlled-release chlorhexidine chip reduces probing depth and improves attachment level compared with scaling and root planing alone. *J Periodontol*. 1998;69:989-997.
35. Suvan J, Leira Y, Moreno Sancho FM, Graziani F, Derks J, Tomasi C. Subgingival instrumentation for treatment of periodontitis. A systematic review. *J Clin Periodontol*. 2020;47(Suppl 22):155-175.
36. Ng E, Lim LP. An overview of different interdental cleaning aids and their effectiveness. *Dent J (Basel)*. 2019;7(2):56.
37. Chen MH, Yin HJ, Chang HH, Kao CT, Tu CC, Chen YW. Baseline probing depth and interproximal sites predict treatment outcomes of non-surgical periodontal therapy. *J Dent Sci*. 2020;15:50-58.
38. Archila L, Bartizek RD, Winston JL, et al. The comparative efficacy of stabilized stannous fluoride/sodium hexametaphosphate dentifrice and sodium fluoride/triclosan/copolymer dentifrice for the control of gingivitis: a 6-month randomized clinical study. *J Periodontol*. 2004;75(12):1592-1599.
39. Mankodi S, Bartizek RD, Winston JL, Biesbrock AR, McClanahan SF, He T. Anti-gingivitis efficacy of a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice: a controlled 6-month clinical trial. *J Clin Periodontol*. 2005;32:75-80.

How to cite this article: Kaur M, Geurs NC, Cobb CM, et al. Evaluating efficacy of a novel dentifrice in reducing probing depths in stage I and II periodontitis maintenance patients: a randomized, double-blind, positive controlled clinical trial. *J Periodontol*. 2021;1-9.
https://doi.org/10.1002/JPER.20-0721