Special Issue Article

Safety and effectiveness of a two-step dentifrice/gel sequence with medication-associated hyposalivation: A randomized controlled trial in a vulnerable population

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Abstract: Purpose: A randomized controlled trial was conducted to evaluate the safety and effectiveness of a two-step dentifrice/gel oral hygiene sequence in a vulnerable population. **Methods:** Prior to the research, institutional review was obtained for the protocol, consent and advertising. The study targeted adults with medication-associated xerostomia, because of the plaque accumulation and possible oral safety risks seen in this population. Eligible subjects with a medication history and measured hyposalivation were randomly assigned to one of two oral hygiene groups: (1) a two-step 0.454% SnF_2 dentifrice and 3% H_2O_2 gel sequence or (2) a regular anticavity toothpaste control. Test products were dispensed with a regular manual brush in blinded over-labeled kits with usage instructions. Subjects were evaluated at baseline and after 2 and 6 weeks of test product use. Safety was assessed as adverse events from clinical examination and interview. Digital plaque image analysis of the anterior facial teeth measured fluorescein-disclosed daytime plaque levels, and unstimulated saliva was collected over a 5-minute period in pre-weighed vials. **Results:** A total of 49 subjects ranging from 31-80 years of age (53% female) were enrolled, and 45 completed Week 6. Only the two-step dentifrice and gel sequence differed significantly ($P< 0.005$) from baseline on daytime plaque coverage, and salivary flow increased significantly ($P= 0.033$) in that group as well. Between-group comparisons for daytime plaque favored the two-step sequence with 41-46% improvements in plaque control. At Week 6, adjusted daytime plaque means (SE) were 5.9 (0.7) and 10.0 (1.1) for the two-step and control groups, respectively ($P< 0.004$). Adverse events were mild in severity, groups differed significantly ($P= 0.02$) on occurrence, and events did not contribute to dropout. (*Am J Dent* 2018;31:24A-28A).

Clinical significance: In a randomized controlled trial among a vulnerable population, use of an oral hygiene sequence comprised of stannous fluoride dentifrice and a hydrogen peroxide whitening gel improved daily plaque control without adversely impacting salivary flow or oral health.

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Introduction

Xerostomia is a subjective sensation of oral dryness that is typically associated with salivary gland hypofunction.[1] Contributing factors include autoimmune diseases, surgical, chemical or radiation therapy, infections and others.[2-4] In addition, several hundred common medications, including antihypertensives, antianxiety agents, psychiatric remedies, antihistamines, and others have hyposalivation as a known side effect.[5] The consequences of combinations of xerostomic medications, especially for the population with no or limited insurance, may be severe in the oral cavity.[6] Prevalence is unknown, but a retrospective survey of dental patients suggests that 12% or more may report xerostomia.[7] At-risk groups may present with much higher (60%+) rates of xerostomia.[8] A systematic literature review suggests prevalence may be 27-32% of the medicated population.[8]

For both the general population and specific risk groups, saliva plays a recognized role in oral health. Chronic hyposalivation may contribute to oral diseases and conditions, including caries, sensitivity, tooth surface loss and various oral infections.[5,10] Surveys comparing severe chronic hyposalivation cases like Sjögren's syndrome to controls show significantly higher levels of plaque in the low-to-no salivary flow population.[11,12] In addition to plaque accumulation, research suggests differences in the prevalence and severity of gingivitis and periodontal disease, plus other adverse oral health outcomes. Various interventions have been proposed, though systematic review provides limited evidence of benefits for certain topical and non-drug therapies.[13,14] A recent review emphasizes the role of dentistry in the diagnosis and multidisciplinary management of xerostomia.[10]

Low salivary flow has also been shown to be related to the occurrence of oral mucosal lesions.[15] One study[16] implicated medication use and increased oral mucosal inflammation among US veterans. Behavioral, physiological and other factors may contribute to tissue fragility and healing impairment. Irrespective of the etiology, hyposalivation represents a potentially important model to study both favorable and unfavorable outcomes of interventions. Research involving some case types can be problematic, because of prevalence, access, or overall health risks, as exemplified by radiation-induced xerostomia. Alternatively, medication-associated xerostomia may represent a reasonably "vulnerable" population that is more amenable to clinical research, with broader inference.

Recently, a novel two-step sequence was developed for daily oral hygiene with 0.454% stannous fluoride dentifrice followed by 3% hydrogen peroxide whitening gel. The in-use esthetics with this novel sequence are impressive and unique, and clinical trials with this two-step sequence have shown promising results in a general population without serious oral adverse events.[17] Because toothpaste is generally used, a controlled clinical trial was conducted among individuals with medication-induced xerostomia to ascertain effectiveness and

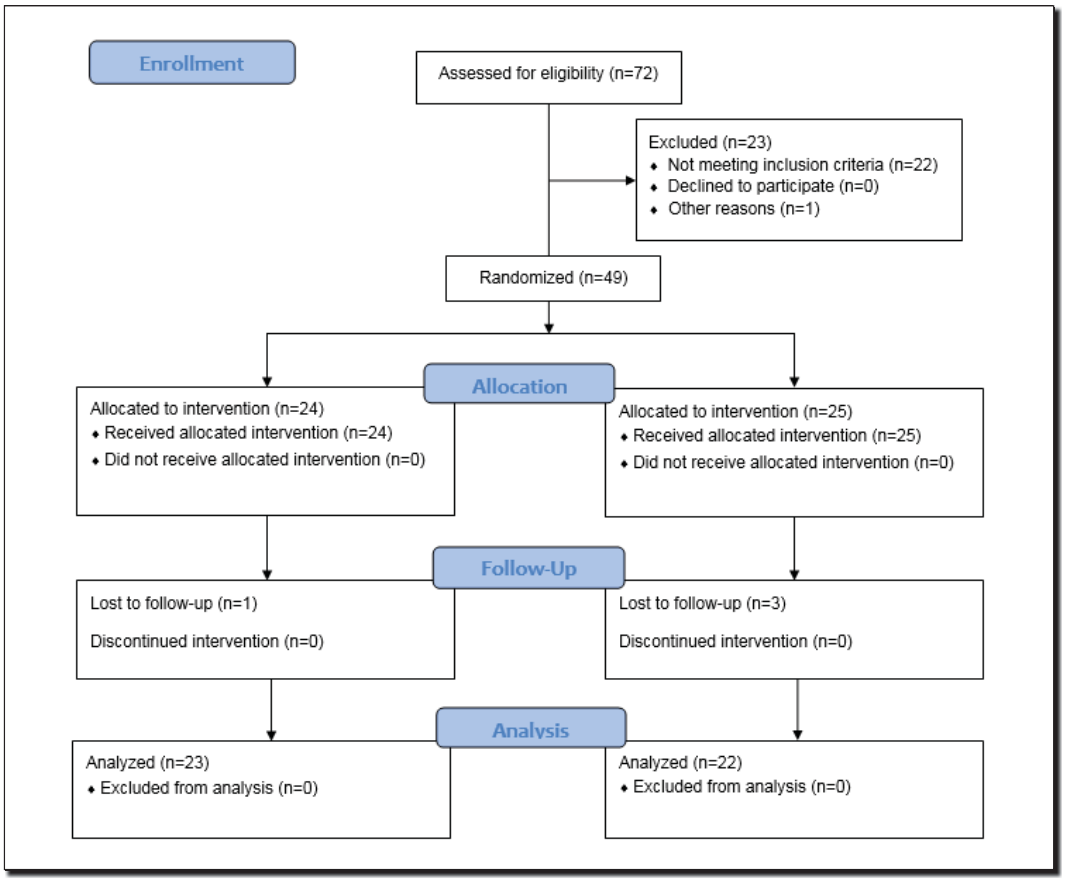

Fig. 1. Subject disposition.

safety of sequential two-step daily oral hygiene in this presumptively vulnerable population.

Materials and Methods

A randomized negatively-controlled clinical trial evaluated the safety and effectiveness of a novel two-step paste/gel oral hygiene sequence using stannous fluoride followed by hydrogen peroxide. The study targeted a vulnerable population, and prior to initiation, the Tufts University Health Sciences Campus Institutional Review Board reviewed (#10576) the study protocol, informed consent and advertising. Subjects with medication-associated xerostomia symptoms were recruited from the Oral Medicine clinic, general School of Dental Medicine, and elsewhere in Boston, Massachusetts, USA. There were four visits: screening, baseline, and after 2 and 6 weeks of treatment. Eligibility was determined at screening, and limited to adult volunteers with overnight plaque accumulation, a xerogenic medication history, and hyposalivation as evidenced by a 5-minute unstimulated salivary flow below 0.2 mL. Subjects were randomly assigned to treatment, and test products were dispensed at baseline for 6 weeks at-home use. Efficacy and clinical safety were measured at baseline, and each post-treatment visit, while salivary flow was measured at screening (for eligibility) and after 6 weeks of treatment.

The clinical trial directly compared two oral hygiene treatment groups: 1) a two-step dentifrice and gel system[a] comprised of 0.454% stannous fluoride dentifrice (step 1) for plaque and gingivitis followed by a 3% hydrogen peroxide whitening gel (step 2). Subjects were instructed to brush two times a day, using step 1 for 1 minute, and then step 2 for the second minute; or 2) 0.76% sodium monofluorophosphate dentifrice[b] (serving as a regular oral hygiene control). Subjects were instructed to brush thoroughly twice daily.

Eligible subjects were randomly assigned to treatment balancing for screening scores. All subjects received a regular manual brush along with marketed instructions as noted above to simulate "real world" usage, and for blinding, all assigned oral hygiene products and printed instructions were dispensed in plain subject-identified kit boxes for at-home unsupervised use.

Efficacy was assessed from daytime plaque levels on the anterior facial dentition, measured instrumentally using a standard image analysis method with daily calibration.[18] Dental plaque was disclosed using 5.0 mL of 1,240 ppm fluorescein dye in a glycerin base rinsed for 1 minute, with before/after rinsing with a phosphate buffer, with all test solutions prepared daily by the Tufts Medical Center pharmacy. Standard orientation and access for illumination were achieved using a chin rest and cheek retractors to allow 45°/0° illumination at a fixed focal distance, consistent with that described for tooth color imaging.[19] A single digital image was collected of the anterior facial dentition using a digital camera and 25 mm lens, polarized ultraviolet flash and portable computer. For each image, quadratic discriminate analysis was used to identify image pixels representing tooth surfaces and disclosed dental plaque surfaces, the latter of which is green under UV illumination. On the 12 anterior teeth, the number of pixels was summed, and plaque area was quantified from pixel counts as percent area coverage (0-100%). Using this instru-

Table. Baseline characteristics.

	Baseline characteristics – All subjects			
	SnF_2/H_2O_2 (N=24)	NaMFP (N=25)	Overall (N=49)	Two-sided P-value
Age (Years)				
Mean (SD)	58.0 (14.3)	56.8 (11.3)	57.4 (12.7)	0.74
Range	39 - 80	31 - 78	31 - 80	
Gender				
Female	13 (54%)	13 (52%)	26 (53%)	0.99
Male	11 (46%)	12 (48%)	23 (47%)	
Unstimulated saliva (mL/5 min)				
Mean (SD)	0.09 (0.07)	0.08 (0.06)	0.09 (0.07)	0.90
Range	0 - 0.20	0 - 0.19	0 - 0.19	
Plaque (Area %)				
Mean (SD)	12.5 (12.8)	11.5 (14.7)	12.0 (13.6)	0.70
Range	1.16 - 57.03	0.01 - 77.32	0.01 - 77.32	

mental approach, all plaque area measurements were collected blind to treatment and period. Baseline and post-baseline (Week 2 and 4) results were compared to quantify change in plaque area coverage over time.

Safety-related measures included assessment of salivary flow and clinical examination to assess possible physiological adverse effects as well as soft tissue irritation. Unstimulated salivary flow was measured after at least 1 hour of daytime fasting. Salivary samples were collected in pre-weighed 50 mL vials every 60 seconds over a 5-minute period. Collected saliva vials were weighed and salivary volume was determined using an assumed density of 1.0 mL/g, after which flow rates were calculated in mL/minute. The oral examination consisted of a thorough evaluation of the oral and perioral region by an experienced dentist who was blinded to treatment assignment. All oral adverse events, irrespective of causality, were recorded for analysis and follow-up.

Demographic data were summarized by treatment and overall. Mean plaque area % responses were compared to baseline using a paired difference t-test, while between-group comparisons used ANCOVA with baseline plaque as a covariate. Salivary flow response was analyzed similarly to plaque. Adverse events were summarized by type and severity using standard pharmaceutical coding practices, and groups were compared on adverse event occurrence and severity using Fishers Exact Test. All comparisons were two-sided using 5% levels of significance.

Results

Informed consent was obtained from 72 adults, 50 met study entrance criteria at screening, 49 had baseline measurements and were randomized and received assigned test products (24 in the two-step group and 25 in the control group). All randomized subjects (Fig. 1) were included in analyses.

The randomized population exhibited considerable diversity. Mean (SD) age was 57.4 (12.73) years, ranging from 31-80, and males and females were similarly represented (Table). All subjects (100%) presented with at least one medication where hyposalivation is a recognized side effect. Of these, antihypertensive and antianxiety medications were most common. In addition, all subjects exhibited hyposalivation at screening, with the overall mean 0.085 mL unstimulated saliva collected in a 5-minute period.

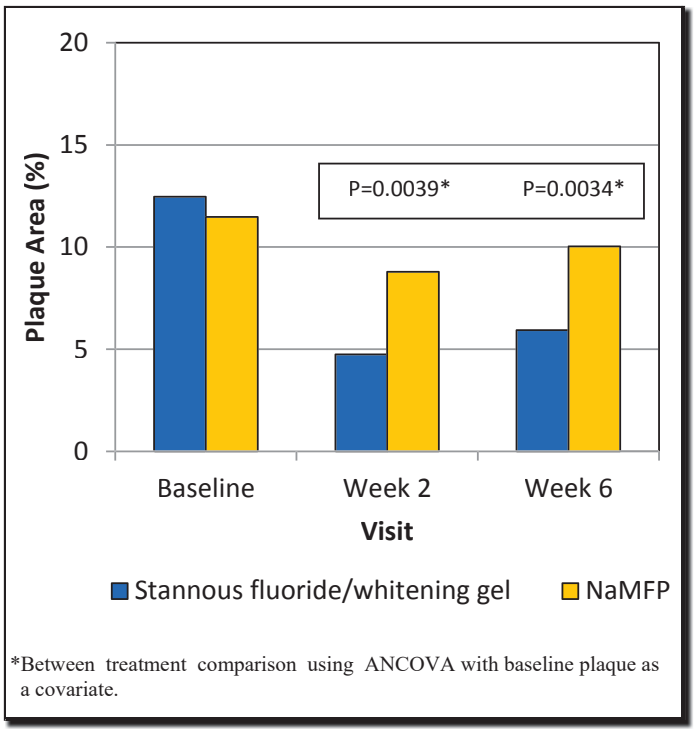

Fig. 2. Daytime plaque (Area % Coverage) by group.

At baseline, individual daytime plaque varied from negligible levels to more than three-quarters of tooth surfaces covered. The overall mean (SD) area was 12.0% (13.6), and groups were balanced (P> 0.70) on daytime plaque. Relative to baseline, only the two-step stannous fluoride dentifrice/hydrogen peroxide gel hygiene sequence yielded significant (P< 0.005) daytime plaque control. Plaque reduction effects were evident at the first treatment visit (Week 2) and persisted through the last treatment visit (Week 6). Between-group comparisons showed significant (P< 0.004) improvements in plaque control ranging from 41-46% for the two-step group relative to the control (Fig. 2).

Safety assessments included salivary flow measurements and adverse events. For saliva, the Week 6 mean (SD) 5-minute unstimulated salivary sample means were 0.15 (0.127) and 0.13 (0.09) in the two-step sequence and control groups, respectively. Only the two-step stannous fluoride plus hydrogen

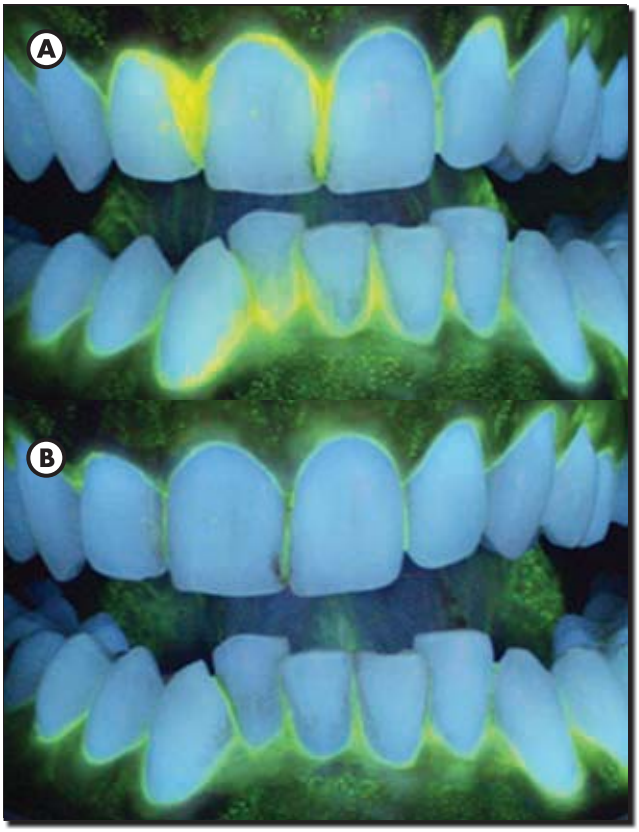

Fig. 3 A, B. Daytime plaque at Baseline and Week 2 (Two-Step Group).

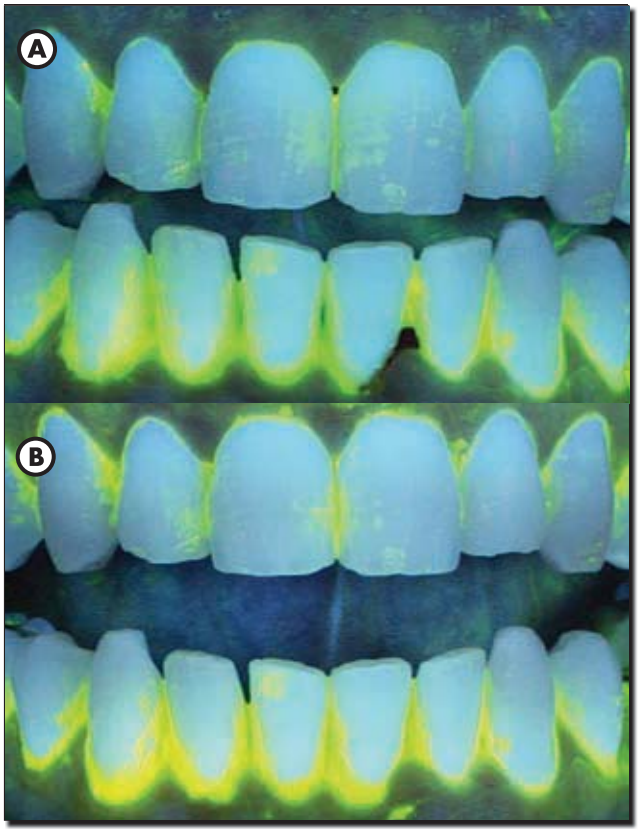

Fig. 4 A, B. Daytime plaque at Baseline and Week 2 (Control Group).

peroxide hygiene sequence demonstrated a significant (P< 0.04) increase in salivary flow versus baseline levels. Between-group comparisons were not significantly different. There were eight adverse events reported or observed during the study, involving both treatment groups. Four were observed on clinical examination, and by group, included two examples of minor desquamation and one example of tongue irritation in the two-step sequence, and one example of palatal irritation in the control group. Groups differed (P< 0.02) on adverse event occurrence, all of which was mild in severity, and none of the occurrences contributed to dropout.

Discussion

This study compared plaque response of an oral hygiene sequence comprised of a stannous fluoride dentifrice and a hydrogen peroxide whitening gel versus a regular dentifrice. Assigned test products were dispensed blind to treatment, and used at-home following the specific marketed instructions for each product, with outcomes measured instrumentally without bias. Results demonstrated significant plaque reductions relative to the control group beginning at Week 2, and persisting through Week 6. In this study of daytime plaque accumulation, use of a 0.454% stannous fluoride dentifrice/3% hydrogen peroxide gel sequence reduced daytime plaque accumulation by 40-50% versus regular oral hygiene.

The measured plaque effects were both generalized and visually evident. Most (92%) of the subjects who used the novel sequence had lower measured plaque levels at Weeks 2 and 6, ranging up to 99% reductions versus baseline levels. These outcomes were observed irrespective of starting levels; even those individuals with high baseline plaque exhibited appreciable reductions over time. Such improvements were readily apparent in the digital images used to measure plaque area, even among subjects with appreciable tooth malalignment that may affect brushing (Figs. 3 A,B). Response differed for the control group, which overall, failed to exhibit either significant measured plaque effects or appreciable visual improvement over time (Figs. 4 A,B).

Of note, the plaque effectiveness was observed without important adverse safety outcomes, and that may be particularly noteworthy given the population and test products in the clinical trial. With respect to the population, the study targeted adults with medication-associated hyposalivation. This population represents a potentially vulnerable population for oral safety, because of the possible impact of hyposalivation on oral mucosa responses.[15] Research suggests that unstimulated whole salivary flow rates of 0.12 - 0.16 mL/minute as the critical range separating individuals with salivary gland hypofunction from those with normal gland function.[20] With respect to the test products, one treatment group received a two-step sequence that included instructions specifying 1-minute brushing with a 3% hydrogen peroxide gel (the second step in this assigned hygiene regimen). Salivary peroxidase has long been identified as having a presumptive role in peroxide decomposition.[21] Differences in oral irritation were observed, but these were minor, and importantly, did not contribute to dropout. Clinical safety of topical peroxide application has previously been studied among individuals with medication-induced xerostomia within the context of esthetic tooth whitening.[22] The new research extends the merits of xerostomia as a model population for safety assessment to other forms of topical peroxide delivery, including dentifrices.

In addition to the safety findings, the research on xerostomia yielded an unexpected outcome. There was a significant ($P < 0.05$) increase in daytime unstimulated salivary flow in the two-step oral hygiene group. While the amount was relatively small (+0.06 mL/5 minute), this represented approximately a 72% increase above the baseline level. The xerostomia in the study was medication-associated, and in contrast to Sjögren's syndrome or similar conditions, it may be reversible with stimulation.[1] The mechanism remains unknown, and of course, further research is needed to ascertain whether this favorable effect on salivation is real and reproducible, and whether it contributes to other positive health or experiential outcomes. What is clear, however, is that use of stannous fluoride followed by hydrogen peroxide did not limit salivary flow relative to baseline or control in this vulnerable population study.

Overall, this research showed a significant and consistent reduction in daytime plaque following use of a stannous fluoride plus hydrogen peroxide oral hygiene sequence. The study was conducted among individuals with hyposalivation, as this population may have an added risk for oral irritation.[23] Safety outcomes in the new study were consistent with other general clinical research using this novel sequential oral hygiene technology.[17] To date, clinical testing in vulnerable populations remains uncommon, but research such as this may provide important evidence on the overall safety and tolerability with broader use.

a. Marketed as Crest Pro-Health [HD] and Oral-B [HD] depending on the region; The Procter & Gamble Company, Cincinnati, Ohio, USA.
b. Colgate Cavity Protection, Colgate-Palmolive, New York, New York, USA.

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