Effects of Cetylpyridium Chloride (CPC) Based Chewing Gum plus Tooth Brushing on Plaque Formation and Gingivitis: a Randomized, Double-Blind, Crossover, Placebo-controlled Clinical Trial

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Effects of Cetylpyridium Chloride (CPC) Based Chewing Gum plus Tooth Brushing on Plaque Formation and Gingivitis: a Randomized, Double-Blind, Crossover, Placebo-controlled Clinical Trial

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BRIEF DESCRIPTION OF PROJECT

A. Introduction & Rationale:

Plaque-induced gingivitis is an inflammatory disease restricted to the epithelial tissues surrounding the teeth. It is estimated that 86% of US population will be diagnosed with gingivitis at some point in their lives(Araujo et al. 2015; Eke, Wei, Borgnakke, Thornton-Evans, Zhang, Lu, McGuire, and Genco 2016b). The primary etiology of gingivitis, as well as most periodontal diseases, are a bacterial biofilm(Araujo et al. 2015; Chambrone et al. 2010). Although, not all individuals are equally susceptible to further tissue destruction, a prior history of gingivitis is required for patients to develop periodontitis(Page et al. 1997; Lang, Schätzle, and Löe 2009a; Jürgensen et al. 2012).

There is a consensus among the dental community that regular mechanical plaque control is enough for caries and periodontal disease prevention in most cases(Lang, Schätzle, and Löe 2009b). In the 1960's, Löe et al. clearly demonstrated the association

between plaque accumulation and gingivitis; furthermore, upon plaque removal, gingival health was re-established(Löe, Theilade, and Jensen 1965). However, research has shown that the average person brushes for 39 seconds each time(Macgregor and Rugg-Gunn 1979). Even more, most patients are not effective in interdental plaque removal(Lang, Schätzle, and Löe 2009b), hence the need for professional prophylaxis three to six times per year. With the premise that chemical agents are equally effective in preventing and reversing gingivitis, several studies investigated the efficacy of mouthwashes as plaque control agents in combination with mechanical regiments(Araujo et al. 2015). However, positive outcomes are often compromised by poor motivation and lack of compliance(). Therefore, delivery of chemical agents by a chewing gum might be an effective method to increase compliance in those patients with limited motor skills, unable or unwilling to perform regular oral hygiene.

Cetylpyridium Chloride (CPC) is a quaternary ammonia compound and a monocationic surfactant that is commonly used in mouthwashes as an antiplaque solution(Araujo et al. 2015). It can act as a detergent and has antiseptic properties, which are desirable characteristics of an ideal plaque control agent. Its ability to inhibit oral biofilm growth is due to the nonpolar region of the molecule that penetrates the cell membrane of the bacteria, leading to an osmotic dysregulation, resulting in loss of cytoplasmatic content, therefore bacterial cell death. In mouthwashes, CPC presents with a good absorption in the oral tissues and is has an anti-plaque, anti-calculus effect(Haps, Slot, and Berchier 2008), but has a low substantivity in the oral cavity of only 3 to 5 hours, which makes a

chewing gum delivery an ideal vehicle for CPC. The purpose of this study is to determine the effect of four times a day mastication of antiplaque Chewing Gum on various factors associated with plaque accumulation and gingivitis.

***Hypotheses:** CPC based chewing gum in addition to tooth brushing will reduce plaque and gingivitis scores in adults similarly to tooth brushing alone.

****Specific aims: Aim 1:*** to test the clinical plaque-inhibiting capacity of CPC based chewing gum, with mechanical oral hygiene, and placebo as a control. ***Aim 2:*** to evaluate the effects of using a CPC based chewing gum, with mechanical oral hygiene, to reduce gingivitis.

B. Research design and methods:

Study Design

This study is a placebo-controlled, double-blind, randomized crossover study to evaluate the plaque and gingivitis reducing capacity of Cetylpyridium Chloride (CPC) based chewing gum.

Study Population

Test group will be composed of up to 73 dental, dental hygiene students, faculty, and staff, who will be recruited from the University of Texas Health Science Center at Houston School of Dentistry (*UTHealth School of Dentistry)*. Those, who meet the inclusion criteria for the study, will meet with the investigators for additional information about the study and informed consent.

Plaque Index (PI)(Löe and Silness 1963) and Gingival Bleeding Index (GBI)(Lobene et al. 1989) and bleeding sites on probing (BOP)(Newbrun 1996) will be recorded at baseline for all selected subjects. After assessment, subjects will undergo oral prophylaxis to bring the plaque levels to zero. After oral prophylaxis subjects will be instructed on the proper brushing technique (Modified Bass techniques) and will be given either the test chewing gum or placebo formulation. The chewing gums will be packaged in similar fashion labeled only as sample A and sample B to ensure proper blinding of the product from the subjects and the examiner. All chewing gums will be supplied by Confadent oral technology, which will be sponsoring the current study. The test and control chewing gum will be dispensed to subjects along with a diary to record product usage and daily oral hygiene activity. All the subjects in both the groups will be given a soft bristled toothbrush and dental floss for use during the study. The study groups will be asked to refrain from all other unassigned forms of oral hygiene for the duration of the study. After four weeks, subjects will be recalled. GBI and PI will be evaluated at the end of 4 weeks using same indices.

Inclusion Criteria:

- Be aged 18 and older
- Be capable of giving informed consent themselves and are able and willing to participate in the study
- Patients willing to forgo any optional dental procedures during the study period, such as dental prophylaxis or teeth whitening
- Patients that regularly brush their teeth twice a day

Exclusion Criteria:

- Pregnant or breastfeeding women
- Patients taking long-term anti-microbial or anti-inflammatory drugs
- Patients unable or unwilling to provide informed consent
- Self-reported use of tobacco products
- Gross oral pathology, including widespread caries or chronic neglect, extensive restoration, pre-existing gross plaque or calculus, or soft or hard tissue tumor of the oral cavity
- Less than 26 teeth in the mouth
- Orthodontic appliances or removable partial dentures that will compromise the ability of the potential subject to participate in the study
- Periodontitis as indicated periodontal pockets greater than 5 millimeters on more than one site
- Inability to comply with assigned treatment regimen

Randomization and allocation:

Randomization will be carried out using a computer-generated random allocation table assigning the participants to one of study groups as follows:

Arms	**Assigned Interventions**
Experimental: CPC 0.09% + Xylitol chewing gum A	Dietary Supplement: CPC 0.09% + Xylitol

	All subjects will be instructed to chew four times a day, for at least 60 seconds, after which they expectorated. Other Name: CPC-Xylitol complex
Experimental: Xylitol only chewing gum B	Dietary Supplement: Xylitol All subjects will be instructed to chew four times a day, for at least 60 seconds, after which they expectorated. Other Name: Xylitol only

Half of the eligible participants will be randomly assigned to get CPC gum in the first treatment period (21 days), a wash-out period of 21 days, and then a placebo gum in the second treatment period (21 days). The other half would be assigned to follow the same schedule but with the treatment reversed. A statistician will perform the randomization whereas the project leader will distribute the chewing gums and instructions after a list generated as described.

C. Outcomes:

Primary outcome:

The primary outcome of interest in this study is the efficacy of the antiplaque chewing gum in reducing existing supragingival plaque and gingivitis will be assessed.

Plaque Index - Plaque will be assessed using the Turesky Modification of the Quigley-Hein Plaque Index(Turesky, Gilmore, and Glickman 1970), where a score of 0 to

5 will be assigned to each facial and lingual non-restored surface of all teeth that are present with the exception of third molars at baseline and week 3 of the study, as follows:

Scores	Criteria
0	No plaque
1	Separate flecks of plaque at the cervical margin of the tooth
2	A thin continuous band of plaque (up to one mm) at the cervical margin of the tooth
3	A band of plaque wider than one mm but covering less than one-third of the crown of the tooth
4	Plaque covering at least one-third but less than two-thirds of the crown of the tooth
5	Plaque covering two-thirds or more of the crown of the tooth

Gingivitis will be assessed using both the Gingival Index (GI), where a score of 0 to 3 will be assigned to six teeth, representing six segments of jaws, at baseline and week 3 of the study according to the following criteria:

Scores	Criteria
0	Absence of inflammation.
1	Mild inflammation - slight change in color and little change in texture.
2	Moderate inflammation - moderate glazing, redness, edema, and hypertrophy. Bleeding on pressure.
3	Severe inflammation - marked redness and hypertrophy. Tendency to spontaneous bleeding. Ulceration.

In addition, the percent of bleeding sites on probing (BOP)(Ainamo and Bay 1975) as described in Ainamo & Bay, 1975, where each of 4 gingival areas (disto-buccal, midbuccal, mid-lingual, and mesio-lingual) around each tooth will be light probed and scored from 0 to 2 as follows:

Scores	Criteria
0	Absence of bleeding after 30 seconds
1	Bleeding after 30 seconds
2	Immediate bleeding

Secondary Outcomes:

Changes from baseline to post-baseline efficacy assessment will be recorded for all parameters.

The antiplaque **chewing gum safety** will be evaluated; the oral soft (OST) and oral hard tissues (OHT) will be examined. Changes from baseline, such as soft tissue erythema, ulceration, and sloughing, will be noted and assessments will be made by the principal investigator as to whether they might be attributable to the antiplaque chewing gum.

Objective observation of **Discoloration of teeth** will be recorded using a Vita 3D scale. Changes on baseline (day 1) and day 22 and will be annotated as none, slight to obvious.

Study period:

The study period will be comprised of two periods of 21 days with a washout period in between. In each 21 days' period, there are three study visits: 1) Baseline Day

1, 2) Day 11 (after ten days of use), and 3) Day 22 (after 21 days of use – completion of the study). An additional screening visit will be required, and may or may not be combined with baseline visit, according to patients' preference.

Statistical analysis:

The Primary Aim is to evaluate the change in in the score of PI, GI, and BOP averaged across the teeth between the CPC based chewing gum and the placebo gum at day 21. Assume there is no carryover effect and no interactions between patients, treatments, and periods; a paired t-test is used to compute the sample size. To detect an effect size for CPC based chewing gum on the changes in the three outcomes at day 21 relative to baseline, with a within-subject correlation of 0.3 and a significance level of 0.05, the study requires 62 participants to achieve 80% power after Bonferroni correction for three tests. Considering a dropout rate of 15%, we need to recruit 73 participants.

Linear mixed model will be used to evaluate treatment effects on the three primary outcomes at day 21 compared to baseline independently, with Bonferroni correction. If normality of the outcomes does not hold, appropriate transformation or generalized estimating equation method can be used. Furthermore, the three outcomes could be analyzed simultaneously while accounting for the within-subject correlation. Similar analyses will be done for the secondary outcomes including changes from baseline to post-baseline efficacy assessment for day 21. Longitudinal data analysis will be used to analyze the data through day 0, 10, and 21, to see the pattern of the outcomes. Descriptive statistics will be provided for safety data. All analyses will be performed in SAS 9.4 (Cary, NC).

D. Significance:

The overall dental services expenses in 2014 in the USA alone was 113.5 billion(Wall, Nasseh, and Vujicic 2014), with dental prophylaxis accounting to approximately one-quarter of all dental services provided by general dentists in the USA(Eke, Wei, Borgnakke, Thornton-Evans, Zhang, Lu, McGuire, and Genco 2016a). In Europe, when periodontal therapy was the focus of the cost-benefit analysis, it was reported that the mean cost of periodontal therapy per tooth per year was € 2.1 (the US $ 2.23), and the average total cost per patient for non-surgical therapy was reported as € 6,450 (US $6,843.13) with 3.5 times increase in the average total cost for surgical therapy per patient (€ 23,000 - US $24,401.85) for the same period(Fardal and Grytten 2013). Furthermore, the authors emphasize that the cost of implant maintenance, due to high risk of peri-implantitis was significantly higher than the cost of maintaining a natural dentition(Watt and Petersen 2012). Analyzing the financial burden of a late periodontitis diagnosis alone would warrant further research to identify efficient techniques for early detection of periodontal disease, more effective methods of promotion of periodontal health, as well as identifying preventive tools for gingivitis and plaque accumulation. As stated by several researchers before: -*Prevention is crucial to periodontal health(Page et al. 1997; Mariotti and Hefti 2015; Hasan and Palmer)*By increasing access to additional prevention tools, patients will have access to discounted treatment options. Thus optimal oral health care will be the expected outcome.

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