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Efficacy of Chlorhexidine Varnish for the Prevention of Adult Caries: A Randomized Trial

ABSTRACT

The Prevention of Adult Caries Study, an NIDCR-funded multicenter, double-blind, randomized clinical trial, enrolled 983 adults (aged 18-80 yrs) at high risk for developing caries (20 or more intact teeth and 2 or more lesions at screening) to test the efficacy of a chlorhexidine diacetate 10% weight *per* volume (w/v) dental coating (CHX). We excluded participants for whom the study treatment was contraindicated or whose health might affect outcomes or ability to complete the study. Participants were randomly assigned to receive either the CHX coating (n = 490) or a placebo control (n = 493). Coatings were applied weekly for 4 weeks and a fifth time 6 months later. The primary outcome (total net $D_{1\text{-}2}FS$ increment) was the sum of weighted counts of changes in tooth surface status over 13 months. We observed no significant difference between the two treatment arms in either the intention-to-treat or *per*-protocol analyses. Analysis of 3 protocol-specified secondary outcomes produced similar findings. This trial failed to find that 10% (w/v) chlorhexidine diacetate coating was superior to placebo coating for the prevention of new caries (Clinicaltrials.gov registration number NCT00357877).

KEY WORDS: caries, chlorhexidine coating, RCT-Randomized Clinical Trial, adults, prevention.

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INTRODUCTION

Despite the high prevalence and impact of dental caries among adults, prevention research has focused primarily on children (Griffin *et al*., 2005), and strategies to prevent adult caries have remained essentially unchanged for many years. Prescription strength or over-the-counter fluoride products are recommended for adults with high caries risk but have not been sufficient to reduce caries (Featherstone, 2008). An NIDCR consensus conference (Horowitz, 2004) emphasized the need to expand the evidence base for preventive agents for adults and suggested that chlorhexidine, an antimicrobial agent, merited further consideration. A 13-month trial in 240 45- to 75-year-old xerostomic individuals with high *S. mutans* counts tested the caries-preventive effects of 3 treatments: CHX dental coating (chlorhexidine diacetate 10% weight *per* volume [w/v] , Prevora®); a placebo coating (benzoin sumatra USP 20% [w/v]); and a sham coating (Banting *et al*., 2000). CHX Technologies, Inc. (Toronto, ON, Canada) supplied all the coatings. In the intention-to-treat analysis, the active treatment group had 40.8% fewer root surfaces with caries ($p \leq 0.02$) and 14.4% fewer coronal surfaces with caries ($p \leq 0.06$) relative to the placebo coating group. No significant difference was seen *versus* the sham coating control group.

This paper reports the primary findings of a trial testing the same agent in a larger, more diverse population of adults.

MATERIALS & METHODS

The Prevention of Adult Caries Study (PACS) was a multicenter, placebo-controlled, double blind, randomized clinical trial designed to test the hypothesis that a CHX coating, compared with a placebo coating, reduces dental caries increment in at-risk adults over a period of 13 mos. The study was conducted under an Investigational New Drug license from the US Food and Drug Administration (FDA).

The detailed study rationale and design are described elsewhere (Vollmer *et al*., 2010). Summary details are provided here and in the Appendix. Four clinical centers provided a diverse sample with respect to fluoride exposure, dental reimbursement, and race: Delta Dental (Westborough, MA, USA);

Kaiser Permanente Dental Program (Portland, OR, USA); Tuba City Regional Health Care Corporation (Navajo Nation in Arizona, USA); and Tufts University School of Dental Medicine (Boston, MA, USA). The study chair was at Tufts; Kaiser Permanente Center for Health Research in Portland, OR, served as the data coordinating center. The Institutional Review Board at each institution approved the study, all participants provided written informed consent, and all study personnel were trained and certified in Good Clinical Practice (Food and Drug Administration, 1996).

Study Population

Participants were from 18 to 80 yrs old and had 20 or more intact teeth and 2 or more lesions (at least 1 cavitated) at screening. We excluded participants for whom the study treatment was contraindicated or whose health might affect outcomes or ability to complete the study.

Sites used a variety of means to identify likely eligible individuals, who were then invited for a formal eligibility screening visit. Before participants were randomized, they received restorative care for all cavitated lesions from a dentist who was independent of the study. A second, baseline oral examination was obtained at the randomization visit, after which the initial treatment was applied. Of 1521 individuals attending an initial screening visit, 124 (8%) were ineligible, 983 (65%) were randomized, and the remainder either refused or were still pending at the close of recruitment (Fig.).

Randomization and Blinding

Participants and staff were blinded to study arm. A centralized Web-based application randomized participants 1:1 to receive CHX or its placebo. Randomization was stratified by clinical center and age tertiles with permuted blocks of various sizes within strata. Staff received a number corresponding to a sealed box containing the treatment vials for that participant. Active and placebo materials were packaged identically by an independent vendor, and were distinguishable only by a numeric label.

Study treatments

Study treatments were applied by blinded and certified personnel after participants received a rubber cup prophylaxis with non-fluoridated paste and gross scaling as needed. The first 4 treatment applications occurred weekly in the first mo after randomization, followed by a fifth treatment 6 mos later. Cavitated lesions discovered at the fifth visit were restored before the coatings were applied. Participants received either the active coating (chlorhexidine diacetate 10% [w/v], Sumatra benzoin 20% [w/v], and alcohol, Prevora®) or the placebo coating (Sumatra benzoin 20% [w/v] and alcohol), followed by application of a methacrylate coating designed to protect the initial coating. CHX Technologies, Inc. (Toronto, ON, Canada) supplied all the coatings. Coatings were applied to all tooth surfaces, and staff weighed each vial before and after application to assess the applied dose. We did not attempt to assess whether material was left on the applicator or lost to evaporation. Although the active and placebo coatings had some differences in taste, this was not noticeable when the materials were applied according to protocol. A detailed rationale for the treatment protocol is included in the Appendix.

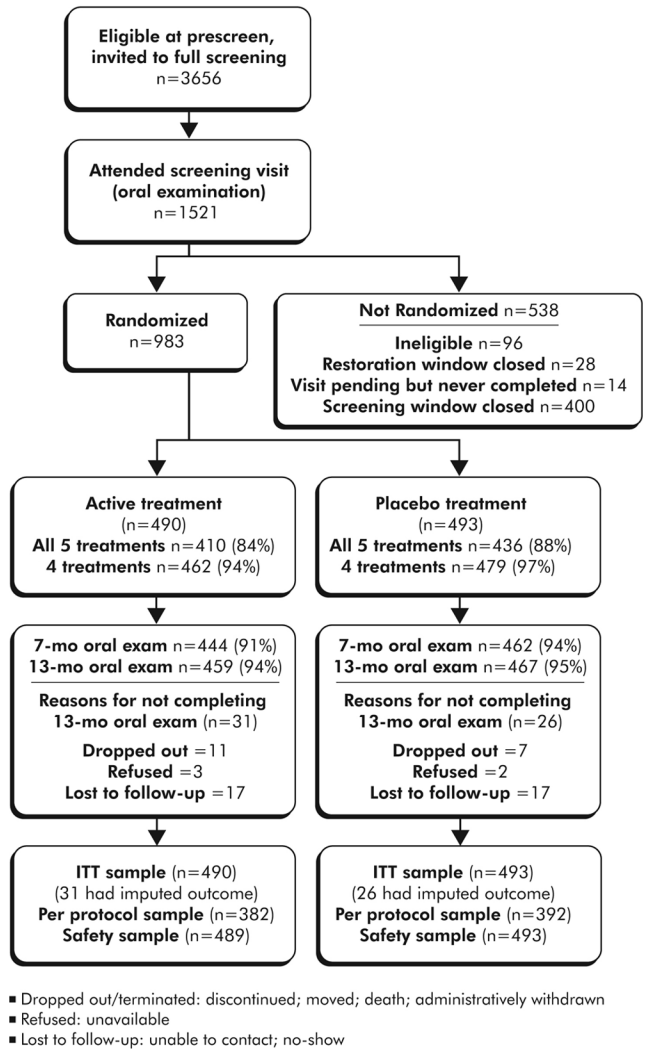

Figure. Flowchart for participants in the PACS trial.

Schedule and Types of Measurements

Demographic information and predictors of caries were collected at initial screening. Medical history, oral health behaviors, and caries data were collected at randomization and again 7 and 13 mos post-randomization. Information about medical history changes, soft tissue changes, adverse events, medication usage, and acidic beverage consumption was collected at each visit. Adverse events were coded by certified coordinating center staff using the Medical Dictionary for Regulatory Activities (MedDRA Maintenance and Support Services Organization, 2005).

Caries Examination

Paralleling previous trials of the same agent (Banting *et al*., 2000; Forgie *et al*., 2000), we used the Pitts & Fyffe taxonomy (Pitts and Fyffe, 1988), which identifies 3 stages of lesions on

coronal surfaces: non-cavitated lesions (D_1); cavitation extending into, but not through, the enamel (D_2); and cavitated lesions that involve the dentin (D_3). The classification was extended to root surfaces with 2 stages: non-cavitated (D_1) and cavitated (D_2). Caries was judged visually (without radiographs) by trained, calibrated examiners using proper lighting, 5 sec of air-drying, and a CPITN probe. Examiners also noted missing teeth (M), unscorable surfaces (Y), and the presence of crowns (C) or fillings (F) on tooth surfaces; for example, a code of CD_1 denoted the presence of both a crown and a marginal D_1 lesion on a surface. Pit and fissure sealants were coded but treated as sound (S) surfaces in our analysis. We also treated D_2 and D_3 lesions equivalently and refer to them hereafter as simply D_2 lesions. Calls for all 32 possible teeth were recorded, and all teeth were judged to have 9 surfaces (5 coronal and 4 root), making a total of 288 surface calls.

Examiners received calibration training annually (Banting *et al*., 2011). Unweighted kappa (Cohen, 1960) was used to estimate intra- and inter-examiner reliability of the 5×5 classification of sound *vs.* D_1 *vs*. D_2 *vs.* filled or crowned *vs.* missing or unscorable. Aggregating over calibration sessions and examiners, the mean intra- and inter-examiner reliabilities were 0.86 and 0.77 (see Appendix for more extensive calibration results).

Outcome Measures

The primary outcome (*total net D*1-2*FS increment*) was the sum of weighted counts of transitions in tooth surface status (root and coronal surfaces combined) from randomization to the 13-month follow-up visit. Disease progression had a positive weight (*e.g.*, S-to-D_1 or D_1-to-D_2 = 1, S-to-D_2 = 2). Reversal had a negative weight (*e.g.*, D_1-to-S = −1). No change, transitions to or from missing or unscorable, and impossible transitions had 0 weight. Incident fillings and crowns were treated the same as incident D_2 lesions for purposes of scoring.

Three secondary outcomes were examined: the *cumulative net* $D_{1\text{-}2}$*FS increment* (which was similar to the total net $D_{1\text{-}2}$FS increment but separately scored and combined transitions from the baseline to 7-month visit and from the 7- to 13-month visits), the *total crude* $D_{1\text{-}2}$*FS increment* (analogous to the total net $D_{1\text{-}2}$FS increment but ignoring reversals), and the *cumulative crude* $D_{1\text{-}2}$*FS increment* (analogous to the cumulative net $D_{1\text{-}2}$FS increment but ignoring reversals). All scores were rank-normalized and re-scaled to observed mean and variance over all participants (Banting *et al*., 2000).

Statistical Analysis

The primary outcome analysis (conducted with SAS® Release 9.2) was performed on the Intention-to-Treat sample (ITT) with standard linear regression, with treatment and site as class variables and age and age-squared as continuous covariates. A planned secondary analysis tested for a site-by-treatment interaction. Identical analyses were carried out in the *per*-protocol subsample (defined as participants receiving all 5 treatments and with data collected on a protocol-defined schedule) and for all 3 secondary outcomes in both samples. No interim analysis was conducted.

We used SAS® PROC MI to create 8 imputed datasets *via* data augmentation with Markov Chain Monte Carlo sampling (Schafer and Graham, 2002). Identical analyses were run on each dataset, with results combined with SAS® PROC MIANALYZE to obtain p-values that were adjusted for the uncertainty inherent in imputing missing data (Rubin, 1987). The statistician was blinded to treatment group in the 13-month data until after the imputations were completed and data were locked.

Sample size was estimated with simulated data with rank normalized scores. We calculated that 832 participants would yield a power of 90% to detect a 20% reduction in caries incidence (from a hypothesized mean increment of 1.5), and adopted a target of 1000 randomized participants to allow for attrition.

Participants who had one or more treatment applications were included in the safety analysis, which computed odds ratios and 90% confidence intervals for adverse events reported by 1% or more of the participants based on the MedDRA® Preferred Term classification.

RESULTS

The two study arms were well-matched by baseline characteristics (Table 1). Follow-up and treatment adherence were excellent (Fig.). The mean dose of CHX over all applications in the ITT sample was 41 mg (95% CI = 40.1, 41.5 mg), with mean cumulative dose of 198.4 mg (95% CI = 194.7, 202.0 mg). The corresponding target doses were 33 mg/application and 165 mg cumulative.

The vast majority (94%) of "transitions" between the baseline and 13-month visits were no change (diagonals in Appendix Table 6). Ignoring the impossible transitions, which are not scored in the analysis, the mean number of cavitated, filled, or crowned tooth surfaces increased from 31.8 to 34.1 *per* participant over this timeframe, while the mean number of surfaces with uncavitated (D_1) lesions decreased from 7.1 to 4.2. Since 93% of root surfaces were not exposed, these represent primarily coronal data.

For the ITT sample, we failed to observe a significant difference in total net $D_{1\text{-}2}$FS increment between the two treatment arms, with the observed increment actually higher for the active group (Table 2). No significant site-by-treatment interaction was observed ($p = 0.49$), although there was a significant site main effect ($p < 0.0001$). Analyses of secondary outcomes for the ITT sample and of all 4 outcomes in the *per*-protocol sample produced qualitatively similar results (Table 3).

In the safety sample, the incidence of adverse events differed for only 2 events. Pharmaceutical product complaint (*e.g.,* unpleasant taste) was higher in the active group (28 *vs*. 12 participants, OR = 2.4, 90% CI = 1.4, 4.3), while dyspepsia was reported more frequently among those in the placebo arm (9 *vs*. 2, OR = 0.2, 90% CI = 0.1, 0.8). To our knowledge, no one became unblinded as a result of the taste of the coatings.

Unplanned exploratory analysis of the net D_2FS caries increment (*i.e.,* treating D_1 lesions as sound) found no overall treatment effect (see Appendix).

Table 1. Baseline Characteristics of Randomized Participants

	Active	Placebo	Overall
	(n = 490)	(n = 493)	(n = 983)
Age (yrs)[a]	42.9 (14.3)	42.8 (14.3)	42.8 (14.3)
Age range (min, max)	18, 78	18, 80	18, 80
Male (%)	49.2	50.7	49.9
Hispanic ethnicity[b] (%)	6.9	6.7	6.8
Race (%)			
American Indian/Alaska Native	18.0	16.2	17.1
Asian/Native Hawaiian/Other Pacific Islander	2.7	4.5	3.6
African American	5.5	6.5	6.0
Caucasian	69.8	69.6	69.7
More than one race/Other	3.1	2.6	2.9
Don't know/Refused	1.0	0.6	0.8
Income [c] (%)			
Less than $30,000	16.8	17.3	17.0
$30,001 to $50,000	19.0	17.1	18.0
$50,001 to $75,000	21.4	22.0	21.7
Over $75,000	29.3	30.0	29.7
Don't know	7.4	7.3	7.4
Refused	6.2	6.3	6.3
Total number of cavitated surfaces[a]	2.8 (2.9)	3.0 (3.0)	2.9 (2.9)
Total number of D_1 surfaces[a]	6.9 (7.0)	7.6 (8.1)	7.2 (7.5)
D_1MFS score (across all 288 possible surfaces)[a,b]	86.9 (37.3)	87.1 (34.8)	87.0 (36.0)

[a]Continuous data presented as mean (standard deviation).
[b]Includes imputed data.
[c]Data not available for Tuba City, n = 816 overall, 406 active arm, 410 placebo arm.

Table 2. Adjusted Mean Combined Coronal and Root Net $D_{1\text{-}2}$FS Increment Scores in the Intent-to-Treat Sample, by Treatment Arm and by Site, with Results of Tests of Main Effects of Treatment and Site

Treatment Arm	Mean	SE	95% Conf. Interval	p-value
Active (n = 490)	2.68	0.32	(2.05, 3.30)	
Placebo (n = 493)	2.43	0.32	(1.80, 3.05)	
Active – Placebo	0.25	0.44	(–0.60, 1.11)	0.56

			p-values for Site Differences		
Site	Mean	SE	Delta	Portland	Tuba City
Delta (n = 180)	3.31	0.52			
Portland (n = 403)	0.50	0.35	< 0.0001		
Tuba City (n = 167)	1.25	0.53	0.0056	0.24	
Tufts (n = 233)	5.15	0.45	0.0074	< 0.0001	< 0.0001

Group means computed by the SAS LSMEANS procedure adjusted for treatment, site, age, and age-squared. Site effects are mean scores across treatment arms and not site-specific treatment differences. Treatment effect and all p-values derived from corresponding linear regression model. Outcome includes imputed data.

DISCUSSION

The PACS study has numerous important strengths, including the randomized design, double-blind treatments, careful attention to quality control, excellent participant retention and protocol adherence, a large sample, and generalizability to populations with varied dental delivery systems, access to dental care, and levels of fluoride exposure.

Our negative findings might have several explanations. First, the 10% (w/v) CHX coating used in this study may not be efficacious for coronal caries prevention. Consistent with our results, Banting and co-workers (Banting *et al.*, 2000) did not see a

Table 3. Results of Secondary Outcome Analyses

	Active	Placebo	Difference	95% CI	p-value
Intention-to-treat sample	n = 490	n = 493			
Cumulative net D_{1-2}FS increment	5.88 ± 0.43	5.53 ± 0.42	0.35 ± 0.57	(–0.77, 1.46)	0.54
Total crude D_{1-2}FS increment	5.96 ± 0.28	6.47 ± 0.27	–0.51 ± 0.38	(–1.25, 0.23)	0.18
Cumulative crude D_{1-2}FS Increment	10.72 ± 0.43	11.39 ± 0.42	–0.68 ± 0.57	(–1.80, 0.45)	0.24
Per-protocol sample	n = 382	n = 394			
Total net D_{1-2}FS increment	2.55 ± 0.36	2.51 ± 0.36	0.04 ± 0.49	(–0.92, 0.99)	0.94
Cumulative net D_{1-2}FS increment	5.62 ± 0.45	5.48 ± 0.44	0.14 ± 0.61	(–1.05, 1.33)	0.81
Total crude D_{1-2}FS increment	5.91 ± 0.30	6.51 ± 0.30	–0.60 ± 0.41	(–1.41, 0.21)	0.15
Cumulative crude D_{1-2}FS Increment	10.35 ± 0.45	11.20 ± 0.44	–0.85 ± 0.61	(–2.04, 0.34)	0.16

Group means ± SEs computed by the SAS LSMEANS procedure adjusted for treatment, site, age, and age-squared. Treatment effects and all p-values derived from corresponding linear regression model. All outcomes include imputed data.

statistically significant effect on coronal caries for chlorhexidine *vs*. either the placebo-coating or sham control groups. Similarly, Forgie and colleagues (Forgie *et al*., 2000) found no greater effect of a chlorhexidine coating on D_{1-2} increment than in a placebo control in a three-year study of 1240 adolescents, although adherence in that study was poor. Systematic reviews have also found the evidence for chlorhexidine to be weak, especially for coronal caries prevention and in patients who are not at very high risk of caries progression (James *et al*., 2010; Bekhuis, 2011; Slot *et al*., 2011). Since PACS participants had very few exposed root surfaces, ours was a study of primarily coronal caries increment.

Second, PACS included transitions to and from uncavitated (*i.e.,* D_1) lesions in the primary outcome. We chose this outcome based on ICDAS reports and on assertions of sensitivity and efficiency of the D_1 outcome from other research (Kingman and Selwitz, 1997; Chesters *et al*., 2002; Biesbrock and Bartizek, 2005). Nonetheless, we acknowledge that D_1 lesions are more difficult to detect than D_2 lesions, especially when they are located interproximally just under the contact.

Third, it may be that our follow-up period was too short for an effect to be observed, but this seems unlikely, given that the estimated overall treatment effect in this study, though essentially zero, was in the opposite direction from that predicted. Moreover, we had greater power than originally planned to detect a 20% drop in mean caries increment, since the observed caries increment in the placebo group was higher than assumed in our sample size calculations (2.4 *vs*. 1.5).

Other factors may also have contributed to our negative findings. Participants had all cavitated lesions restored at baseline and again midway through the study, and had a rubber cup prophylaxis and gross scaling as needed prior to each treatment application. These factors, together with the fact that a protective coating was applied at each treatment visit, may have reduced the cariogenic microflora in all participants (Axelsson *et al*., 2004). Certainly the decrease in D_1 surfaces that occurred in participants in both treatment arms suggests that remineralization was achieved in both groups, though the lack of a prophy cleaning at the final examination could also have impaired visibility and thus contributed to an increase in missed D_1 calls at that visit. In addition, participants had varying use of fluoride products (including the fluoridated toothpaste provided by the study) and varying exposure to fluoridated community water. While this may have improved the generalizability of our findings, it may also have inflated the variance of our study outcomes. Finally, lack of radiographs (done at the request of the FDA) may have reduced the accuracy of the calls made during the oral examinations.

This trial of 10% CHX dental coating found no evidence of anti-caries effect on the net or crude D_{1-2}FS increment. Based on these findings and the available literature, we conclude that chlorhexidine is not effective in preventing coronal caries. It may have a role in the prevention of root caries in very high-risk populations, although further studies would be needed to confirm this.

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