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ORIGINAL ARTICLE

Efficacy of a 10% chlorhexidine coating to prevent caries in at-risk community-dwelling adults

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Abstract

Objective. The purpose of the study was to determine the efficacy of a 10% chlorhexidine tooth coating in reducing the incidence of cavitated carious lesions in adults. ***Materials and methods.*** The trial was a randomized, double-blind, multi-center, placebo controlled study with 983 participants, receiving the application of either the active or the placebo coatings to the entire dentition. Four applications were made in the first month and one at the 7th month. The final examination was performed at 13 months. ***Results.*** Coronal caries showed a statistical reduction ($p = 0.02$). Examination of the results by site showed that the highest risk participants experienced the most significant preventive effect ($p = 0.003$). When two sites (uninsured and public health) are pooled the treatment p-value is 0.0009, interaction term has a p-value of 0.0001. ***Conclusion.*** 10% Chlorhexidine was highly effective in high risk participants with more than two cavities at the initial examination. This trial in conjunction with other published trials of this topical medication indicates that chlorhexidine exerts its action by preventing the transition of D1 lesions to cavitated lesions, not on sound to D1 lesions.

Key Words: *clinical trial, antibacterial, tooth decay*

Introduction

Caries is a chronic bacterial disease, usually low grade and slowly progressive. As such it should show a response to antibacterial agents. The causative organisms, principally *Streptococcus mutans*, reside in the biofilm covering the teeth. They ferment dietary sugar, producing lactic acid, which dissolves the tooth substance in progressive stages. These stages of the carious process were described by ICDAS [1] and earlier by Pitts and Fyffe [2] in a modified form to encompass fewer stages of progression. In this classification D1 is the earliest stage, showing decalcification but no cavitation. D2, the next stage, shows cavitation, as do D3 and D4.

The antibacterial agents used to control caries by their action on *Streptococcus mutans* have primarily been halides, fluorine, iodine and chlorine in various formulations. Chlorine in the form of chlorhexidine has been widely used both in medicine and industry. Early encouraging reports of the efficacy of a chlorhexidine varnish applied to the teeth were published in the early 1980s [3,4], but the results of further clinical trials by different authors have been mixed.

There is a lack of consistency in the published literature, with widely different concentrations of chlorhexidine being used (0.02–40%), different dosage forms and methods of application, different treatment regimes and different study populations and end-points. Varnishes, gels and mouthwashes have been employed, as have chlorhexidine-containing toothpastes.

The objective of the Prevention of Adult Caries Study (PACS) was to examine the preventive effects of a tooth coating containing 10% chlorhexidine acetate applied to the entire dentition in a representative population of community dwelling adults. Four controlled studies have been conducted using this particular formulation and the results reported [5–8]. The United States Federal Drug Administration (FDA) approved the protocol for this version of PACS (the fifth study), the results of which are presented in this paper.

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Materials and methods

Study design

The study was double-blinded, multi-center, randomized and placebo controlled. The chlorhexidine and the placebo were provided in containers to which randomized numbers had been given. The study population was representative of the community-dwelling adult population of the US. Four sites were chosen for the trial on the basis of the method of delivery of dental care. These recruitment centers were a third-party managed care program in Portland, Oregon, third party fee-for-service program in suburban Boston, Massachusetts, an uninsured program in the inner-city of Boston and a center delivering public dental health benefits to Native Americans in northern Arizona. The protocol demanded that all cavitated lesions were restored prior to randomization.

Randomization was achieved in blocks of eight participants. Balance for patient's age in the sample was achieved using stratification by age groups. The study medications were provided by an independent pharmacist according to the randomization code.

Dental examiners were staff dentists at the four study centers. They were trained and calibrated by an experienced teacher using methods described by Banting et al. [9]. The hygiene teams were trained on methods for applying and weighing the study medications and for reporting adverse events. All members of the teams were trained on Good Clinical Practice (GCP), were monitored for this and for accuracy during the trial and the study's procedures and standards audited by an independent expert.

Statistical analysis

Statistical hypotheses were tested with two-sided Type 1 error at $\alpha \leq 0.05$. Interaction terms were assessed at $\alpha \leq 0.10$. The Intent-to-Treat (ITT) population included all randomized participants, while the per-protocol population was required to meet all the criteria. The primary efficacy variable is the total number of new cavitated carious surfaces (NNCS) during the 13 month baseline-to-end of study (Visit 1 to Visit 6) analytical period. The primary efficacy analysis was the mean NNCS per participant at Visit 6 (13 months).

Table I. Characteristics of the participants; the prevention of adult caries study.

	Insured, fee for service model	Insured, managed care model	Public health	Uninsured	Total or significance
Randomized participants (active + placebo in the ITT group)	180 (18.3% of total)	403 (41.0% of total)	167 (17.0% of total)	233 (23.7% of total)	983
Demographics					
Mean age	39	47	38	42	43
Range in age	18 – 78	18–78	18–73	18–80	18–80
% Female	52.2%	49.4%	59.9%	42.5%	50.1%
Race					
Non-Hispanic/White	79.4%	87.1%	0.%	65.2%	65.7%
Non-Hispanic Black/ African American	3.3%	3.7%	0.%	15.%	5.7%
Hispanic	8.9%	3.7%	6.%	11.2%	6.8%
Non-Hispanic Other Minority	7.2%	5.2%	94.%	8.2%	21.4%
Don't know/Refused	1.1%	0.2%	0.%	0.4%	0.4%
Cavities at the screening visit					
Mean cavities per participant at screening	2.16	1.59	5.02	4.12	$p < 0.0001$
Participants with 1 cavity at screening	75 (42%)	263 (65%)	25 (15%)	40 (17%)	$p < 0.0001$
Participants with 2 cavities at screening	53 (29%)	89 (22%)	34 (20%)	49 (21%)	$p = 0.1332$
Participants with 3 or more cavities at screening	52 (29%)	51 (13%)	108 (65%)	144 (62%)	$p < 0.0001$
Other characteristics related to cavities					
% of participants reporting household income of less than $50,000	24%	31%	Not reported (est. >50%)	51%	

Table II. Mean number of cavities per subject at the end-of-study visit; the prevention of adult caries study. Least-squared means and standard error.

Tooth surfaces	Placebo (n = 467)	Active (n = 459)	Active–Placebo	Clinical effect (% reduction)	Statistical significance (p-value)
Coronal	0.17 ± 0.023	0.010 ± 0.023	−0.07 ± 0.031	42.9%	0.02
All (coronal + root)	0.21 ± 0.027	0.15 ± 0.027	−0.06 ± 0.037	29.1%	0.09

Significance of factors in Prevora's preventive effect.
For coronal surfaces: Study center p-value < 0.0001. Age-group p-value = 0.3044.
For all surfaces: Study center p-value = 0.0001. Age-group p-value = 0.3426.

ANOVA was employed with treatment group, site and age as model terms. Secondary efficacy variables were the NNCS on coronal surfaces and the NNCS on root surfaces. Sensitivity analyses validated the robustness of the primary efficacy analysis and were conducted with respect to dropouts/missing data using ANOVA of rank transformed data.

Results

Analysis using primary end-points

There were 983 randomized subjects in the study (Table I). However, observed-case analysis was performed using 926 subjects (467 placebo and 459 treated subjects), as data for these subjects were available at the end-of-study visit. Analysis of variance (ANOVA) using three factors, treatment, age group (3 levels) and study center (4 levels) in the model showed no treatment effect in reducing the coronal and root caries at the end-of-study visit. Only study center was found to be a significant factor (p-value = 0.0001) in reducing caries. However, there was a statistically significant reduction (placebo = 16.6% and active = 9.5%, treatment effect = 42.9%) in coronal decay due to treatment (p-value = 0.02) (Table II). No statistical analysis was performed on the root surfaces because of the small number of surfaces that were exposed given the young mean age of the participants.

Analysis using secondary end-points

The ANOVA model with treatment, age-group, site and an additional interaction term for treatment by site showed that the interaction term was highly significant (p-value = 0.0001).

The significance of the interaction term showed that the treatment effect was not the same in different sites and some sites performed better than others. The treatment effect on reducing the total number of cavities per subject was evaluated by pooling four sites into two homogenous groups: (1) uninsured subjects with public health recipients; and (2) insured subjects. The treatment effect was highly significant amongst the uninsured group (p-value = 0.0009) (Table III).

Table III. Mean number of cavities per subject at end-of-study visit by socio-economic status; the prevention of adult caries study. Least squared means and standard error.

	Insured (n = 545)	Un-insured and public health (n = 381)
Placebo	0.06 ± 0.031	0.38 ± 0.049
Active	0.11 ± 0.031	0.16 ± 0.049
Active–placebo	0.05 ± 0.040	−0.22 ± 0.067
Clinical effect (%)	+93%	−58.3%
p-value	0.180	0.0009

Discussion

The FDA in giving approval of the protocol stipulated that the subjects in the trial population should be representative of the population of the US and that the outcome analysis be confined to cavitated lesions, in the event a prescient condition.

In interpreting the regulatory requirement it was realized that the general population was not socially homogenous, but displayed homogenous groups depending on the nature of the investigation and which could be readily identified. In terms of this investigation the division into insured and uninsured populations seemed a reasonable approach and the trial protocol was devised with this as part of the secondary analysis. Factors impinging on this analysis were socio-economic status, considered with the uninsured group. Different health-seeking behaviours were apparent in the North American Indians and the inner city uninsured population in Boston, MA, compared to the more affluent insured populations of Delta and Kaiser Permanente dental clinics.

The four groups determined by the different methods of delivery of dental services (employer sponsored managed care, employer sponsored fee for service, uninsured and public health dentistry) showed apart from the results of the individual group analyses, a further revealing result by combining the groups into two, the insured and the uninsured. The results of these sub-group analyses introduced the concept of risk.

Risk of caries can be divided into endogenous factors (a recent history of caries), the most

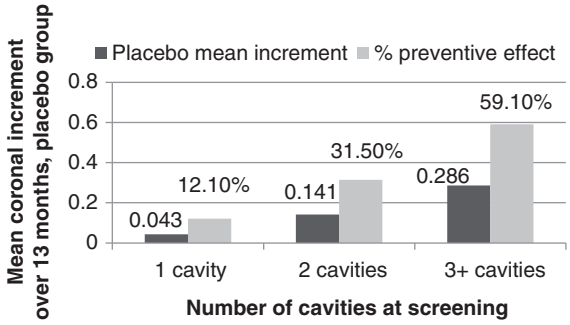

Figure 1. The 10% chlorhexidine coating's preventive effect and mean coronal caries increment by number of cavities at screening, community-dwelling adults, US.

important contributing factor being previous tooth decay, or exogenous factors such as multiple medication use, systemic disease giving rise to xerostomia, or socio-economic status and associated health risk behaviour. This trial showed at the time when subjects were selected for participation, those who presented with three or more cavities were at greatest risk of further decay. The annual increment amongst those with three or more carious lesions at screening was significantly more than those with one cavity. It is of interest that those at greatest risk also showed the greatest response to chlorhexidine, probably because subjects with lesser levels of tooth decay (≤2) were at lower risk of further tooth decay (Figure 1).

The validity of the results observational trials of this nature depend on the accuracy of the clinical findings. In PACS the consistency and accuracy of the examiners in identifying carious lesions was determined by the kappa scores obtained during the training sessions. Kappa ranges from −1 to +1, the former representing results which are entirely due to chance, while the latter represents a result from which chance is entirely absent [10].

The kappa scores in PACS have been dealt with in depth [9]. Although the results were quite variable, the scores are reported as highest when S/D1 is compared to D2/D3. This gives support to the requirement by the FDA to consider only cavitated lesions in the end-point analyses.

Further support for using D2/D3 as the outcome measure can be obtained by considering the results of this report together with the four previously published clinical trial reports using this topical medication. The three clinical trials which used the D2/D3 outcome measure all showed statistically significant results. When D1 (non-cavitated lesions) were included as caries in two trials, no statistically significant results were obtained.

PACS provides a number of considerations for further clinical research into adult caries prevention. The study established that high risk adults are needed to demonstrate a preventive effect over the course of 1 year's treatment and observation. High risk was determined by more than two cavitated lesions at screening. A generalized approach to recruiting community dwelling adults can challenge a controlled study. Many adults with cavities at screening have such a low level of the disease during the study to challenge any measurement of efficacy. Adults presenting with one or even two cavities at screening may have episodic disease which may or may not occur during the study. In the absence of disease in the control group it is difficult to show a treatment effect. The reliable end-point for adult caries is the cavitated lesion. PACS demonstrated that the conventions of ICDAS even in a modified form are difficult to implement, despite regular and rigorous training.

PACS showed that the 10% chlorhexidine coating was highly effective in preventing cavitated lesions in those community-dwelling adults who were most at risk. As adult caries has clustered in the population amongst groups with lower socio-economic status and limited access to professional dental care, this finding is highly relevant to public dental health policy.

A reliable numerical categorization of risk of further decay was established which should be of benefit to the general dental practitioner. The greater reliability of using D2/D3 over D1/D2/D3 as the outcome measure is clearly demonstrated.

This trial, although primarily explanatory in nature, has components of a pragmatic and complex nature [11,12].

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