Dose Response Efficacy of Sodium Fluoride Dentifrice at 9 and 21 Months

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ABSTRACT

This was a randomized, double-blind study conducted for a period of 21 months with a supervised school oral hygiene regimen to assess whether dentifrices with increasing fluoride levels could be differentiated with small sample sizes in short time frames. Subjects (N=644, with ~215 per group) with a mean age of 10.4 years old (9-12 y.o.) used a placebo dentifrice, an 1100 ppm F dentifrice or a 2800 ppm F dentifrice for the first 9 months of the study. Subjects in the placebo group were then switched to either 1100 ppm or 2800 ppm F dentifrice for the remainder of the study, while subjects in the fluoride groups continued with their original treatment assignments. Three calibrated examiners measured visual-tactile caries as DMFS that was supplemented with a radiographic examination at baseline, 9 months and 21 months for each subject. The results of this study are consistent with the previous results reported for sodium fluoride dentifrices. For all examiners, the 1100 ppm and 2800 ppm fluoride dentifrices delivered statistically significantly ($p < 0.05$) lower DMFS scores than the placebo control dentifrice at 9 months, while at 21 months the 1100 ppm and 2800 ppm fluoride dentifrices delivered statistically significantly lower DMFS scores compared to the both the placebo/1100 ppm and the placebo/2800 ppm dentifrice groups. In addition, one of the three examiners observed a directional ($p = 0.11$) dose response (2800 ppm F < 1100 ppm F) at 9 months, while at 21 months all three examiners observed evidence of a dose response, with one examiner observing a statistically significant difference between 1100 ppm and 2800 ppm F. Caries scores on occlusal surfaces provided the strongest evidence of an 1100 ppm F vs. 2800 ppm F difference. In this study, the effectiveness of the two fluoride dentifrices was observed at 9 months and these outcomes were still present at 21 months, confirming that caries benefits can be observed in time frames as short as 9 months with approximately 200 subjects per treatment group.

INTRODUCTION

Over the past 40 years, the caries clinical trial "standard" has remained relatively constant despite the extraordinary changes in disease prevalence and severity, and the rapidly changing landscape around caries diagnosis. Consensus guidelines for caries prevention studies recommend randomized clinical trials of 2-3 years in duration with a clinical endpoint of frank caries detected by visual-tactile examination and radiography. Conventional caries trials based on these guidelines have historically employed large sample sizes, often ranging from 500-2000 subjects per treatment group. The changing epidemiology in the fluoride-era has exacerbated this situation, in so much as clinical trials participants were even less likely to experience new lesions over a finite study period. The uncontrolled nature of typical caries clinical trials further contributes to increased sample sizes and extended duration of these studies. Because of the study length and infrequent examination periods, caries trials have been subject to less than optimal compliance and product exposure, as well as high dropout rates that were often unrelated to product use. An additional significant confounding factor has historically been the level of uncontrolled restorative dentistry during the 2-3 year study period, which directly affected the "filled" component of observed caries. Collectively, such factors as variable product exposure, high dropout rates, and inconsistent treatment led to large studies over long durations to afford adequate discriminatory power.

PURPOSE

A randomized, double-blind, partially placebo-controlled, 21-month clinical trial was conducted to evaluate the dose discrimination potential of an alternative caries research model.

MATERIALS AND METHODS

Both the research protocol and consent were reviewed and approved by a qualified institutional review board. Study participation was voluntary, with a priori written and verbal informed consent of the parent and child. The study population was composed of children ages 9-12 years attending 2 elementary schools in an urban Guatemala setting that had community water service with natural, sub-optimal fluoride levels (< 0.3 ppm). Individuals were excluded because of orthodontic or prosthetic appliances, emergency treatment need, or other factors that prevented a thorough oral examination. Subjects were stratified based on gender, age, and baseline DMFS scores derived from the visual-tactile baseline examination and randomly assigned to one of the three dentifrices: 0.243% sodium fluoride (1100 ppm fluoride ion), 0.619% sodium fluoride (2800 ppm fluoride ion), or placebo (0 ppm fluoride ion). During the first nine months of the study, toothbrushing was supervised twice a day at school during the week and used *ad libitum* at home outside of school hours (evenings and weekends). Following the 9 month caries examinations, subjects in the placebo treatment group were randomized to either the 0.243% sodium fluoride (1100 ppm fluoride ion), or the 0.619% sodium fluoride (2800 ppm fluoride ion) treatments for the remainder of the study. This change in product assignment was necessitated by ethical concerns, as supervised brushing could not be conducted over the school vacation period.

Visual-tactile and radiographic examinations were conducted on each subject at baseline and after 9 and 21 months of treatment by three calibrated examiners. After brushing, a visual-tactile caries examination was performed using an artificial light, a mouth mirror, compressed air, and a dental explorer. Caries detection followed the clinical criteria described by Radike, with both enamel and frank lesions recorded. The clinical examination was supplemented by up to four bitewing radiographs per subject, depending on the number of permanent teeth present and the clinical availability of proximal surfaces. The DMFS increment scores were statistically tested using an analysis of covariance with gender, treatment group, and gender by treatment group interaction as terms in the model. Age, baseline DMFS score, baseline dental age (number of permanent teeth erupted), baseline surfaces at risk (number of surfaces of permanent teeth erupted minus the baseline DMFS score), and dental age served as covariates. The adjusted treatment group means from this analysis were compared using Least Significant Difference tests. This same method was used to analyze the increment data for each tooth surface category (occlusal, buccal-lingual, and mesial-distal). The appropriate baseline score was used as the covariate for each variable. As specifically detailed in the study protocol and reflecting the increasing fluoride levels in the treatment groups, all pairwise treatment group comparisons were performed as one-sided tests.

RESULTS

The examiners were found to be repeatable, with weighted kappa scores of 0.77-0.96 for visual-tactile caries detection. With respect to radiographic interpretation, the examiners exhibited high sensitivity and high specificity relative to the expert panel. Sensitivity and specificity were > 97% and > 88%, respectively. A total of 644 subjects who completed baseline exams were randomized and enrolled in the study. At baseline, the three treatment groups were well balanced with respect to age, gender, and DMFS at baseline. In each group, mean age was 10.4 years, with males comprising 67% of the sample. The 600 subjects (93% of the sample) who completed the 9 month examination exhibited considerable prior caries experience. Baseline DMFS within the treatment groups ranged from 7.76 to 8.92, 11.05 to 12.67, and 7.56 to 8.51 for examiners A, B, and C, respectively. Initial baseline demographics and DMFS score for the 494 subjects that completed the 21 month examination remained balanced across the four treatments.

Table 1: Nine Month Caries Increment (Integrated)

Treatment	N	Exam. A	Exam. B	Exam. C
Placebo	203	2.73	2.61	3.47
1100 ppm F-	201	1.79*	1.19*	2.00*
2800 ppm F-	196	1.74*	1.33*	1.57*

*$p < 0.05$, compared to placebo group via Least Significant Difference (LSD) following Analysis of Covariance (ANCOVA)

Table 2: Twenty-One Month Caries Increment (Integrated)

Treatment	N	Exam. A	Exam. B	Exam. C
Placebo-1100	83	3.05	2.68	2.08
Placebo-2800	90	2.52	1.25	2.56
1100 ppm F-	168	1.47*	0.37*	1.04*
2800 ppm F-	153	1.25*	- 0.24*	- 0.06*#

*$p < 0.05$, compared to placebo-1100 and placebo-2800 groups via Least Significant Difference (LSD) following Analysis of Covariance (ANCOVA)
#$p < 0.05$, compared to 1100 group via Least Significant Difference (LSD) following Analysis of Covariance (ANCOVA)

Table 3: Predicted and Observed Caries Visual-Tactile Increment

Treatment	Age 9	Age 10	Age 11	Age 12
Cross-sectional DMFS[a]	8.45	9.17	11.85	16.52
Est. 1 year increment[a]	0.72	2.68	4.67	———
Baseline DMFS[b]	6.39	8.90	10.27	13.44
Est. 1 year increment[b]	2.51	1.37	3.17	———
Actual Observed Increment[b]	0.95	0.32	1.96	1.23

[a] previous study in this population
[b] placebo group in current study

CONCLUSION

- The results confirm that caries benefits can be observed in time frames as short as 9 months with approximately 200 subjects per treatment group.
- Both the 1100 and 2800 ppm fluoride dentifrices were highly effective at preventing caries and there was evidence of a dose response between the 1100 and 2800 ppm fluoride dentifrices.
- Subjects using placebo dentifrice in conjunction with a rigorous twice a day supervised brushing regimen over 9 months were not placed at increased risk for caries experience and in fact derived an apparent benefit through participation in the trial relative to historical norms.

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