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In situ anticaries efficacy of dentifrices with different formulations – A pooled analysis of results from three randomized clinical trials

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ABSTRACT

Objectives: Data generated from three similar in situ caries crossover studies presented the opportunity to conduct a pooled analysis to investigate how dentifrice formulations with different fluoride salts and combinations at concentrations of 1400–1450 ppm F, different abrasive systems and in some cases, carbomer (Carb), affect enamel caries lesion remineralization and fluoridation.

Methods: Subjects continuously wore modified partial dentures holding two gauze-covered partially-demineralized human enamel specimens for 14 days and brushed 2×/day with their assigned dentifrice: Study 1: sodium fluoride (NaF)/Carb/silica, NaF/silica, NaF + monofluorophosphate (MFP)/chalk; Study 2: NaF/Carb/silica, NaF + MFP/dical, amine fluoride (AmF)/silica; Study 3: NaF/Carb/silica, NaF + stannous fluoride (SnF_2)/silica/hexametaphosphate (HMP). All studies included Placebo (0 ppm F) and/or dose-response controls (675 ppm F as NaF [675F-NaF]) ± Carb. Specimens were evaluated for percentage surface microhardness recovery (SMHR) and enamel fluoride uptake (EFU).

Results: All 1400–1450 ppm F dentifrices except NaF + SnF_2/silica/HMP provided significantly greater lesion remineralization than Placebo ($p < 0.0001$): differences in SMHR ranged from 17.46% (NaF + MFP/dical) to 26.66% (AmF/silica). For EFU (back-transformed log EFU), all 1400–1450 ppm F dentifrices gave significant fluoride uptake compared to Placebo ($p < 0.0001$): increases in EFU ranged from 4.95 μg F/cm^2 (NaF + SnF_2/silica/HMP) to 16.32 μg F/cm^2 (NaF/carb/silica). Dentifrices containing NaF or AmF as sole fluoride source provided the greatest remineralization and fluoridation; Carb addition did not alter fluoride efficacy; some excipients appeared to interfere with the cariostatic action of fluoride. Treatments were generally well-tolerated with ≤4 treatment-related adverse events per study.

Conclusion: Commercially available fluoride dentifrices varied greatly in their ability to remineralize and fluoridate early caries lesions.

Clinical significance: Fluoride dentifrices are the most impactful anticaries modality worldwide. While clinical caries trials have not consistently shown the superiority of one formulation over another, these findings using a sensitive in situ caries model indicated that dentifrices containing NaF or AmF as the sole fluoride source provided the greatest remineralization and fluoridation benefits.

1. Introduction

It is generally agreed that the anticaries effect of fluoride is predominantly by decreasing the rate of enamel demineralization and enhancing the rate of remineralization [1–3]. However, different formulations of fluoride dentifrices may not have the same anticaries efficacy potential [4]. There has been a controversy over the relative merits of sodium fluoride (NaF) versus sodium monofluorophosphate (MFP), with published reviews reaching different conclusions from basically the same clinical studies [5,6]. Not only can different fluoride salts have intrinsically different anticaries activities, but the formulation environment of the fluoride species can affect its delivery to the oral cavity and its ability to interact with enamel in vivo [4]. Furthermore, other dentifrice ingredients may positively or negatively impact the caries process by directly inhibiting demineralization by offering surface protection, or by interfering with remineralization.

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To examine this further, a series of three studies were carried out using an in situ caries model to evaluate the efficacy of a dentifrice where carbomer (high molecular weight copolymer of acrylic acid crosslinked with a polyalkenyl polyether) had been added to NaF as a possible aid to increase bioavailability of fluoride compared to a variety of commercially available dentifrice formulations. These dentifrices contained fluoride from a number of different sources (NaF, MFP, stannous fluoride [SnF_2], amine fluoride [AmF]) and combinations thereof. The efficacy of these was compared to a variety of dose-response control dentifrices including low fluoride dentifrices (675 ppm F) and fluoride-free dentifrices.

Clinical studies are limited in regard to how many treatment and control groups can be compared. Here we present a pooled analysis of three studies whose similar designs present a unique opportunity to compare the in situ remineralization performance of several commercially available products in a well-characterized model. The three studies carried out here were compared using a network meta-analysis (NMA) technique applied to pooled data. Of note, this is not intended to be a full meta-analysis, as comparison was only within the three studies reported herein. The in situ caries model involving partial denture appliances [7] with partially demineralized enamel specimens used in these studies to evaluate enhancement of net remineralization has been validated based on response to a variety of different dentifrice fluoride concentrations [3,8,9]. This model is advantageous as fluoride is delivered in the presence of physiologically secreted saliva and there are intermittent cycles of demineralization and remineralization during the experimental period as with the natural caries process. The in situ model system is used with the surface microhardness (SMH) test as the primary outcome measure [3,7,9–14]. Here, the hardness of sound enamel is measured and compared with the hardness of enamel after exposure to an in vitro acid challenge and then after intra-oral exposure, simulating the caries process [3]. The in situ model has also been applied to measure fluoride uptake from enamel specimens (enamel fluoride uptake: EFU) [3,9].

2. Materials and methods

The three studies followed a similar single-center, randomized, examiner-blind, reference-controlled crossover design. They were undertaken as part of an Investigational New Drug (IND) program (IND 75222), with the protocols reviewed and approved by the IUPUI/Clarian Institutional Review Board (Study 1: IRB# 0803-14; Study 2: IRB# 0809-15; Study 3: IRB# 0910-29). All studies were conducted at the Oral Health Research Institute (OHRI), Indianapolis, IN, USA with subjects selected from the OHRI's IRB approved database of previous research subjects, if suitable, or recruited from the area. Prior to study initiation all subjects gave informed consent in accordance with the Declaration of Helsinki. Details of these studies and results can be found at ClinicalTrials.gov (NCT00708097, NCT01005966, NCT01128946). There was one amendment, to Study 3 only, an administration change that did not affect study procedure or outcomes.

2.1. Clinical procedures

All studies followed the same protocol with only minor variations, as noted. At the screening visit (Visit 1), demographic details, medical history and concomitant medications were recorded followed by oral soft tissue (OST) and oral hard tissue examinations. Study entry criteria included: healthy volunteers aged 18–80 years with a normal saliva flow rate (unstimulated: $\geq$0.2 mL/minute; stimulated: $\geq$0.8 mL/minute) who wore a removable mandibular partial denture able to be adjusted to hold enamel test specimens and lived in the Indianapolis, IN area (with a fluoridated water supply of approximately 1 ppm). Subjects could not be taking fluoride supplements or using fluoride mouthrinse and could not have any clinically significant/relevant abnormalities of medical history or physical examination including current active caries or periodontal disease that could have compromised the study or the subject's health. Exclusion criteria included: pregnant; breast feeding; intolerance to any study material; currently taking antibiotics or had taken antibiotics within 2 weeks prior to screening; participation in another clinical study or receipt of an investigation drug within 30 days of screening.

At Visit 2, 2–3 days before the start of the first treatment period, subjects received a prophylaxis and their partial denture was prepared for enamel specimen placement. They then brushed at home twice-daily with a supplied fluoride-free dentifrice until Visit 3. Eligible subjects were assigned treatments in an order according to a randomization sequence generated by the Biostatistics and Data Management department of GSK Consumer Healthcare (GSKCH). Details of the test dentifrices can be found in Table 1, including fluoride source and concentration, abrasive, surfactant and viscosity and rheology modifiers. Test dentifrices were supplied in plain white 100 ml tubes; commercially sourced dentifrices were supplied overwrapped with opaque white vinyl to aid in blinding participants and site staff to dentifrice type.

At the start of each treatment period, two partially demineralized enamel specimens covered with Polyester Knit Fabric (Item# 401628, Impra, Tempe, USA) to encourage plaque formation [7] were placed in the buccal flange of the subject's partial denture. Subjects performed their first brushing under site supervision where they applied a full ribbon (Studies 1 and 2) or 1.5 $\pm$ 0.1 g (Study 3) of dentifrice to a wet toothbrush and brushed their natural teeth for one timed minute, taking care not to brush the enamel specimens, then rinsed for 10 s with 10 ml (Studies 1 and 2) or 15 ml (Study 3) water. Subjects continued the study brushing/rinsing regimen at home twice daily for 14 days, recording brushing on a supplied diary card that was used to check compliance. During the treatment period subjects wore their partial denture 24 h a day except when cleaning it with water. The combination of the fabric-covered specimens and the subjects' normal diet provided a cariogenic environment simulating the caries process [3].

After the 14-day study period, enamel specimens were removed and stored until analyzed. To control for carry-over effects there was a 7-day wash-out period between treatments during which subjects followed their usual dental hygiene regimen for at least 4 days, followed by a prophylaxis and 2–3 day lead-in period. At the start of the next treatment period, each subject received an OST examination, eligibility check, their partial denture was re-fitted with new specimens, and the brushing procedure was repeated. This sequence was continued until all subjects had used all test dentifrices within their respective study.

2.2. Enamel specimen preparation

Specimens obtained from human permanent teeth were used as the hard tissue study substrate and were prepared as previously described [20] such that each had an enamel surface with a central minimum flattened and polished area of 3 $\times$ 3 mm. For SMH testing, five baseline indentations 100 µm apart were placed in the center of each prepared enamel specimen using a Knoop diamond under a 50 g load. Only specimens with mean baseline indentation lengths of 43 $\pm$ 3 µm were accepted. Before placement, the enamel specimens were partially demineralized, to simulate early carious lesions, using a modification of the method described by White [21]. The modification involved decreasing the demineralization time from 96 h to 24 h. SMH testing was repeated with five indentations placed to the left of the baseline