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A randomised clinical evaluation of a fluoride mouthrinse and dentifrice in an *in situ* caries model

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ABSTRACT

Objectives: Fluoride mouthrinses provide advantages for fluoride delivery by maintaining elevated intra-oral fluoride concentrations following fluoride dentifrice use. This *in situ* caries study investigated potential anti-caries efficacy of a 220 ppm fluoride mouthrinse.

Methods: This was an analyst-blinded, four-treatment, randomised, crossover study using partially demineralised, gauze-wrapped, human enamel samples mounted in a mandibular partial denture. Participants brushed twice daily for 14 days with either a 1150 ppm fluoride or a fluoride-free placebo dentifrice and either rinsed once daily with the 220 ppm fluoride mouthrinse or not. Following each treatment period, percent surface microhardness recovery (%SMHR) and enamel fluoride uptake (EFU) were assessed.

Results: Fifty three participants completed the study. Compared with the placebo dentifrice/no rinse treatment, the fluoride-containing regimens demonstrated greater enamel remineralisation (%SMHR) and fluoridation (EFU): fluoride dentifrice/fluoride rinse (%SMHR difference: 21.55 [95% CI: 15.78,27.32]; EFU difference 8.35 [7.21,9.29]); fluoride dentifrice/no rinse: 19.48 [13.81,25.15]; 6.47 [5.35,7.60]; placebo dentifrice/fluoride rinse: 16.76 [11.06,22.45]; 5.87 [4.72,7.00] (all $P < .0001$). There were no significant differences in%SMHR between fluoride regimens. The fluoride dentifrice/fluoride rinse regimen was associated with higher EFU than the fluoride dentifrice/no rinse (1.88 [0.75,3.01], $P = .0013$) and placebo dentifrice/fluoride rinse regimens (2.48 [1.34,3.62], $P < .0001$). Treatments were generally well-tolerated.

Conclusions: The *in situ* caries model demonstrated that the fluoride mouthrinse is effective in promoting enamel caries lesion remineralisation and fluoridation whether used following a fluoride or non-fluoride dentifrice. Additive (potential) anti-caries benefits of a fluoride rinse after a fluoride dentifrice were confined to enhancements in lesion fluoridation (EFU).

Clinical significance: In conjunction with a fluoride dentifrice, fluoride mouthrinses enhance enamel fluoridation, which may be useful in caries prevention.

1. Introduction

Brushing with fluoride-containing dentifrice products has been shown in numerous clinical trials to be effective in reducing dental caries [1,2]. Fluoride has two relevant mechanisms of action: inhibition of acid-induced demineralisation (that could lead to dental caries), which is beneficial as fluoridated enamel is more acid-resistant than native enamel, and enhancement of remineralisation of partially demineralised enamel during the early stages of caries in the presence of calcium and phosphate ions from saliva [3,4].

For individuals at high risk of developing dental caries, fluoride mouthrinses are recommended in addition to fluoride dentifrices [5,6]. Cochrane Collaboration systematic reviews of fluoride mouthrinses have reported that the supervised use of fluoride mouthrinse by children is associated with a clear reduction in caries increment based on a meta-analysis of 35 trials [7], and that use of fluoride mouthrinse can reduce dental caries irrespective of exposure to fluoridated water [8]. A systematic review of fluoride mouthrinses in populations of various ages found a caries-preventive effect in the permanent teeth of schoolchildren and adolescents with no additional fluoride exposure [9]. While the authors found a caries-preventive effect of fluoride mouthrinses on root caries in older adults, they questioned the additional benefit in children using fluoride dentifrice daily. Although a number of clinical studies have explored the adjunctive benefit of

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fluoride mouthrinses, few studies have explored the role of fluoride mouthrinses in the fundamental aspects of the caries process.

The use of *in situ* surrogate caries models as an approach to evaluate the anti-caries efficacy of fluoride dentifrices and other fluoride-containing dental products, such as mouthrinses, is generally well-recognised and accepted [10]. In particular, modifications of the Koulourides intra-oral model [11] have led to the development of an *in situ* caries model [10] with sufficient sensitivity and reproducibility to respond in a dose-dependent manner to meet the requirements for model validation [12]. For the current study, the potential anti-caries efficacy of dentifrices and mouthrinses in remineralising previously demineralised enamel specimens was investigated using the surface microhardness (SMH) test to accurately determine the changes occurring at the enamel surface during the early stages of the caries process [10]. The SMH test has been used widely to evaluate enamel remineralisation in studies involving *in situ* caries models and has been shown to have greater sensitivity in comparison to other techniques such as cross-sectional microhardness and transverse microradiography to evaluate enamel remineralisation of shallow caries-like lesions. [10,11,13–16].

The primary objective of this study was to evaluate and compare the potential anti-caries efficacy of a regimen consisting of a fluoride mouthrinse once daily plus brushing with a fluoride-free placebo dentifrice twice daily versus only twice daily brushing with the placebo dentifrice, to remineralise previously demineralised enamel specimens, as measured by percent SMH recovery (%SMHR). Secondary objectives were to compare the potential anti-caries efficacy of other treatment regimens comprising the fluoride mouthrinse plus a fluoride dentifrice and the fluoride dentifrice alone. Further secondary objectives were to evaluate and compare treatments with respect to enamel fluoride uptake (EFU), and pre- and post-treatment changes in salivary fluoride concentrations, and to explore the relationship between EFU and salivary fluoride concentrations and the results of enamel remineralisation based on %SMHR.

2. Materials and methods

This was a single-centre, analyst-blind, four-treatment, crossover, randomised *in situ* model study performed at the Oral Health Research Institute, Indiana University School of Dentistry, USA. It was approved by the Indiana University Institutional Review Board (# 1503890832) and was conducted in accordance with the Declaration of Helsinki. This study is registered at clinicaltrials.gov, study number NCT02399163.

2.1. Participants

Healthy participants aged 18–85 years were recruited from the Indianapolis area (where community water contains approximately 1 µg/mL fluoride). All participants provided written informed consent prior to screening. Participants were required to have a removable mandibular partial denture suitable to retain two enamel specimens and be willing and capable of wearing their denture 24 h/day during the experimental periods. They were required to be in good general and dental health with an unstimulated and stimulated saliva flow rate of at least 0.2 mL/min and at most 0.8 mL/minute, respectively, and not to have had a professional fluoride treatment within 14 days before the first treatment visit. Participants could not have any active caries or periodontal disease that in the opinion of the investigator could compromise the study. Participants were excluded if they were pregnant, intending to become pregnant, or were breastfeeding; had a known or suspected intolerance to the study materials; were taking antibiotics or had taken antibiotics in the 2 weeks before the screening visit; or if they were taking or had taken a bisphosphonate drug for treatment of osteoporosis.

2.2. Experimental design and study procedures

At the screening visit, participants underwent an oral soft tissue (OST) and oral hard tissue (OHT) examination and their salivary flow rate was measured. An OST examination was also performed during the visit before and after each treatment period; an additional OHT examination was performed at the first prophylaxis visit before the first treatment period.

Each participant undertook treatments in a crossover design in four successive 2-week treatment periods. Between each treatment period, participants used their usual dentifrice for at least 4 days, and then reported to the study site 2–3 days before the start of each of the four treatment periods, where they had an OST examination and underwent dental cleaning using a fluoride-free prophylaxis dentifrice. The fluoride-free dentifrice formulation used during the study period and a study toothbrush (Aquafresh® Toothbrush 3-Way head; GSK Consumer Health, Weybridge, Surrey, UK) were dispensed to participants for use before starting the next treatment period.

At the start of the first treatment period, eligibility to continue in the study was assessed and then participants were randomised to the sequence in which they received the four study-treatment regimens. The order in which each participant received the treatment regimens was determined by a randomisation schedule provided by the Biostatistics Department of GSK Consumer Healthcare. A Latin square was use to ensure uniform design (Williams square design). Randomisation numbers were assigned in ascending numerical order as each participant was determined to be fully eligible for the study. The following dentifrices and mouthrinse were used in the study:

- **Fluoride dentifrice**: Aquafresh® Extreme Clean® Pure Breath Action fluoride dentifrice containing 1150 ppm fluoride as sodium fluoride (GSK Consumer Healthcare, Weybridge, Surrey, UK; USA marketed product);
- **Fluoride mouthrinse**: containing 220 ppm of fluoride as sodium fluoride (non-marketed formulation);
- **Control placebo dentifrice**: non-fluoride dentifrice (non-marketed formulation).

In each treatment period, participants were assigned to one of the following treatment regimens: fluoride dentifrice/fluoride rinse; fluoride dentifrice/no rinse; placebo dentifrice/fluoride rinse; placebo dentifrice/no rinse. By the end of the study, all participants experienced all four treatment regimens. Supplied dentifrices were overwrapped to blind as far as possible participants to dentifrice allocation; however, study group could not be fully blinded as participants would know whether or not they were in a fluoride rinse group. The site laboratory analyst, study statistician, data management staff and other employees of the Sponsor who could have influenced study outcomes were blinded to treatment allocation.

Study product(s) were dispensed to the participants, who completed the initial brushing/rinsing under supervision at the study site then used the study products at home for the rest of the 2-week treatment period. Participants were provided with a diary card to record brushing and/or rinsing times, any adverse events (AEs), and concomitant medications until their next visit. The diary cards were used to assess compliance to study procedures.

At the start of each treatment period, two partially demineralised enamel specimens were mounted in the participant's mandibular partial denture. During the 2-week treatment periods, participants brushed twice daily (after breakfast and just before bedtime) and wore their mandibular partial denture continuously for 24 h, except as specified during the brushing procedure and for cleaning. At each brushing, participants removed their partial denture and cleaned their natural teeth with water and the study toothbrush. They cleaned the denture outside of the mouth with the study toothbrush and water only, taking care not to brush the enamel specimens, and then reinserted the