A clinical assessment of the efficacy of a Stannous-containing Sodium Fluoride Dentifrice on Dentinal Hypersensitivity

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Aim: To measure the desensitizing benefits of an experimental stannous-containing sodium fluoride dentifrice versus a regular sodium fluoride negative control.

Methods and Materials: This study was a randomized, double-blind, parallel group, four-week clinical trial. Subjects were stratified into one of four strata depending on their gender (female or male) and the baseline self-reported tooth hypersensitivity (low or high). Within strata, subjects were randomly assigned to one of the two treatment groups using an encoded program. Subjests residing in the same house...

Efficacy assessments (Air Blast) were performed at baseline and weeks two and four. Separate analyses were performed for the two most sensitive teeth at baseline and for all 12 teeth. Results for weeks two and four combined were also analyzed.

Results: Thirty-one subjects were included in the analyses. For the two most sensitive teeth, the experimental dentifrice showed statistically significantly less sensitivity (p<0.05) versus the control at weeks two and four and for weeks two and four combined. The sensitivity reduction ranged from 24.9% to 45.2% over the control. For all 12 teeth, the experimental group had statistically significantly lower sensitivity scores versus the control group at week two, week four, and for weeks two and four combined.

Conclusion: The experimental dentifrice demonstrated significant desensitizing advantages versus the control.

Clinical Significance: This stannous-containing sodium fluoride dentifrice provides an effective treatment for patients with dentinal hypersensitivity, significantly reducing sensitivity versus a negative control in this four-week clinical trial.

Introduction

Dental hypersensitivity is a highly prevalent condition reported to affect from 4% to 57% of the population. The causes of sensitivity are well characterized as exposed dentinal tubules most commonly resulting from gingival recession followed by loss of cementum. The mechanism by which nerves are triggered to result in the pain associated with hypersensitivity is now widely accepted as that of the Brinnström hydodynamic theory. This postulates that changes in physical conditions on the dentin surface such as heat, pressure, or osmotic potential give rise to fluid movement in the tubules. The consequent pressure change stimulates the nerves giving rise to the pain.

The mechanism of action of stannous ions in reducing dentinal hypersensitivity has been found to be the precipitation of stannous compounds occluding the dentinal tubules and thus preventing stimulation of the nerves in the pulp cavity. In vitro studies using various techniques, such as scanning electron microscopy, electron probe microanalysis, and Vickers surface microhardness, demonstrate deposition of tin and fluoride on the surface and covering of the dentinal tubules. One laboratory evaluation showed that while both zinc and tin covered or obliterated tubules, zinc was largely removed by washing whereas tin remained covering the tubules. Another study showed specimens treated with stannous fluoride (Crest® Pro-Health®, The Procter & Gamble Company, Cincinnati, OH, USA) appeared to resist solubilization.

A number of clinical studies have also been conducted to investigate the effectiveness of stannous-containing oral care products upon dentinal hypersensitivity. Most of the early studies focused on gels containing 0.14% stannous fluoride, whereas the majority of contemporary trials have evaluated stannous-containing dentifrice formulations. The collective findings demonstrate the effectiveness of numerous stannous-containing products in reducing sensitivity.

Recently, a new stannous-containing sodium fluoride dentifrice was developed. This clinical trial was conducted to evaluate the effectiveness of this formulation relative to a negative control in the treatment of dentinal hypersensitivity.

Methods and Materials Study Design

This was a randomized, parallel group, double-blind, four-week clinical trial to assess changes in subject perceived tooth hypersensitivity via air blast induced examiner grade assessment among subjects using a stannous-containing sodium fluoride dentifrice compared to those using a negative control dentifrice. Measurements were conducted at baseline, week two, and week four visits.

Entrance Criteria

Following Ethics Committee approval, at least 50 healthy adults aged 18-70 reporting tooth sensitivity were sought. Subjects had to agree to refrain from using anti-hypersensitivity products or having elective dental procedures (including prophylaxis) performed during the study.

Subjects who were currently using an antisensitivity toothpaste or another anti-sensitivity product or who had used such a product in the previous month were excluded. Subjects with various teeth or with any other condition that the investigator considered may compromise the results also were excluded. Subjects taking daily doses of antioxidants, sedatives, tranquillizers, or other mood altering drugs were excluded as well as subjects with a history of significant adverse effects following the use of oral hygiene products such as toothpaste and mouth rinse.

Test Dentifrices, Assignment to Treatment Sequence

The two treatments used in this study were:

1. An experimental stannous-containing sodium fluoride dentifrice with 1450 ppm F- sodium fluoride and stannous chloride as a key excipient (Procter & Gamble UK, Surrey, United Kingdom)
2. Crest® Decay Protection (UK) with 1450 ppm F- sodium fluoride (Procter & Gamble UK, Surrey, United Kingdom).

Both were supplied to the subjects with (medium) Oral-B Advantage 40 toothbrushes (The Procter & Gamble Company, Cincinnati, OH, USA). The test products were supplied in kits containing the assigned toothpaste, toothbrush, and written usage instructions. The dentifrice in both kits was supplied blinded in white tubes.

Subjects were stratified at baseline into one of four strata depending on their gender (female or male) and the baseline self-reported tooth hypersensitivity (low or high). Within strata, subjects were randomly assigned to one of the two treatment groups using an encoded program. Subjects residing in the same house...
hold were assigned to the same treatment group.

Treatment Regimens
Subjects used the assigned products for the first time under supervision at the clinical site. Subjects used the products at home in their usual oral hygiene regimens (e.g., brushing and flossing) with the exception that anti-tooth hypersensitivity products should be used.

Air Blast Tooth Specific Sensitivity
The thermal sensitivity perceived by the subject was measured by the examiner by directing an air blast individually at each of the premolars and canines twice daily for two minutes each. Each tooth was isolated with cotton rolls and the dental philosopher was delivered from a distance of 1.0 centimeter for 1.0 second. The following scale18 was used to assess the level of hypersensitivity for each of the 12 teeth examined:

• 0 – Absence of pain, but perceiving stimulus
• 1 – Slight pain
• 2 – Pain during application of stimulus
• 3 – Pain during application of stimulus and immediately thereafter

Statistical Methods
For air blast-induced hypersensitivity scores, separate analyses were performed for the two teeth at baseline and for all 12 teeth combined. A baseline was used as a factor and the baseline score and age of the covariates were used to assess for any differences in hypersensitivity at the post-baseline visits. Also for the hypersensitivity scores, separate repeated measures models were used to investigate the overall relationship between the treatment groups and the post-baseline visits (weeks two and four) with statistical testing for the interaction and overall treatment effects using a two-sided 5% significance level. In this study, the interaction between treatment and week was not statistically significant (p=0.45) for each hypersensitivity score, and the interaction was removed from the repeated measures models.

Results
The twelve subjects were enrolled at the baseline visit, received their products and completed the study. All subjects completed both the baseline and all four post-baseline visits. Subjects ranged in age from 25 to 65 years with an average of 42 years. Two of the subjects were female. The treatment groups were balanced (p=0.86) for all demographic characteristics. Mean baseline scores were not significantly different (p=0.56) between groups at baseline for either two most sensitive teeth or for all 12 teeth combined.

Efficacy Results
At week two and week four after treatment, a combined treatment group of baseline and treatment group had a mean air blast score for two most sensitive teeth that was 28.4%, 24.9%, and 27% lower, respectively, than the control group (p=0.05, Figure 1). At week two, mean scores for the experimental and control groups were 1.17 and 2.31, respectively (Table 1). At week four, the experimental group had a mean score of 1.42 compared to 1.55 for the control group. The week two and four combined mean score was 1.46 for the experimental group and 2.00 for the control group.

At week two and combining weeks two and four, the experimental group provided significantly greater reductions in air blast scores for all 12 teeth relative to the control group (Table 2). The experimental group had a mean air blast score for all 12 teeth that was 28.4%, 24.9%, and 27% lower, respectively, than the control group (p=0.05, Figure 1). At week two, mean scores for the experimental and control groups were 1.17 and 1.76, respectively (Table 1). At week four, the experimental group had a mean score of 1.42 compared to 2.08 for the control group. The week two and four combined mean score was 1.46 for the experimental group and 2.00 for the control group.

In this clinical trial, the experimental group exhibited a significantly greater reduction in tooth sensitivity via air blast measurements than the control group (p=0.05, Table 2). There were no significant differences between the two treatments at either week four or eight (p=0.54) for either treatment.

Discussion
In this clinical trial, the experimental group exhibited a significantly greater reduction in tooth sensitivity via air blast measurements than the control group (p=0.05, Figure 1). There were no significant differences between the two treatments at either week four or eight (p=0.54) for either treatment.

These results are aligned with other studies evaluating stannous-containing dentifrices. Five trials in the literature evaluated the effect of a combination of 0.454% stannous fluoride and 5% potassium nitrate relative to fluoride control. Two trials compared the dentifrice to a positive control sensitivity dentifrice.21 The effectiveness of the product combining the stannous fluoride with potassium nitrate was found to be greater than that of the sodium fluoride product with potassium nitrate22,23 and the nondesensitizing control.22 16 Two published randomized parallel group studies were conducted on a dentifrice containing stannous fluoride compared to a sodium fluoride negative control toothpaste.24 In both studies, the sensitivity scores of the stannous fluoride group after four and eight weeks of product usage were significantly lower than the control group.

One advantage of this stannous-containing sodium fluoride dentifrice formulation relative to other desensitizing treatments is its effectiveness against other common oral conditions. A recent study by He and colleagues evaluated plaque prevention efficacy relative to a positive (Colgate®Total/Colgate, Palmolive, New York, NY, USA) and negative (Crest® Cavity Protection, The Procter & Gamble Company, Cincinnati, OH, USA) control dentifrice.25 The effectiveness of the product was evaluated by the Turesky Modified Plaque Index (TMQPI). The study indicated plaque index scores after treatment for both the experimental and the positive control were statistically significantly lower than those for the negative control by 14.1% and 8.4%, respectively (p<0.001).

Another recent study showed the benefit of this stannous-containing sodium fluoride dentifrice against caries.26 While many sodium fluoride products can produce minor extrinsic tooth stain, this formulation uses a polyethylene glycol (a-plascore) to stabilize the stannous fluoride complexes and prevent stain. The study also included an experimental stannous-containing control and a nonstaining marketed dentifrice (Colgate® Total®), and a nonstaining marketed dental clicker (Crest® Gum Care, The Procter & Gamble Company, Cincinnati, OH, USA) previously shown to induce extrinsic stain. Following a baseline Lobene stain examination, subjects received a prophylaxis on the 12 anterior teeth to remove extrinsic stain and tartar. Subjects were randomly assigned based on baseline stannous fluoride teeth present of the four treatments and to use them twice daily over a five-week period. It was confirmed that there was significantly less stain after product use in the stannous fluoride group compared to the sodium fluoride dentifrice group, the experimental stannous-containing sodium fluoride dentifrice group, and the Colgate Total group compared to the Crest Gum Care group (p<0.0001). There were no other statistically significant treatment differences between the stannous fluoride groups and the Colgate Total group at baseline, all 12 teeth combined at baseline relative to other products; others (p<0.0001).

Further research is warranted on this formulation to demonstrate the full breadth, as well as magnitude, of benefits.

Conclusions
This stannous-containing sodium fluoride dentifrice provides statistically significant benefits for dentinal hypersensitivity and should be considered as a home care option for patients who experience this condition.

Clinical Significance
This stannous-containing sodium fluoride dentifrice provides an effective treatment for patients with dental hypersensitivity.

References

Full list of references available from the publisher.
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Removal of interproximal dental biofilms by high-velocity Water Microdrops

By A. Rimaile, D. Carugo, L. Capretto, M. Aspiras, M. De Jager, R. Ward and P. Stoodley

Abstract

The influence of the impact of a high-velocity water microdrop on the detachment of Streptococcus mutans UA159 biofilms from the interproximal (IP) space of teeth in a representative typodont was studied experimentally and computationally. Twelve-day-old S. mutans biofilms were exposed to a prototype AirFloss delivering 115 μL wa

ter at a maximum exit velocity of 60 m/sec in a 30-msec burst. Using confocal microscopy and image analysis, we obtained quantitative measurements of the percentage removal of biofilms from different locations in the IP space.

The 3D geometry of the typodont and the IP spaces was obtained by micro-computed tomography (μ-CT) imaging. We performed computational fluid dynamics (CFD) simulations to calculate the wall shear stress (τw) generated by the prototype AirFloss and its spatial distribution on the teeth surface played a key role in dictating the efficacy of biofilm removal in the IP space. Key words: oral hygiene, Streptococcus mutans, micro-computed tomography, microscopy, interproximal cleaning, dental plaque.

Introduction

Good oral hygiene practice maintains a healthy oral cavity, biofilm-free interdental spaces and clean tooth surfaces utilizing the additional effect of generating a “surface-tension force” in the IP space by the passage of an air/water interface (González-Suárez et al., 2001). An advantage of using fluid forces to remove biofilms is that mechanical forces can be projected beyond the device itself, by generating currents in the fluid surrounding the teeth by powered brushing (Adams et al., 2002) or through the generation of water jets by oral irrigation (Lyle, 2011). However, continuous water jets have a disadvantage of requiring large reservoirs and can be messy to use because of the large volumes of water involved. Moreover, the SoniCare™ AirFloss device has been introduced for removing IP plaque. The AirFloss shoots a microburst of water volume and entrained air at a high velocity into the IP space in a discrete burst, each burst has high wall shear stress (τw) and high impact pressure over short periods of approximately 0.033 sec (Ap et al., 2013). However, since the IP space was symmetric (Figs. 3C, 3D).

We previously reported the influence of high-velocity water microdrop impact on the detachment of artificial plaque from the IP spaces, to demonstrate how a real biofilm might detach (Renaile et al., 2015). Here, we go on to use the same in vitro model to look at bacterial biofilm removal and appropriate computational fluid dynamics (CFD) numerical techniques to model and predict the spatial distribution of fluid wall shear stress (τw) required to remove the biofilm. This paper reports the results of an experimental and numerical study on the influence of a high-velocity water microdrop impact on the detachment of Streptococcus mutans biofilms from the IP spaces of a typodont model.

Materials and Methods

Bacteria and Growth Media Biofilms were grown from S. mutans UA159 (ATCC 700610). Stock cultures of S. mutans were stored at -80°C in 10% glycerol in physiological buffered saline (PBS). Biofilms were cultured with sucrose (2% w/v) supplemented brain heart infusion (BHI-S) broth (Sigma-Aldrich, Dorset, UK) and incubated at 37°C and 5% CO2. A typodont, maintaining the relevant juxtaposition between the typodont, the IP surfaces of the typodont teeth and the other typodont materials.

Micro-computed Tomography (μ-CT) Geometry Reconstruction of the Typodont Model

μ-CT was used to image the typodont in 3D and construct a model of the IP space to be used in subsequent CFD modelling (Fig. 1B, Appendix III).

Streptococcus mutans Biofilms inside Microfluidic Channels

To estimate the critical hydrodynamic shear stress required for S. mutans biofilm detachment, which could be used as a model input parameter for predicting the spatial distribution of biofilm removal, we used a BioMx™ (Thermo Fisher Scientific, South San Francisco, CA, USA) (Appendix IV).

Computational Fluid Dynamics Simulations

To model the dynamic behavior of the microburst created within the IP space, the tomato gel obtained from μ-CT was converted to a 3D computer-aided design (CAD) file geometry with Amira software (Mercury Computer Systems, Fürth, Germany). The computational domain, represented by the IP space, was discretized with surface Gambit 2.4.6 (Sintef Inc., Mountain View, CA, USA) using a tetrahedral meshing scheme. A cell size of 153 μm was chosen, which led to a total number of 145,085 mesh tetrahedral cells. Since the IP space was symmetric, only half of it was modeled, reducing computational cost and time.

CFD simulations were performed with ANSYS Fluent 12.1.4 software (ANSYS Inc., Canonsburg, PA, USA), which allowed for the determination of the flow field within the IP space and τw generated on the tooth surface (Appendix V).

Statistical Analysis

Statistical comparisons were made by one-way analysis of variance (ANOVA) (Excel 2003, Microsoft). Differences were reported as statistically significant for p < 0.05.

Results

3D Imaging of Typodont Model High-resolution 3D images detailing the micro-architecture of the typodont were obtained by μ-CT (Fig. 1B). This allowed us to computationally assemble the typodont, maintaining the relevant juxtaposition between the individual teeth, and to create a computational computer-aided design of the teeth without interference from the other typodont materials.

Quantification of Biofilm Removal

With confocal microscopy, S. mutans biofilms grown in the IP space showed bacterial cells aggregating and forming complex cell cluster colonies consisting of ‘tower’-, ‘mushroom’-, and ‘mound’-shaped structures. The thickness of the resulting biofilm on each tooth surface was approximately 200 to 500 μm. After the microburst, the images taken for the proximal surface of the teeth showed almost no biofilm close to the nozzle tip of the prototype AirFloss. Image analy-

sis showed 95% removal close to the tip, 62% removal at approximately 0.033 sec (Ap et al., 2013). The resulting curve showed 95% removal close to the tip, 62% removal at approximately 0.033 sec (Ap et al., 2013).

Critical Shear Stress for Biofilm-Margggregate Detachment

The morphology of the biofilms in the IP space of the typodont by confocal microscopy channels varied markedly between one channel and the
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[References]
Effect of the Nozzle z-position on Wall Shear Stress Distribution

Curves of fluid $\tau_w$ on the tooth surface, which were obtained to investigate the effect of tip positioning on the device's hydrodynamic performance. Figure 4 shows the tooth surface area where $\tau_w$ is lower than the shear stress value of Pa. Computational results predicted that the maximum $\tau_w$ of biofilm removal would take place when the nozzle tip is placed at z/H = 0.5 or z/H = 0.66, while the effect of the sinewave z-profiles, namely, z/H = 0.5 (close to the initial edge) and z/H = 0.85 (close to the initial edge), was minimal.

Discussion

In the flow cell experiments, S. mutans biofilms were successfully grown inside microchannels under gravitational flow forces, thus allowing simultaneous light microscopy (Appendix Fig. 2). The biofilm size and morphology were consistent with previously reported data (Corteron et al., 1999; Henschke et al., 2005). When $\tau_w$ was increased to an subjected an increased shear stress from 0 to 2 Pa, the large aggregates remained intact from the surface until the wall shear stress reached a critical value ($\tau_w$ $\approx$ 0.5 Pa). At this critical value, even at this critical value, the smaller bacterial individual biofilms remained attached. Generally, detachment of biofilms from the surface is triggered by the formation of large cell aggregates, which tend to be approximated by the streamers that usually form around the bacterial mass (ranging from 0.155 mm was selected for the simulations (circular nozzle tip; z/H = 0.5). The color bar is a linear scale to tooth surface (determined computationally). Datapoints were interpolated with a linear trend line.

Quantification of Wall Shear Stress Distribution

A representative contour plot of the wall shear stress $\tau_w$, spatial distribution on the tooth surface is shown in Fig. 5B. This simulation corresponded to the range of shear rates between 0.3, with the circular nozzle tip located at z/H = 0.5, gingivo-incisally, where z (mm) is a spatial coordinate from the supragingival base of the tooth, perpendicularly to the tip of the tooth, and H (mm) is the supragingival height of the tooth. Thus, $\tau_w$ = 0.5 Pa corresponds to the midpoint of the palatal surface of the tooth ($\tau_w$ $\approx$ 0.5 kPa).

Computational Prediction of Shear Stress and Experimental Biofilms Removal

The $\tau_w$ distribution obtained computationally was compared with the post-experiment removal of biofilms. A linear correlation of $\tau_w$ removal as a function of $\tau_w$ was found according to:

$$\text{Percent removal} = k \cdot \tau_w^p$$

where $\tau_w$ is wall shear stress (in Pa), and k (in Pa$^{-p}$) is the slope of the interpolating function (Figs. 5C, 5D).

The simulations predicted $\tau_w$ distribution on the tooth surface caused by the microbial biofilm to be in the kPa range in the IP space, except in areas on the proximal side of the tooth, where $\tau_w$ became significantly lower (~200 Pa). The simulations predicted computationally for the fluid $\tau_w$ were ~1,000 times higher than the $\tau_w$ obtained from the flow-cell experiments, and ~20 times higher than the estimated in vitro shear stress, required to dislodge bacteria, according to the literature, for biofilm detachment (Ohashi and Harada, 1994; Stoolsey et al., 2002). Thus, the simulations predict a significant percentage area of the tooth where $\tau_w$ values are capable of removing the plaque from the IP spaces. The large differences between $\tau_w$ in the zones between the 2 systems illustrates the importance of the physical growth conditions and surface type on adhesion strength. It was beyond the scope of this study to determine the influence of surface or hydrodynamics on adhesion strength. In mechanical testing, it’s reported for the same species commonly vary by 5 orders of magnitude (Morelli and Shafie, 2001). Whether this variability is true at different locations in the mouth or between patient is unknown, but measurements of the adhesion strength of real oral biofilm plaques would be useful in developing relevant in vitro models which look at mechanically induced detachment.

The 3D simulations for predicting $\tau_w$ were consistent with the experimental results obtained. As might be expected, the biofilm survived in the region of low $\tau_w$, but was flushed away at areas where $\tau_w$ was higher. A linear relationship was evident between the predicted fluid $\tau_w$ and the amount of detached biofilm obtained experimentally (Eq. 1). This relationship could be used to predict the efficacy of oral health care devices that use shear forces to remove plaque.

The computational model predicted the critical value of the effect of changing the position of the nozzle tip in the z-direction on the efficacy of biofilm removal efficacy. The numerical simulations predicted that the for the experimental setup, the flow was a steady state (Rimaile et al., 2013). Even though the shearing force was applied over very short periods of 50 msec, the generated fluid $\tau_w$ was significantly higher.

For the exit velocity of the microplasmodium, the results were consistent with the increased value in or close to the middle of the incisogingival height (z/H = 0.5 Pa). The computer fluid $\tau_w$, in comparison with placing the tip closer to either the incisal edge or the gingival edge (Fig. 4). To the best of our knowledge, this is the first time that CFD has been used to calculate the wall shear stress distribution, caused by water drops ejected from the device, on the tooth surface.

In this study, an experimental set-up was built and a methodology was developed to characterise the efficiency of biofilm detachment by high-velocity water droplets, evaluating the effect of the orientation of biofilm and automatically translates into prevention of dental caries formation at these sites.

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