Comparing Three Caries Prevention Products on Dentinal Hypersensitivity – A Pilot Study

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I) Introduction

A) Aim/Hypothesis/Objective

The aim of this pilot research project is to compare the clinical effect on dentinal hypersensitivity of three products: Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) paste with fluoride, 5000 Sodium Fluoride (NaF) dentifrice containing Tri-Calcium Phosphate (TCP), and a dentifrice containing Potassium Nitrate.

The hypothesis of this study is that CPP-ACP with fluoride and 5000ppm NaF with TCP will exhibit a greater reduction in dentinal hypersensitivity compared to the control (dentifrice containing Potassium Nitrate).

The results of this pilot study will validate or negate the need for a larger clinical study that may provide generalizable results for using caries-prevention products with the additional benefit of minimizing dentinal hypersensitivity.

II) Background and Rationale

Dentinal hypersensitivity commonly occurs in patients with gingival recession, resulting from a reduced periodontium or in patients who have undergone non-surgical and surgical periodontal therapy.[1,2] When the gingiva recede, the root surfaces of the teeth are exposed.[3] In addition, after a non-surgical or surgical periodontal procedure, the cementum of the root surface is removed as a result of scaling and root planing. This leaves dentin exposed on the root surface with open dentinal tubules. In addition, dentin is less mineralized than enamel and has a greater susceptibility to and a faster progression of root caries and dentinal hypersensitivity.[4] Root caries commonly occurs in patients who have undergone periodontal therapy and extensive root caries often results in the extraction of the tooth.[5]

Dental professionals often make a variety of recommendations to remedy dental hypersensitivity, including the application of fluoride varnishes, anti-hypersensitivity toothpaste, gingival grafting procedures and various restorative procedures, aiming to occlude the dentinal tubules or desensitize the pulpal nerve endings.[6,7]

Since the introduction of CAMBRA (CAries Management By Risk Assessment) in the Journal of the California Dental Association in 2007,[8,9] the marketplace for anti-caries products has surged. As a result, many approaches to the management of dental caries have been introduced and dental practitioners and sales representatives have promoted several anti-caries products. In addition, the reduction or the abatement of the progression of dental caries (coronal, root and interproximal) as a result of a caries management program has been reported.[10,11] Many caries management products have ingredients that include fluoride and calcium phosphate (Amorphous Calcium Phosphate-Casein Phosphopeptide (Recaldent ™),[12] Tri-Calcium Phosphate ™ or Novamin ™).[13]

Moreover, encouraging clinical findings have been reported, including, but not limited to the reduction of white spot enamel lesions and dentinal hypersensitivity.[14]

The topical application of "antihypersensitivity" materials is a common recommendation (least invasive of the "standard of care" recommendations) to diminish dentinal hypersensitivity and will serve to provide data for the research study. The study will evaluate which of these products result in the greatest reduction of dentinal hypersensitivity. The application of the experimental products for the reduction of dentinal hypersensitivity is for research purposes.

The methods used to test sensitivity in this study have been used in published studies.[6,15,16] The VAS scale used in this study has also been used for tooth sensitivity studies.[16,17] A 30% decrease in VAS score has been shown to be clinically meaningful.[18,19]

This pilot study would investigate the ability of anti-caries products to reduce dentinal hypersensitivity when compared to a sensitivity-reducing dentifrice. It would be a novel contribution to the dental community if a material that is proven to reduce tooth decay is also proven to reduce dentinal hypersensitivity. The results may potentially have a tremendous impact on the dental community because it may provide dental professionals a scientifically-supported approach to improve the comfort and quality of life of periodontal patients (patients who are treated for gum disease/ bone loss around teeth) and increase the lifespan of teeth that undergo periodontal treatment.

III) Research Plan

A) Experimental Design

This pilot study utilizes a single center, blinded, IRB-approved, randomized, prospective, paralleled group design to compare the reduction of dentinal hypersensitivity using CPP-ACP with fluoride or 5000ppm NaF with TCP to potassium nitrate (control).

B) Sample Size and Statistical Analysis

Sample Size

The primary analysis will be to compare the percent change in dentinal hypersensitivity between the 3 groups. We assume that the control group may exhibit a modest improvement in dentinal hypersensitivity (~5%) whereas the two test groups should demonstrate a more significant improvement (~30%). Assuming a common standard deviation of 25%, we will have 58% power to detect a difference between the 3 groups using one way analysis of variance, with 10 subjects per group, and setting alpha to 0.05 (nQuery Advisor, Version 7.0). Up to 13 subjects per group will be recruited, to allow for a more than 20% dropout rate.

The literature is varying on the amount of improvement possible with the products. Guidelines for sensitivity studies indicate that a main objective

should be to produce a clinically significant reduction in symptoms[20]. With the use of VAS scores, a 30% decrease in VAS score has been shown to be clinically meaningful.[18,19] For this study we anticipate a clinically meaningful decrease in sensitivity for the two test groups.

Statistical Analysis
Normality will be assessed using the Kolmogorov-Smirnov test. If the assumptions of normality hold, then means and standard deviations will be reported and the relationship between treatment arm and percent change in dentinal hypersensitivity will be tested using one-way ANOVA. If the assumptions of normality do not hold, then medians and interquartile ranges will be reported and relationships will be tested using the Kruskal-Wallis test. If the initial analyses are significant, then the *post hoc* pairwise comparisons will be made using either independent-sample t-tests or Mann-Whitney U-tests. When patients are lost to follow-up, their information will be excluded from the analyses.

All p-values less than 0.05 will be considered statistically significant.
Analyses will be performed using SAS, Version 9.2 (SAS Institute, Cary, NC).

Randomization
Each subject will be randomized to a treatment arm using a randomization website (www.random.org). When subjects have multiple teeth eligible for the study, a separate randomization scheme (also from www.random.org) will be used to select that tooth. A printout of the randomization scheme will be used by the investigator distributing the products.

Blinding
Examiners collecting the sensitivity data will be blinded as to which group the subject is in. An investigator who did not examine the subject will distribute the product.

C) Products

Group	Product 1	Product 2
Group I (Control)	Sensodyne (Potassium Nitrate) manufactured by GalaxoSmithKline	N/A
Group II	Crest Cavity Protection manufactured by Procter and Gamble	MI Paste Plus (CPP-ACP with fluoride) manufactured by GC America
Group III	Clinpro 5000 (5000ppm NaF with TCP) manufactured by 3M ESPE	N/A

Senosydne is FDA approved for decreasing tooth sensitivity. It is approved for use as it is being used this study.

Clinpro 5000 has been FDA approved for the prevention or reduction of dental caries. A reduction in dentinal hypersensitivity has been anecdotally documented in the literature.

MI Paste Plus is FDA approved for the reduction of dentinal hypersensitivity. It is approved for use as it is being used this study.
Crest Cavity Protection Toothpaste is FDA approved as an anticavity drug.

Oral-B 35 soft manual toothbrush is FDA approved and being used as approved for this study.

All products are being used according to manufacturer's instructions.

D) Subject Characteristics

1) Inclusion Criteria
   - At least 18 years of age
   - Tooth with exposed root surface and/or exposed dentin
   - Tooth with a VAS score greater than or equal to 3
   - No adjacent tooth/teeth with sensitivity (as defined as greater than 2 on the VAS)

2) Exclusion Criteria
   - Participation in another dental study that may alter the results of this study.
   - A medical condition that could interfere with reliable pain reporting (e.g., pain disorders)
   - Any chronic medical condition that requires the regular use of pain or anti-inflammatory medications
   - Used a desensitizing dentifrice within the preceding four weeks
   - Have received an antihypersensitivity treatment (varnish or precipitating solution) of the identified tooth within the preceding four weeks
   - Undergoing active orthodontic treatment.
   - Teeth with carious lesions, buccal vertical cracks in enamel, evidence of irreversible pulpitis (pain lasting more than five seconds after air stimulation)
   - Pregnant/ lactating patients (Clinpro5000 has 5000ppm fluoride and there is a risk of ingesting the product)
   - Patients with Milk Allergy (CPP-ACP is a dairy based product)
   - Patients on Kidney Dialysis (due to the free calcium in CPP-ACP, dialysis patients should be on a diet with limited calcium)

3) Subject Withdrawal/Termination Criteria
   - Subjects will be withdrawn from the study if they report the use of other dental hygiene products, including but not limited to: toothpaste, rinses, fluoride varnishes

- Subjects will be withdrawn from the study if they undergo any phase I periodontal procedures, including a prophylaxis or scaling and root planing
- Subjects would be withdrawn if they experience a negative side effect from any product used in the study.
- The tooth being studied is extracted, damaged from trauma or receives endodontic therapy.
- Subjects may participate in another research study at the same time, as long as it does not impact the results from this study.
- Subjects who do not comply with the study procedures, such as not returning for visits, not using product as documented in diary, may be withdrawn from the study.
- Subjects who become pregnant during the course of the study will be withdrawn. Subjects will be informed in the informed consent form to inform principal investigator or their designate if they become pregnant.
- Subjects who decide to stop participating in the study will be withdrawn.

The Principal Investigator will determine whether subjects (either withdrawn subjects or subjects completing the study) are in need of additional treatment and/or follow-up observation as a result of participation in this trial.

E) Assessment

1) Risk

This study poses minimal risk to subjects as these are products that approved for use.

With Clinpro5000, although the patient will be instructed not to ingest the product, ingestion may result in GI discomfort, nausea, vomiting, diarrhea, cramping and fluorosis in children. Fluoride exposure should be monitored in pregnant and nursing women. Pregnant and lactating women and children will be excluded from this study.

MI Paste Plus contains Recaldent (Amorphous Calcium Phosphate-Casein Phosphopeptide) which is a milk-derived product. This product is contraindicated with patients who have a milk protein (Casein IgE) allergy (this product is safe for lactose-intolerant patients). Fluoride exposure should be monitored in pregnant and nursing women. Pregnant and lactating women and children will be excluded from this study.

Sensodyne contains fluoride and should not be ingested in large doses, especially by children. Fluoride exposure should be monitored in pregnant and nursing women. Pregnant and lactating women and children will be excluded from this study.

There is no anticipated risk with the completion of subject diaries.

There is the risk of some discomfort/sensitivity during tooth sensitivity scoring.

There is the risk of loss of confidentiality to the subject by participating in this study. This risk will be kept to a minimum by following procedures listed under confidentiality.

2) Benefits
The subject may experience some decrease in tooth sensitivity.

3) Alternatives
The alternative for the patient is to not participate in this study. An alternative for the patient to receive alternative procedures (e.g., fluoride treatment, topical desensitizer, composite restoration, or gingival graft) for sensitivity at normal clinic fees.

F) Study Procedures

Visit 1: Screening Visit/ Baseline:
The subjects will be instructed to read the informed consent form (ICF). Subjects will be given ample time to have any questions answered. If a subject decides to participate, he or she will be instructed to sign the ICF. A copy of the ICF will be given to the subject.

Subject will be asked to complete demographic information and a medical history.

An oral exam, including evaluation of oral cavity and soft tissues, will be completed following standard of care procedures.

All potential qualifying teeth will be evaluated for dentinal hypersensitivity and the one tooth with the most severe dentinal hypersensitivity (in response to air) will be selected for the study. If two or more teeth have the same score, one will be randomly selected.

Each subject will be evaluated for the severity of dentinal hypersensitivity utilizing the VAS Scale to determine the subject's perception of pain. Testing methods described by Brahmbhatt et al.[6] will be utilized in this study. Testing is for research purposes.

Air test: A 1 second blast of air from an air-water syringe that is set to 45psi at a distance of 10mm will be applied to the tooth. Adjacent teeth will be protected with fingers or cotton rolls. The subject will classify the extent of the sensitivity on the VAS. If the discomfort becomes intolerable, the stimulus will be immediately removed.

Water test: The patient will be given a 5-minute rest between tests. Disposable, plastic syringes filled with water will be kept in an ice water bath until use. Then, cold water will be applied to tooth using a plastic syringe with a plastic tip. Three drops of water will be placed on the tooth[16]. Adjacent teeth will be protected with fingers or cotton rolls. The subject will classify the extent of the sensitivity on the VAS. If the discomfort becomes intolerable, the stimulus will be immediately removed.

Schiff Test: The Schiff Sensitivity Scale[21] will be utilized by the examiners to evaluate the response of the subjects to both the air and water test. This analog scale scores for the tooth as 0, 1, 2 or 3.

0-Tooth/Subject does not respond to stimulus.
1-Tooth/Subject responds to stimulus, but does not request discontinuation of stimulus.
2-Tooth/Subject responds to stimulus and requests discontinuation or moves from stimulus.
3-Tooth/Subject responds to stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus

If the subject qualifies for the study, they will be entered into randomization.

Intraoral photographs of the study teeth will be taken. Photographs are for research purposes. Photographs will be taken at Visits 1 and 4. Additional photographs may be taken to document any adverse reactions.

After taking the data, the examiner will leave the operatory and another study team member will do the randomization. In this way the examiner will be blinded as to which group the subject is a part of.

Subject will be randomized to one of three groups:

Group I: Control
The control group will use Sensodyne toothpaste twice daily (2 minutes each time in the morning and the evening) during the duration of the study.

Group II:
Subjects will be instructed to brush twice daily (2 minutes each time in the morning and the evening) using Crest Cavity Protection toothpaste. They will be instructed to apply MI Paste Plus (CPP-ACP with fluoride) twice daily to the study teeth after brushing their teeth. MI Paste Plus will be applied to the study teeth with a finger.

Group III:

Subjects will be instructed to brush twice daily (2 minutes each time in the morning and the evening) using Clinpro 5000 (5000ppm NaF with TCP).

The study team member will describe the proper use for the products and will review oral hygiene instructions. Once the subject demonstrates understanding for the use of the products, the products and a handout for the use of the products will be distributed. A toothbrush and 2-minute timer will also be given to the subject. The use of any other topical dental products (e.g., rinses, toothpastes, fluoride varnish) will be discontinued. The subjects may use additional products (e.g., dental floss, interproximal devices) to remove plaque. Subjects will be given a diary in which to track product usage. Diary is for research purposes.

VAS

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst pain imaginable

Visit 2 (2 weeks +/- 2 days after Visit 1):
A study team member who did not examine the subject at the initial visit will ask the subject for any changes in the medical or dental history. The study team member will also discuss patient compliance, adverse events, review and collect the patient's diary, hand out a new patient diary, and answer any questions that the subject has regarding the products and dispense additional products, if necessary.

Eligibility and subject withdrawal criteria will be reviewed to ensure the subject still qualifies for the study.

The same examiner from the initial visit will then conduct the oral exam and collect the sensitivity data (if necessary, another examiner may see the subject, however, this will be avoided if possible).

An oral exam, including evaluation of oral cavity and soft tissues, will be completed following standard of care procedures.

The same sensitivity tests will be done as at Visit 1. Tests are for research purposes.

Visit 3 (4 weeks +/- 2 days after Visit 1):
A study team member who did not exam the subject at the initial visit will ask the subject for any changes in the medical or dental history. The study team member will also discuss patient compliance, adverse events, review and

collect the patient's diary, hand out a new patient diary, answer any questions that the subject has regarding the products.

Eligibility and subject withdrawal criteria will be reviewed to ensure the subject still qualifies for the study.

The same examiner from the initial visit will then conduct the oral exam and collect the sensitivity data (if necessary, another examiner may see the subject, however, this will be avoided if possible).

An oral exam, including evaluation of oral cavity and soft tissues, will be completed following standard of care procedures.

The same sensitivity tests will be done as at Visit 1. Tests are for research purposes.

Visit 4 (8 weeks +/- 1 week after Visit 1):
A study team member who did not exam the subject at the initial visit will ask the subject for any changes in the medical or dental history. The study team member will also discuss patient compliance, adverse events, review and collect the patient's diary, answer any questions that the subject has regarding the products.

Eligibility and subject withdrawal criteria will be reviewed to ensure the subject still qualifies for the study.

The same examiner from the initial visit will then conduct the oral exam and collect the sensitivity data (if necessary, another examiner may see the subject, however, this will be avoided if possible).

An oral exam, including evaluation of oral cavity and soft tissues, will be completed following standard of care procedures.

The same sensitivity tests will be done as at Visit 1. Tests are for research purposes.

Intraoral photographs will be taken of the study teeth. Photographs are for research purposes.

All products may be kept by the subject at the end of the study.

Subject timeline

Appointment / Procedures	Visit 1 Screening/ Baseline	Visit 2 (Treatment Day 14)	Visit 3 (Treatment Week 4)	Visit 4 (Treatment Week 8)
Informed Consent	X			
Demographics	X			X
Medical/Dental History	X	X	X	X
Evaluate Eligibility and Subject Withdrawal Criteria	X	X	X	X
Oral Examination	X	X	X	X
Subject VAS Score (Air/Cold Water)	X	X	X	X
Examiner Schiff Sensitivity Scale	X	X	X	X
Digital Intraoral Photographs	X			X
Assignment into Study Group	X			
Adverse Event Assessment		X	X	X
Handout Diary	X	X	X	
Collect Diary		X	X	X
Stipend	X	X	X	X

G) Subject Safety

1) Adverse Event Reporting

Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal physical exam or laboratory finding, symptom, or disease, temporally associated with a subject's participation in the research.

Adverse events will be recorded in source documents and on case report forms. All adverse events and non-serious situations will be recorded, monitored, and reported to the IRB at time of continuing review.

Serious Adverse Events

A serious adverse event is one that results in death, or is life-threatening, or results in hospitalization or prolongation of existing hospitalization, or results in a persistent or significant disability/incapacitation, or results in a congenital anomaly/birth defect, or may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above.

Serious adverse events will be recorded in source documents and on case report forms. Serious Adverse Events will be reported to the IRB within 15 business days.

Unanticipated Problems

An unanticipated problem is an incident, experience, or outcome that meets all of the following criteria: 1) The nature, severity, or frequency is unexpected for the subject population or research activities as

described in the current IRB approved protocol, supporting documents, and the ICF(s); 2) it is related or possibly related to participation in the research; 3) it suggests the research may place the subject or others at a greater risk of harm then was previously recognized.

Unanticipated problems will be recorded in source documents and on case report forms. Unanticipated problems will be reported to the IRB within 5 business days.

H) Subject Participation

1) Screening
The study co-investigators will conduct screening examinations to identify subjects who meet the inclusion / exclusion criteria for enrollment into the study.

2) Informed Consent
An investigator or study coordinator (who is GCP and CITI trained) will introduce the study. Patients will be asked to read the consent form and given ample opportunity to have their questions answered. An investigator will assess the patient's competency to provide consent by discussing the study with the patient and ensuring that they understand the study. Patients will certify their willingness to participate in the study by signing and dating the IRB approved informed consent document. The subject will be given a copy of the consent form.

If any new finding requires any change to the informed consent form, the subject will be reconsented.

Non-English speaking subjects will not be enrolled in the study because study staff at this time are not certified, prepared, or trained to translate or communicate in any language other than English. The study budget does not allow for the payment of translation services at this time.

3) Study Location
Tufts University School of Dental Medicine

4) Personnel
Responsible for ongoing communication with the IRB – PI

Obtaining informed consent – PI, Co-Is, and study coordinator (who is GCP and CITI trained)

Maintaining study records – PI

Sensitivity testing and oral exam – PI and Co-Is

Product distribution and instructions, answering any questions that the subject has regarding the products. – Study coordinator (with instruction from PI/Co-I who has not treated subject).

Reviewing and collecting the patient's diary, handing out diaries - PI, study coordinator/team member

Intraoral photographs – PI, Co-Is

Gift card distribution – PI, study coordinator/team member

5) Payment for Participation
   (a) Compensation
   The subject will be given up to $100 in gift cards. $25 upon completion of visit 1, $25 upon completion of visit 2, $25 upon completion of visit 3, $25 upon completion of visit 4.

   (b) Transportation
   No reimbursement will be given for transportation or parking

   (c) Payment and Insurance
   There will be no fees associated with the study procedures. Neither the subject, nor their insurance company, will be billed for any study procedures.

6) Study Results
   If interested, a copy of the published paper will be mailed to interested study participants. A log will be kept of the participants who are interested in receiving study results.

7) Confidentiality
   (i) To ensure confidentiality of subject information, each subject enrolled in the study will be assigned a unique alphanumeric code. Subjects' files will be kept in a secure, locked cabinet in a secure room (DHS-1418) when the files are not reviewed. The information will only be shared between the researchers. All HIPAA requirements will be followed. All electronic files will be kept on a password protected computer in a secure, locked office.

   (a) Coding
      (i) Each will be assigned a subject identification number. Alphanumeric identification numbers will be assigned sequentially. The full subject identification number will consist of the three letters from the subject's initials and their enrollment number. This will be accessible by study personnel only.

   (b) Access / Data Safety Monitoring Board

Only study personnel will have access to data. Investigators will permit monitoring, audits, and regulatory inspections and will provide direct access to study related documentation.

10) Data Safety Monitoring Plan:
Study personnel will monitor this trial for all safety related issues to determine whether an unreasonable risk to subjects develops. Quality control measures include routine inspection of case report forms, source documents, data tabulations, and tracking of adverse events

11) New Findings
The subject will be informed of any significant new findings discovered during the course of this study that might influence the subject's continuation and participation in the study. Subjects will be told at a study appointment or via telephone of new findings during the study.

If new findings require revisions to the ICF, the subject will be re-consented.

I) Collaboration
N/A

J) Record Retention
1) Study Records
The Investigator will maintain all study records and documents during the study period. All paper files and documents will be kept in a locked file cabinet, within a locked room (DHS-212). Electronic records will be kept on a password protected computer and only be accessible to study personnel.

2) Long Term Retention
The investigator will maintain all study records following completion or termination of this study in accordance to state law and institutional policy (at least 7 years after study is completed or terminated).

K) Reporting
1) Final Report
Unanticipated problems and adverse events will be reported per the Tufts MC/TUHS IRB Unanticipated Problem and Adverse Event Reporting Policy.

The IRB will be notified of any deviations from the protocol in cases of medical emergencies when the change is necessary to eliminate an apparent immediate hazard to the subject

Progress reports on the investigation shall be submitted to the IRB at regular intervals, but in no event less often than yearly, e.g., at continuing review.

L) Protocol Deviations

No protocol changes or deviations will be made without prior agreement by the IRB unless implemented to prevent an immediate hazard to subjects. All other protocol changes or deviations will be made by a formal amendment subject to IRB approval. All such changes or deviations will be reported to the IRB as they occur and included in the final study report.

M) Study Termination

This study may be terminated for the following reasons:

Discovery of unforeseen risk that could jeopardize the dental/physical well-being of subjects.

Enrollment or recall rates that are not likely to produce sufficient data for evaluation of safety and efficacy

Non-compliance with the clinical investigational plan, the Investigator

Agreement, applicable FDA regulations or conditions of approval imposed by the reviewing IRB

Withdrawal of IRB approval

In the event of study termination, the Principal Investigator will determine whether subjects are in need of additional treatment and/or follow-up observation as a result of participation in this trial.

N) Subject Recruitment/Advertising

Paper flyers will be posted throughout TUSDM, Tufts University School of Medicine and Tufts University School of Nutrition Science and Policy. Permission is not required for these posting locations. Flyers will remain posted until enrollment goals are met. Subjects will be recruited through responding to posted study advertisements. The same language from the approved flyers may be posted on the TUSDM website and screen in the lobby.

Investigators may also verbally inform clinic patients, faculty members who oversee students in the clinic, and post-graduate residents about the study.

Investigators may send messages to colleagues via axiUm or inform colleagues verbally, asking for their help in recruiting eligible subjects.

An email that alerts the TUSDM community to ongoing studies may include information on this study for recruiting purposes.

Advertisements/information regarding the study may be posted on Facebook and/or Craigslist.

All of the forms of recruitment will be submitted to the IRB for approval prior to use.

A screening interview/questionnaire or screening script will be used for recruitment. Screen failure data will be retained by PI. Screening ID number

and demographic information will be recorded. Identifiable information will not be recorded in the screening log.

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