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The importance of bioavailable calcium in fluoride dentifrices for tooth enamel remineralization (repair)

Submission date	Recruitment status	[ ] Prospectively registered
07/06/2018	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
12/06/2018	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
08/06/2018	Oral Health	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Many commercially-available fluoride toothpastes now contain added calcium in different forms. The aim of this study is to compare remineralization (repair) of tooth enamel by these toothpastes.

Who can participate?
Healthy staff and students of the University of Melbourne, aged 18-60

What does the study involve?
Human enamel pieces cut from extracted third molar (wisdom) teeth with artificially-created subsurface lesions (early tooth decay lesions) are prepared and inserted into intra-oral palatal appliances (similar to removable partial dentures) that are worn by the participants. A slurry of toothpaste and water is rinsed for 60 seconds, 4 times per day for 14 days. Seven toothpastes (two fluoride toothpastes and five fluoride toothpastes with added calcium) are tested in a random order with a one-week break between toothpastes. The toothpastes are commercially available in Australia. Enamel lesion mineral content of the enamel pieces in the worn appliances is measured after each 14-day treatment in the laboratory after the enamel pieces are removed.

What are the possible benefits and risks of participating?
The expected benefit of the study is that once published it will provide important information on the relative effectiveness of these toothpastes. It is expected that all calcium and fluoride containing toothpastes will be superior to the fluoride alone toothpastes in the remineralization of enamel subsurface lesions. There is very little risk for the participants as the toothpastes are manufactured by multinational oral care companies and are safe for human use.

Where is the study run from?
University of Melbourne (Australia)

When is the study starting and how long is it expected to run for?
April 2017 to March 2018

Who is funding the study?
Department of Industry, Innovation and Science, Australian Government

Who is the main contact?
Prof. Eric Reynolds

Contact information

Type(s)
Scientific

Contact name
Prof Eric Reynolds

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
University of Melbourne ID:1646383

Study information

Scientific Title
A double-blind, randomized, cross-over, in situ clinical trial of seven commercially available dentifrices

Acronym
Dentifrice in situ clinical trial

Study objectives
Addition of bioavailable calcium to fluoride dentifrice enhances tooth enamel lesion remineralization in situ.

Ethics approval required
Old ethics approval format

Ethics approval(s)
University of Melbourne Human Research Ethics Committee, 26/08/2016, ID: 1646383

Study design
Single-centre double-blind randomized cross-over design

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Dental caries (tooth decay)

Interventions
Dentifrices
The dentifrices purchased for the study will include (1) Maximum Cavity Protection containing CaCO3/Arg/CaHPO4 and 1450 ppm F as Na2MFP (Colgate); (2) Sensodyne Protect and Repair containing calcium sodium phosphosilicate (CSP, NovaMin) and 1450 ppm F as Na2MFP (GSK); (3) Enamelon containing ACP and 1150 ppm F as SnF2 (Premier Dental); (4) ClinPro 5000 containing TCP and 5000 ppm F as NaF (3M ESPE); (5) MI One containing (CPP-ACP) and 1100 ppm F as NaF (GC America); (6) 5000 ppm F as NaF control (Colgate) and (7) 1450 ppm F as NaF control (generic).

The required sample size was calculated using the G*Power Version 3.1 sample size package and was based on a repeated measures analysis of variance with 7 levels, an effect size of 0.97, a correlation, ρ, between any pair of treatment means of 0.5 and a non-sphericity correction ε of 0.5. The effect size of 0.97 was based on detecting differences between ΔZd-ΔZr means of 70 (fluoride control and fluoride plus calcium phosphate technology) and a common standard deviation of 100 within groups. The non-sphericity correction adjusts for heterogeneity in the variances of the repeated measures. With a 5% significance level and a power of 90% at least 6 subjects will be required. To allow for subject attrition eight subjects will be recruited for the study.

Intra-oral Appliances and Enamel Subsurface Lesions
Extracted human third molars will be sterilized, enamel slabs cut and subsurface lesions created as described by Shen et al. (2011). After lesion formation, one half of each enamel slab will be

retained as the control half-slab and stored in a humidified container. The other half slab (test) will be inset into an intra-oral appliance to form a plaque retention site over the enamel lesions as described by Cochrane et al. (2012). Removable palatal appliances covering the first premolars to the last tooth in the arch will be fabricated for each participant as described by Cochrane et al. (2012). Two enamel half-slabs, containing two demineralized subsurface lesions per half-slab, will be inset bilaterally in each appliance adjacent to the palatal surfaces of the maxillary premolar/molar teeth to give four half-slabs per appliance.

In situ Trial Protocol
The in situ study will be conducted at the Royal Dental Hospital of Melbourne. The study design will be a double-blind, randomized, cross-over design to assess the effects of the seven dentifrice formulations (two fluoride control dentifrices and five test dentifrices containing fluoride with calcium phosphate technologies). Participants will be randomly assigned to one of the dentifrices and then cross over to the other dentifrices with one week washout between each dentifrice. Each participant will be assigned a number and randomization will be effected using a standard randomization table for the seven coded dentifrices.

Each dentifrice will be prepared as a standardized solution (1.0 g of paste plus 4 ml of distilled, deionised water) in sealed, coded tubes. The paste and water will be mixed thoroughly by vortex for 1 min. Each participant will wear the custom made palatal appliance containing the four enamel half-slabs with subsurface lesions and four times per day for 14 consecutive days (treatment period) rinsed for 1 min with 5 mL of dentifrice solution. The four rinses per day will be performed after (i) breakfast; (ii) lunch; (iii) dinner and (iv) before bed. Participants will keep a diary of times and duration they rinsed with the dentifrice solution. Participants will be instructed to maintain their normal diet and oral hygiene procedures for the duration of the treatment periods. Intra-oral appliances will be removed during normal oral hygiene procedures during the study period. After removing the appliances for oral hygiene procedures, subjects will clean their appliances as instructed with a toothbrush and fluoride-free denture paste (both supplied) avoiding the inset enamel and biofilm and gently rinse their appliances with DDW before replacing them in the mouth. When out of the mouth the appliances will be stored in sealed humid containers. All subjects will brush their teeth with standard 1450 ppm fluoride toothpaste for the duration of the study. The subjects will return to the clinical site with their appliances, diary and empty tubes at the conclusion of each 14-day treatment period. Researchers and participants will be blind to the treatment code. An independent staff member will hold the treatment code which will only be released after data collection and analysis.

At the end of each treatment period the enamel half-slabs will be removed from the appliance and replaced with new pre-sterilised enamel half-slabs for the beginning of a new test period. After each treatment period each test half-slab will be paired with its control half-slab and embedded, sectioned and analysed by transverse microradiography to determine mineral content as described previously (Cochrane et al. 2012). Lesion parameters, lesion depth (LD) and integrated mineral loss (ΔZ) will be determined and the ΔZ value for the control demineralized lesion will be designated ΔZd and that for the treated lesion will be designated ΔZr. These values will then be used to calculate total mineral loss or gain ΔZd-ΔZr and percentage mineral change (%R) as (ΔZd-ΔZr/ΔZd) x 100. The change in lesion depth will be calculated as LDd-LDr.

Intervention Type
Other

Primary outcome measure

The effects of the dentifrices on enamel remineralization will be compared using integrated mineral gain/loss, ΔZd-ΔZr, as the primary outcome measure. At the end of each treatment period each test half-slab will be paired with its control half-slab and embedded, sectioned and analysed by transverse microradiography to determine mineral content as described previously (Cochrane et al. 2012). Lesion parameters, lesion depth (LD) and integrated mineral loss (ΔZ) will be determined and the ΔZ value for the control demineralized lesion will be designated ΔZd and that for the treated lesion will be designated ΔZr. These values will then be used to calculate total mineral loss or gain ΔZd-ΔZr and percentage mineral change (%R) as (ΔZd-ΔZr/ΔZd) x 100. The change in lesion depth will be calculated as LDd-LDr.

Secondary outcome measures
Secondary outcome variables will be the percentage change in mineral (%R) and the change in lesion depth (LDd-LDr). At the end of each treatment period each test half-slab will be paired with its control half-slab and embedded, sectioned and analysed by transverse microradiography to determine mineral content as described previously (Cochrane et al. 2012). Lesion parameters, lesion depth (LD) and integrated mineral loss (ΔZ) will be determined and the ΔZ value for the control demineralized lesion will be designated ΔZd and that for the treated lesion will be designated ΔZr. These values will then be used to calculate total mineral loss or gain ΔZd-ΔZr and percentage mineral change (%R) as (ΔZd-ΔZr/ΔZd) x 100. The change in lesion depth will be calculated as LDd-LDr.

Overall study start date
01/04/2017

Completion date
31/03/2018

Eligibility

Key inclusion criteria
1. Eight healthy adults living in Melbourne, Australia with a fluoridated (0.9 ppm F), reticulated water supply
2. Staff and students of the University of Melbourne
3. Age 18-60 years
4. At least 22 natural teeth
5. Unstimulated whole salivary flow rate of ≥ 0.2 ml/min
6. Gum-stimulated whole salivary flow rate ≥ 1.0 ml/min

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
60 Years

Sex
Both

Target number of participants
8

Key exclusion criteria
1. Currently using antibiotics or medications that may affect salivary flow rates
2. A history of severe oral disease

Date of first enrolment
01/06/2017

Date of final enrolment
01/07/2017

Locations

Countries of recruitment
Australia

Study participating centre
University of Melbourne
Level 6, 720 Swanston Street
Carlton
Australia
3053

Sponsor information

Organisation
The University of Melbourne

Sponsor details
-
Victoria
Australia
3010

Sponsor type
University/education

Website
https://www.unimelb.edu.au/

ROR
https://ror.org/01ej9dk98

Funder(s)

Funder type
Government

Funder Name
Department of Industry, Innovation and Science, Australian Government

Alternative Name(s)
Department of Industry, Innovation and Science

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Australia

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
30/10/2018

Individual participant data (IPD) sharing plan
No personal data on the participants will be provided only enamel mineral content data of the enamel pieces worn in the appliances by each participant after treatment with the various toothpastes. This information will be made available when the study is published. Prof. Eric Reynolds can be contacted for that information plus the analytical information on the tested toothpastes. The participants did provide informed consent in writing to be part of the study.

IPD sharing plan summary
Available on request