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The effect of antibacterial photothermal therapy on plaque in healthy adults

Submission date	Recruitment status	[ ] Prospectively registered
27/08/2020	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
02/09/2020	Completed	[X] Results
Last Edited	**Condition category**	[ ] Individual participant data
01/06/2021	Oral Health	

Plain English summary of protocol

Background and study aims
This is an early feasibility study of a method for the prevention of infective dental diseases, mainly periodontitis (severe gum infection) and caries (tooth decay). The aim of this study is to measure the effects of a near-infrared light/indocyanine green applicator for photodynamic therapy on the development of plaque, plaque bacteria and markers of periodontitis.

Who can participate?
Healthy volunteers aged 18 to 65

What does the study involve?
The treatment period comprises four treatment sessions over four consecutive days, and the treatment itself consists of a light applicator and the indocyanine green photoactive substance. Teeth on one side of the mouth are randomly allocated to be treated, and the opposite side is not treated and serves as the control. The participants are not allowed to brush or otherwise clean their teeth during the treatment period. Gingival crevicular (gum) fluid is collected before each treatment and at the end of the study, just after the last treatment. Photographs are taken of the teeth before treatment, daily during the treatment sessions, and after the treatment period, to assess the development of plaque on the treated and untreated teeth. Mouth bacteria and markers of periodontitis are analysed before and after the treatment period.

What are the possible benefits and risks of participating?
The results will improve the understanding of oral health and ways to maintain good oral health. There are no major identified risks.

Where is the study run from?
University of Helsinki (Finland)

When is the study starting and how long is it expected to run for?
May 2017 to June 2017

Who is funding the study?
Finnish Funding Agency for Technology and Innovation (TEKES) (Finland)

Who is the main contact?
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Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Patila_K1

Study information

Scientific Title
Indocyanine green-mediated antibacterial photothermal therapy in the development of plaque in healthy adults

Acronym
IDENTA

Study objectives
This is an early feasibility study of a method, investigated for clinical use for the prevention of infective dental diseases, mainly periodontitis, and caries.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 11/05/2018, ethics committee of the Hospital District of Helsinki and Uusimaa (no postal address available; +358 (0)40 359 4618; eettiset.toimikunnat@hus.fi), ref: HUS/827/2018

Study design
Randomized split-mouth study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Prevention

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

Health condition(s) or problem(s) studied
Infective dental diseases, mainly periodontitis and caries

Interventions

The treatment period comprises four treatment sessions within four consecutive days, and the treatment itself consists of a light applicator and the ICG photoactive substance. Medications that could affect the oral microbiome, such as antibiotics, chlorhexidine, and antimicrobial mouthwashes, are not permitted during the study.

Maxillary first premolars are measured. Two days before the study, a meticulous professional cleaning is performed on both sides of the maxilla. The treatment side is randomized by a coin flip, and the contralateral side serves as the control. The study subjects are not allowed to brush or otherwise clean their teeth during the treatment period. Gingival crevicular fluid (GCF) is collected before each aPDT application, and at the end of the study, just after the last aPDT application. Photographic imaging of the teeth under observation is performed prior to treatment, daily during the treatment session, and following the treatment period to evaluate the development of plaque on the treated and untreated teeth. Bacterial flora analyses by 16S RNA sequencing are conducted before and after the treatment period.

Indocyanine green powder (Verdye, Diagnostic Green GmBH) is diluted into water at a ratio of 7 mg of powder/25 ml of water, and the solution is spurted for 60 s into the subject's mouth and spit out prior to the light application. Near-infrared imaging is performed to ensure the localisation of the ICG in the dental plaque.

According to the randomisation, an oral light applicator developed at Aalto University, Department of Neuroscience and Medical Engineering, is used as the light applicator. The device includes 16 0.5 W LEDs in a lollipop form, optimally located for producing an even light distribution.

The light application time is determined by the target light dose of 100 J/cm2, and the treatment time is set accordingly for 8 minutes per session. The light intensity is decreased if the person under examination feels that the heat of the light applicator is too intense. In this case, the reduction in light intensity is adjusted by an increase in treatment time to regulate the target dose. This adjustment is performed with a light power meter (Thorlabs PM 100D with S121C sensor head, Thorlabs Inc, US).

The premolar teeth are photographed daily on both sides of the maxilla using a ProDENT PD740 dental camera (Venoka USA Inc, Windermere, FL, US), under near-infrared lighting and white light lighting conditions, and using a SoproCare camera (Acteon Group Ltd, Norwich, England). The near-infrared imaging is performed to estimate the indocyanine green adherence to dental plaque, and the Sopro imaging is done to assess the daily development of plaque formation. The final plaque imaging is performed with the ProDENT PD740 camera subsequent to a plaque staining with an erythrosine tablet (according to the manufacturer's instructions). The amount of plaque is measured as an area of stained plaque surface area on the total tooth surface area, by analysing the photographs with Photoshop software. Finally, the total area of each premolar is delineated from the original image, using the magnetic lasso tool as well as the plaque area, and the plaque area is divided by the total premolar surface area in order to calculate the surface area.

From all study subjects, GCF is collected from the first molar teeth understudy on each side of the maxilla. The sample collection is performed before the treatment and daily until the end of the study. For each site, the collection of GCF and measurement of clinical parameters are performed prior to any treatment measures, daily before the treatment, and after the last treatment. Thus, from each studied site, five samples are collected, and a total of 72 GCF samples are collected at the treatment sites, and 72 GCF samples at the control sites. The procedure of the GCF sampling is performed by inserting a Periopaper strip (Oraflow Inc, NY US)

into the orifice of the gingival sulcus. Samples are collected at the buccal surface, and the insertion point is minorly changed with every sample. Strips contaminated by blood are discarded. The samples are stored in small aliquot containers and kept at -20°C until the analysis was performed. MMP-8 levels are determined by a time-resolved immunofluorescence assay. To determine the effect of GCF fluid sampling on the MMP-8 values by dilution, during the last day of the trial, MMP-8 sampling is performed before and after the light application procedure, and the values are compared.

Plaque samples are obtained with Iso Taper Paper Points, size-20 (VDW, GmbH, Munich, Germany), by scrubbing the plaque on the tooth enamel. After this sampling, the paper points are placed into sterile, small aliquot containers, and are immediately stored at -20°C, where they are kept until the analysis is performed.

The 16S rRNA analysis is performed at the DNA Sequencing and Genomics Laboratory, Institute of Biotechnology, University of Helsinki. The V3-V4 regions of the 16S rRNA genes are amplified using universal bacterial primers and sequenced with an Illumina MiSeq sequencer (San Diego, CA, USA).

The sequencer analysis, including operational taxonomic unit (OTU) clustering and taxonomy assignment is done using Mothur software.

Statistical analyses are performed using GraphPad Prism 6 version (GraphPad Software, Inc., San Diego, California, USA). Unpaired comparisons between the groups are performed with the Mann-Whitney test. The paired rank-sum Wilcoxon test is used for the paired samples. Two-way Anova is used to compare the daily values of MMP-8 between the groups. Comparisons of categorical variables are performed using Fisher's exact test.

Intervention Type
Device

Phase
Not Applicable

Primary outcome measure
Change in the plaque area after the treatment period in treated and untreated teeth, measured using indocyanine green and photography under near-infrared lighting and white light lighting conditions; images taken daily during the 4-day study period

Secondary outcome measures
1. The amount of plaque measured as an area on the dental surface, measured using indocyanine green and photography under near-infrared lighting and white light lighting conditions (images taken daily during the 4-day study period)
2. The percentage of plaque area of the selected dental surface area, measured using indocyanine green and photography under near-infrared lighting and white light lighting conditions (images taken daily during the 4-day study period)
3. Amount of MMP-8 in gingival crevicular fluid by a time-resolved immunofluorescence assay pre-and post-intervention (samples taken daily during the 4-day study period)
4. 16S bacteriological ecology pre- and post-intervention: V3-V4 regions of the 16S rRNA genes amplified and sequenced with an Illumina MiSeq sequencer (San Diego, CA, USA) (samples taken at day 0 (preintervention) and at day 4 (postintervention) of the study)

Overall study start date
11/05/2017

Completion date
01/06/2017

Eligibility

Key inclusion criteria
1. Generally healthy
2. Age between 18 to 65
3. Ability to refrain from brushing one's teeth during the treatment period
4. Informed consent given

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
15

Total final enrolment
15

Key exclusion criteria
1. Diabetes
2. Medications that may affect the immune response or saliva secretion
3. Malignancy
4. Pregnancy
5. Dental implants or prosthesis
6. Fixed orthodontic appliances
7. An active or a chronic oral infection

Date of first enrolment
01/04/2017

Date of final enrolment
11/05/2017

Locations

Countries of recruitment

Finland

Study participating centre
University of Helsinki
Department of Oral and Maxillofacial Diseases
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Sponsor type
University/education

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https://ror.org/020hwjq30

Funder(s)

Funder type
Government

Funder Name
Tekes

Alternative Name(s)
Finnish Funding Agency for Innovation

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Finland

Results and Publications

Publication and dissemination plan
Planned preprint publication of results at Biorxiv.org or Medarxiv.org. Planned publication in a high-impact peer-reviewed journal. Additional documentation is available from the study's central contact person Dr Tommi Pätilä (tommi.patila@gmail.com).

Intention to publish date
01/10/2020

Individual participant data (IPD) sharing plan
Participant-level data can be made available upon request, please contact the study contact persons for details and further requirements for releasing the data:
Central contact person: Tommi Pätilä, MD, PhD (tommi.patila@gmail.com)
Central contact backup: Sakari Nikinmaa, MSc (sakari@koitehealth.com)

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		03/05/2021	01/06/2021	Yes	No