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Vitamin A for viral smell loss

Submission date	Recruitment status	[X] Prospectively registered
23/02/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
10/08/2021	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
03/07/2024	Ear, Nose and Throat	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Loss of smell affects an estimated 5% of people leading to depression, anxiety and isolation as well as changes in weight due to reduced appetite. Viral infections in the nose, including common colds and COVID-19, are the second most common cause of this smell loss. A recent limited study in Germany using vitamin A nasal drops showed that those in the treated group improved twice as much as those in the untreated group, lasting at least 10 months. It is thought that this treatment works to help repair tissues in the nose damaged by viruses. This work will explore whether this is correct. The aim of this study is to find out whether there is an increase in the size and activity of damaged smell pathways in patients' brains when they are treated with vitamin A nasal drops. This would show recovery of the damage caused by common viral infections in the nose.

Who can participate?
People with smell loss due to a previous viral infection

What does the study involve?
People can join the study when they attend the Norfolk Smell & Taste Clinic, or through Fifth Sense, the UK smell and taste disorders charity. Those able to join will be randomly allocated to one of two groups: 38 patients will receive a 12-week course of nasal vitamin A drops and 19 will receive standard care which is currently no treatment. Both sets of patients will receive brain scans, before and after the 12-week interval. The researchers will look for changes in the size of the olfactory bulb (an area above the nose where the smell nerves join together and connect to the brain), that can be measured. They will also look at activity in areas of the brain linked to recognising smells. The patients will be smelling odours (roses and rotten eggs) while special brain scans are taken that use a magnetic coil to create images. A smell test and a questionnaire will also measure smell loss and its daily impact at the two visits.

What are the possible benefits and risks of participating?
There is a possibility of minor side-effects from using the drops such as irritation of the nose. Some people may also feel claustrophobic inside the MRI scanner; participants who suffer from claustrophobia should discuss this with the research team. Women who are pregnant or planning to become pregnant should not participate in the study as there is a risk of vitamin A causing harm to the unborn child.

Where is the study run from?
University of East Anglia (UK)

When is the study starting and how long is it expected to run for?
February 2021 to August 2024

Who is funding the study?
National Institute of Health Research (NIHR) (UK)

Who is the main contact?
Prof. Carl Philpott
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Study website
https://rhinology-group.uea.ac.uk/

Contact information

Type(s)
Public

Contact name
Prof Carl Philpott

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
294741

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
1.1, IRAS 294741, NIHR201978, CPMS 50043

Study information

Scientific Title

A proof-of-concept study for vitamin A nasal drops in post-viral olfactory loss

Acronym
APOLLO

Study objectives
It is theorised that topical Vitamin A treatment will encourage regeneration of the olfactory epithelium which is damaged by respiratory viruses responsible for the common cold and help to restore the sense of smell in sufferers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/08/2021, West Midlands - Black Country Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS; +44 (0)207 104 8010; blackcountry.rec@hra.nhs.uk), ref: 21/WM/0179

Study design
Mechanistic proof of concept double-blind placebo-controlled randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Post-viral (infectious) olfactory loss/dysfunction (PVOL/PIOD)

Interventions
The researchers will invite people who have been found to have smell loss due to a previous viral infection to join the study. They can join when they attend the Norfolk Smell & Taste Clinic, or through Fifth Sense, the smell and taste disorders charity. Those able to join will be randomly allocated to one of two groups: 38 patients will receive a 12-week course of nasal vitamin A drops (Vitadral Topfen Oral Drops [Aristo Pharma, Berlin, Germany]) and 19 will receive standard care which is currently no treatment. Both sets of patients will receive brain scans, before and after the 12-week interval. The researchers will look for changes in the size of the olfactory bulb. They will also look at activity in areas of the brain linked to recognising smells. The patients will be smelling odours (roses and rotten eggs) while brain scans are taken that use a magnetic coil to create images. A smell test and a questionnaire will also measure smell loss and its daily impact at the two visits.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Vitadral Topfen Oral Drops (vitamin A)

Primary outcome measure
Olfactory bulb volume measured using MRI scan at 3 months

Secondary outcome measures
1. Right orbital sulcus volume measured using MRI scan at baseline and 3 months
2. Blood-oxygen-level-dependant (BOLD) signal in primary olfactory areas (amygdala, piriform, and insula) measured using fMRI scan at baseline and 3 months
3. Olfactory function measured using the psychophysical smell test (TDI) score at baseline and 3 months
4. Olfactory-related quality of life measured using the olfactory disorders questionnaire (ODQ) score at baseline and 3 months

Overall study start date
16/02/2021

Completion date
31/08/2024

Eligibility

Key inclusion criteria
1. A partial or total loss of smell due to post-viral olfactory loss as confirmed on history, examination and with a smell test (TDI) score of <31/48
2. Within 3 years of the precipitating viral infection

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
57

Total final enrolment
57

Key exclusion criteria
1. Participants with a history of:
1.1. Chronic rhinosinusitis with/without nasal polyposis
1.2. Severe nasal septal deviation
1.3. Major prior head injury
1.4. Congenital olfactory loss
1.5. Use of concurrent intranasal medications or possible medications know to affect olfaction
1.6. Chronic renal disease
1.7. Chronic hepatic disease
1.8. Allergy to peanuts, soy or vitamin A (drops contain peanut oil)
2. Significant medical, surgical or psychiatric disease that in the opinion of the PI would affect subject safety or influence the study outcomes
3. Current taking oral vitamin A supplements
4. Age less than 18 years
5. Pregnant women
6. Depending on the situation with regards to nasal endoscopy and COVID-19 at the time of study commencement we will exclude the following based on the endoscopy or the initial MRI scan:
6.1. Participants with any endoscopic findings of:
6.1.1. Chronic rhinosinusitis with/without nasal polyposis
6.1.2. Severe nasal septal deviation (preventing passage of 4mm endoscope)
6.1.3. Other inflammatory sinonasal disease
6.2. Participants with MRI changes indicating oedema in the sinuses and/or olfactory clefts
7. Participants must not have any metal implants, such as a pacemaker etc, as is standard for MRI scanning.
8. Any participants who move excessively during scanning
9. Any participant with a combined OBV of >85 mm^3 as it is unlikely they will demonstrate a significant increase in overall volume based on previous studies of OBV

Date of first enrolment
01/02/2022

Date of final enrolment
30/04/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of East Anglia
Norwich Medical School
Norwich
United Kingdom
NR4 7TJ

Sponsor information

Organisation
University of East Anglia

Sponsor details
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Sponsor type
University/education

Website
https://www.uea.ac.uk/

ROR
https://ror.org/026k5mg93

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan

Specialty specific dissemination:
The researchers anticipate dissemination through traditional channels including conference presentations, abstracts and open-access peer-reviewed publications. These will be targeted at specialist ENT and chemosensory experts. As a proof of concept study, the study findings will provide a benchmark for the next stage of the research.

Dissemination in the public domain:
Beyond informal and specialist publications, the researchers also plan to use wider communication channels and in conjunction with PPI input and they will utilise existing websites such as Fifth Sense to engage the public. Fifth Sense, where Prof. Philpott is the Director of Research and Medical Affairs (and a trustee), has a track record in public engagement, both with its members and the wider public (see https://www.fifthsense.org.uk/fifth-sense-news/). There has recently been heightened interest in smell loss in relation to COVID-19 as evident from the wide uptake of recent articles written by Prof. Philpott (e.g. https://theconversation.com /coronavirus-loss-of-smell-and-taste-reported-as-early-symptoms-of-covid-19-134564) - read by over 370,000 globally). Follow up articles to announce progress in relation to the potential for therapeutic interventions for PVOL will be expected to be popular in light of this.

Projected outputs:
The researchers expect the outputs of this study to enable a subsequent randomised controlled trial of Vitamin A versus placebo with an internal pilot to establish the place of a suitable placebo. As mentioned at the top of the application. The PPI input will ensure that our outputs are also publicly available in a way that is meaningful and relevant to patients. As aforementioned in the application, the researchers had previously submitted a study proposal to the NIHR EME funding stream to conduct a randomised controlled trial but were asked to provide more proof of concept. They have already prepared a draft RCT proposal in partnership with the Norwich Clinical Trials Unit and would plan to develop this further in light of the findings of this proof of concept study.

Expected research outputs:
1. Open access publications in appropriate journals such as Rhinology and Chemical Senses
2. Conference presentations and proceedings
3. Funding proposal for a randomised controlled trial

Intention to publish date

30/12/2024

Individual participant data (IPD) sharing plan

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the trial management group (TMG). Considerations for approving access are documented in the TMG Terms of Reference. The final trial dataset will be held at Norwich Clinical Trials Unit on a secure server and will be accessible by the research team. The University of East Anglia will own the foreground IP (as the employer of the Chief Investigator) and James Paget University Hospitals will have rights via a royalty-free licence to use for their own non-commercial purposes and patient benefit. Any exploitation shall be managed through

the University's Intellectual Property Team who shall put into place appropriate royalty share agreements although it is not anticipated that this will be the case as further research will be required.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.3	02/08/2021	06/08/2021	No	Yes
Protocol file	version 1.2	12/05/2021	06/08/2021	No	No
HRA research summary			28/06/2023	No	No
Protocol article		12/10/2023	16/10/2023	Yes	No