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Obstructive sleep apnoea and retinal vasculature reactivity

Submission date	Recruitment status	[X] Prospectively registered
17/09/2014	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
23/10/2014	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
25/02/2022	Nervous System Diseases	

Plain English summary of protocol

Background and study aims
Obstructive sleep apnoea is common problem that happens when the muscles and soft tissues in the throat relax and collapse to cause blockage of the airway. This leads to pauses in breathing and, therefore, a dip in oxygen levels. The lack of oxygen, in turn, results in arousal, whereby the brain pulls the person out of a deep sleep to a lighter one or causes them to wake up, so the airway is reopened and they can breathe normally again. The constant arousal leads to broken sleep and often causes the person to feel very sleepy during the day. Obstructive sleep apnoea is treated by wearing a mask at night which blows air onto the back of the throat, either by nose or nose and face mask. This is called CPAP and this stops the back of the throat collapsing and therefore keeping the airway open. Here, we want to look at how obstructive sleep apnoea affects the retina (the back of the eye which is responsible for picking up light). Patients with obstructive sleep apnoea, who also have diabetes, experience higher levels of damage to the blood vessels in the retina. We dont know why this happens so are going to look at it in more detail. We hope to better understand what is a common problem for these patients which may help in the development of future treatments. Patients with obstructive sleep apnoea have an increased chance of developing high blood pressure, heart attack and stroke as well. By studying the small blood vessels at the back of the eye we also hope to gain more understanding of the way in which this occurs.

Who can participate?
Adults aged between 20 and 75 that have been diagnosed as having obstructive sleep apnoea and having been treated with CPAP for more than a year for at least 4 hours every night.

What does the study involve?
Participants are randomly allocated into one of two groups. Those in group one are treated with CPAP as usual. Those in group two receive sub therapeutic CPAP. The study involves two stages. After completing written consent at their normal sleep unit at visit 1 patients are given a pulse oximeter which is stage 1 of the trial. This is a device, worn overnight whilst sleeping, which sits on the wrist like a watch and also clips onto a finger to measure oxygen levels. Participants wear this on CPAP for three nights and then off of CPAP for 4 nights. They then post this back to us and we analyse the data to check eligibility for stage 2 of the trial. Once we have confirmed that they are eligible for the trial they then go back onto CPAP for at least two weeks before

entering stage 2. After two weeks back on treatment they come for their first visit where we measure their retinal vasculature reactivity at Aston University. We do this by using a specialist camera that shines a flickering light in the back of the eye whilst at the same time recording the size of the blood vessels at the back of the eye. Along with this we will also check their blood pressure, pulse, take blood tests, collect urine and supply them with a blood pressure machine and with their trial CPAP machine (either normal or sub therapeutic depending on their random assignment). After this visit they then use the new CPAP machine every night at home for two weeks whilst checking their blood pressure twice daily which is stage 2. Their final visit is again at Aston University. At the final visit we will repeat the measurements with the specialised retinal camera, repeat blood tests, urine tests and blood pressure measurements. After this visit the trial ends and patients return study equipment and go back onto their normal treatment.

What are the possible benefits and risks of participating?
There are no direct potential benefits as this will not directly lead on to a new treatment but will improve our understanding of eye disease in obstructive sleep apnoea. The major risk or downside for the patients are that they may experience return of excessive sleepiness in the daytime. All participants will be made aware of this and for this reason professional drivers will be excluded.

Where is the study run from?
University Hospital Birmingham Sleep Unit (UK)

When is the study starting and how long is it expected to run for?
October 2014 to March 2020

Who is funding the study?
1. Oxford Radcliffe Hospitals Charitable Fund No. 0189 (UK)
2. ResMed Charitable Foundation (USA)

Who is the main contact?
Professor John Stradling
john.stradling@ouh.nhs.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
149068

Protocol serial number
IRAS protocol ID 149068

Study information

Scientific Title
Effect of obstructive sleep apnoea on retinal vasculature reactivity following CPAP withdrawal

Study objectives
Obstructive sleep apnoea causes reduction in the retinal vasculature reactivity during and treatment of sleep apnoea stops this reduction. The reduction in retinal vasculature is linked to disease severity, catecholamine activity and cardiovascular risk. This reduction in retinal vasculature reactivity causes a change in gene expression.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 26/09/2014, NRES Committee South Central – Berkshire (Bristol Research Ethics Committee Centre, Whitefriars, Level 3 Block B, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)117 342 1389; nrescommittee.southcentral-berkshire@nhs.net), REC ref: 14/SC/1235

Study design
Randomised controlled double-blind intervention trial

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Obstructive sleep apnoea

Interventions
Patients on established CPAP treatment will be randomised to receive continued treatment on with CPAP or with sub therapeutic CPAP for two weeks. Patients will be blind to their allocation and will continue with their normal mask. This allows us to directly compare the retinal vasculature of patients will fully treated obstructive sleep apnoea and those in whom obstructive sleep apnoea has returned for two weeks.

Intervention Type
Procedure/Surgery

Primary outcome(s)
To establish if OSA reduces retinal vascular reactivity. This will be done using retinal vascular response to flicker light protocol. Outcome measure will be the intervention effect of OSA versus no OSA on retinal vascular reactivity following 14 days CPAP withdrawal, with appropriate controlling for baseline reactivity, OSA severity, BMI and cardio-vascular co-morbidities (via Pocock risk score).

Key secondary outcome(s))
Whether any change in retinal vascular reactivity correlate with OSA severity and/or change in markers of sympathetic activity. This will be measured by correlation between change in retinal vascular reactivity (from baseline to two weeks in the CPAP withdrawal arm), with the severity of OSA (>4%ODI) returning, and/or change in both heart rate and blood pressure in the same group (from home measurements over penultimate 3 days), and/or urinary catecholamines.

Tertiary outcomes will be whether any change in retinal vascular reactivity and retinal vessel oxygen saturation variables correlate with changes in mRNA expression. This will be measured by collection of blood samples for later analysis of mRNA expression.

Completion date
31/03/2020

Eligibility

Key inclusion criteria
1. Objectively confirmed obstructive sleep apnoea (at the time of original diagnosis) with an oxygen desaturation index (ODI, >4% dips) or AHI of >20 (this threshold will exclude participants with borderline OSA, in whom there may be little experimental effect)
2. Currently >20/h oxygen desaturations (>4% dips) returning on any night during home nocturnal pulse oximetry performed for a 4-night period without CPAP, prior to entry into the study
3. Treated with CPAP for more than 12 months, minimum compliance 4h per night
4. ODI <10 during treatment (obtained during the preliminary week of oximetry monitoring,

from the first 3 nights of oximetry monitoring on CPAP, before the 4 nights CPAP withdrawal)
5. Age between 20 and 75 years at trial entry
6. Written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
37

Key exclusion criteria
1. Previous ventilatory failure (awake resting arterial oxygen saturation <93% or arterial PCO2> 6kPa) or severe respiratory disorders other than OSA
2. Unstable, untreated coronary or peripheral artery disease, severe arterial hypertension(>180 /110mmHg), severe arterial hypotension (<90/60mmHg)
3. Previously diagnosed with Cheyne-Stokes breathing
4. Current professional driver
5. History of any sleep-related driving accident or other accident
6. Acute inflammatory disease
7. Acute or chronic hepatic or renal disease
8. Known type 1 or 2 diabetes (likely to have low retinal reactivity even on CPAP)
9. Known severe vascular disease (likely to have low retinal reactivity even on CPAP)
10. Mental or physical disability precluding informed consent or compliance with the protocol
11. Non-feasible trial follow-up (for example, distance from follow-up centre, physical inability)
12. Epilepsy: flickering light used for retinal provocation could lead to a seizure
13. Lens opacities: this could lead to insufficient contrast and make it impossible to image the retinal vasculature

Date of first enrolment
19/01/2015

Date of final enrolment
31/07/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Churchill Hospital
Oxford University Hospitals
Oxford
United Kingdom
OX3 7LE

Study participating centre
Queen Elizabeth Hospital
University Hospitals Birmingham
United Kingdom
B15 2TH

Study participating centre
Birmingham Heartlands Hospital
Heart of England NHS Trust
United Kingdom
B9 5SS

Study participating centre
Coventry Hospital
University Hospitals Coventry and Warwickshire
United Kingdom
CV2 2DX

Sponsor information

Organisation
University of Oxford (UK)

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
Oxford Radcliffe Hospitals Charitable Fund No. 0189 (UK)

Funder Name
ResMed Foundation

Alternative Name(s)
The ResMed Foundation, Resmed Foundation Ltd, Resmed Foundation Limited

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
Requests for data can be made by contacting Chris Turnbull (Christopher.turnbull@ouh.nhs.uk). Anonymised patient data will be available without time restriction following completion of the trial, for use in ethically approved research. Patients have consented for such third party anonymised data usage.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		24/02/2022	25/02/2022	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version V5.0	03/02/2016	09/12/2020	No	No