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Improvement of pain and quality of life in patients with sickle cell disease with auto-adjusting continuous positive airways pressure therapy

Submission date
30/06/2015

Recruitment status
No longer recruiting

Registration date
02/07/2015

Overall study status
Completed

Last Edited
17/12/2020

Condition category
Haematological Disorders

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Sickle cell anaemia (SCA) is a genetic blood condition that affects around 15,000 people in England, causing long-term health problems including pain, heart and brain problems. Several SCA complications appear to be associated with low daytime and night-time oxygen levels. These complications can be made worse if patients have extra dips in night time oxygen levels when the upper airway closes repeatedly during sleep: this is known as obstructive sleep apnoea (OSA) and is common in SCA. A treatment for OSA, Auto-adjusting Continuous Positive Airways Pressure (APAP), is feasible in Sickle Cell Anaemia at least for short periods (weeks). A pilot study showed that adults and children preferred APAP rather than oxygen at night but we don't know whether they can use the machine for months and whether this will prevent complications. The aim of this study is to compare APAP with standard care in patients with Sickle Cell Anaemia (SCA) and mild-moderate nocturnal hypoxia to see if, compared with standard care, 6 months of APAP provides a benefit in terms of reduced complications.

Who can participate?
Patients with sickle cell anaemia over 8 years of age.

What does the study involve?
You will undergo tests including an overnight test of oxygen levels at home, MRI scans of the heart and brain, as well as 'brain games' and a blood test. You will be issued with a smartphone /iPad and will be asked to complete a daily pain diary every day for 2 weeks. You will then be randomly allocated to be treated with either APAP or standard care for 6 months. You will undergo check-up blood tests for safety after 2 weeks and 3 months and will be asked to complete a daily pain diary every day in the last 2 weeks of the study. At the end of the 6 months you will repeat the tests from the start of the study.

What are the possible benefits and risks of participating?
APAP used regularly over 6 months may reduce complications. We think that APAP is safe but we need to check that by making sure patients do not become more anaemic or have more pain.

Where is the study run from?
Guy's Hospital, St Thomas' Hospital and King's College Hospital (UK).

When is the study starting and how long is it expected to run for?
December 2015 to April 2018

Who is funding the study?
The National Institutes of Health Research for Patient Benefit Funding Stream (UK).

Who is the main contact?
Prof. Fenella Kirkham
Fenella.Kirkham@ucl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Fenella Kirkham

ORCID ID
https://orcid.org/0000-0002-2443-7958

Contact details
Developmental Neurosciences
UCL Institute of Child Health
30 Guilford Street
London
London
United Kingdom
WC1N 1EH
+44 (0)20 7242 9789
Fenella.Kirkham@ucl.ac.uk

Additional identifiers

Protocol serial number
RHMCHI0753

Study information

Scientific Title
Prevention of Morbidity in Sickle cell disease: Phase II (improvement of pain and quality of life in patients with sickle cell disease with auto-adjusting continuous positive airways pressure: Phase II) (POMS 2b)

Acronym
Prevention of Morbidity in Sickle cell disease: Phase II (POMS 2b)

Study objectives
Sickle cell disease (SCD) is a genetic blood condition causing long-term health problems including pain and brain problems. Many SCD complications are made worse if patients have low night-time oxygen levels or extra dips in night time oxygen levels when the upper airways closes during sleep.

The aim of this Phase II trial is to compare Auto-adjusting Continuous Positive Airways Pressure (APAP) with standard care in patients with Sickle Cell Anaemia (SCA) and mild-moderate nocturnal hypoxia to establish if the intervention provides physiological and physical benefits.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee Yorkshire & The Humber - South Yorkshire, REC ref: 15/YH/0213, protocol number: RHM CHI0753, IRAS project ID: 179171

Primary study design
Interventional

Study design
Single-blind randomised controlled trial
Added 01/08/2017: This trial consists of two independent cohorts of children and adults containing 30 participants each

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Sickle cell disease

Interventions
Patients will be randomised to six months of overnight APAP treatment or to standard care alone. Patients will not be blinded to treatment as the use of a sham treatment was not thought to be ethical. The Chief Investigator, statistician and technicians performing physiological tests will be blinded to treatment arm.
Patients will initially be given the patient information sheet and given adequate time to read it and to ask questions before they are consented to the study. As patients will only be included in the trial if they have slightly low levels of oxygen at night they will have an overnight sleep study performed (unless this has been done in the last 12 months as part of standard care). This involves wearing a monitor on a finger which is attached to a wristband over night. Patients who meet the eligibility criteria will be asked to give consent to join the study.
If they agree they will have further investigations at day -14 (Trial Entry). This will include oxygen level (via a finger probe), blood tests, medical review including neurological examination and urine tests. They will be issued with a smartphone/iPad and will be asked to complete a daily electronic pain diary for two weeks.
During these two weeks they will undergo other baseline investigations including brain function

testing, MRI scan of the brain, heart and oropharynx, echocardiography, 6 minute walk and will be asked to complete quality of life questionnaires. They will be randomised to receive APAP or not and if they are to receive APAP will be reviewed by a trial respiratory physician.
At Day 0 if they are randomised to receive APAP this will be delivered to their home and will be set up. They will be supported by the respiratory physiologist over the next few days. A repeat sleep study will be performed at day 14 to assess whether or not they need additional oxygen and all patients will have a medical review at day +14 which will include blood and urine tests. A further medical review, with blood and urine tests, will take place at month 3 and month 6 (at the end of treatment). At month 1, 2, 4 and 5 patients will be reviewed by the trial co-ordinator and will be asked about side effects of treatment. Patients using APAP will have additional support from the respiratory physiologist regularly during the trial. All patients will be asked to complete another two week electronic pain diary during the last month of the trial and at month 6 (at the end of treatment) will have repeat investigations including brain function testing, MRI scan of the brain and heart, echocardiography, 6 minute walk and will be asked to complete quality of life questionnaires. Once these have been completed the trial will be complete.

Intervention Type
Procedure/Surgery

Primary outcome(s)
1. Pain is the most common symptoms experienced by patients with SCD and will be measured before starting treatment and in the last month of treatment using an electronic pain diary. This was used effectively in the first part of the study
2. Brain function will be measured before and after six months of treatment by a psychologist who will use several different tests. The trial will also look at MRI brain scans before and after treatment and at heart function

Added 01/08/2017: As described in the study protocol (24/12/2015), this trial was powered on change in cancellation from the Wechsler scales comparing results before and after the intervention.

Key secondary outcome(s)
Current secondary outcome measures as of 01/08/2017:
Based on the final study protocol (24/12/2015), the secondary outcomes of interest are:
1. Other Cognitive endpoints at baseline and after interventions
1.1. Change in assessment of processing speed/attention indices
1.2. Learning/memory indices and executive functions
2. Pain endpoints and pain characteristics/descriptors :
2.1. Current pain, using a 0 to 10 electronic numerical rating scale (e-NRS)
2.2. The highest e-NRS in past 24h
2.3. The lowest e-NRS in past 24h
2.4. The average-e-NRS in the past 24h
2.5. Location of pain on a body outline diagram
2.6. How much pain interfered with everyday activities in past 24h (2 week baseline compared with 2 week diary at end of study)
The same measurements are obtained for one week at the end of the 2nd and 4th months after baseline. In addition at the end of every week a phone call and the above pain end points are recorded. The same measurements are obtained at the end of the two measurement weeks at the end of the 2nd and 4th months after baseline.
3. Quality of Life is measured via Peds-QL and EQ-5D/CHU-9D at baseline and six months
4. Physiological investigations

4.1. Daytime oximetry
4.2. Renal function
4.3. 6 minute walk
4.4. Echocardiography
4.5. MRI brain and heart
4.6. Biomarkers via blood spot
5. Safety endpoints: full blood count, reticulocytes at baseline, 2 weeks, 3 months and 6 months
6. Adverse events/Side effect profile are measured using adverse events and serious adverse events reported monthly
7. Health economic analysis using EQ-5D and client service receipt inventory (CSIR) inventory that covers the trial period:
7.1. GP/nurse visits, secondary care visits, days off work/school, money spent getting health care
7.2. Pain medications and number of pharmacological strategies used for pain,
7.3. Healthcare visits to determine whether there is any obvious effect of either intervention or its withdrawal, particularly if detrimental (number of visits to A+E, Day care and Hospital admissions, plus length of stay).
7.4. Blood transfusion therapy

Previous secondary outcome measures:
From day -14 to day 0 patients will use the smartphone device for daily pain and symptom reporting.
This will repeated for two weeks during the last month of treatment.

On day 0 the patient will be issued with the overnight respiratory support. This will be installed at their home by the sleep physiologist, who will ensure they understand how to use the device. They will have a follow up phone call from the sleep physiologist the following day, 2 weeks later and at least monthly during the rest of the trial. Patients will have a telephone help line and will be able to call the sleep physiologist for further advice during the intervention period. They will use the intervention for 6 months.

On day 14 the patient will be reviewed in the hospital. They will have a medical review for adverse events and adherence and will have daytime oximetry and blood and urine tests. They will also have a repeat overnight oximetry at home on day 14 to ensure that they are receiving optimal therapy.
They will have further reviews in hospital at month 3 and month 6. They will have a medical review for adverse events and adherence and will have daytime oximetry and blood and urine tests.

At month 1, 2, 4 and 5 patients will be contacted by the study co-ordinator for review of adverse events and adherence.
At the end of trial (month 6) the patient will have end of study tests including
1. Quality of life
2. Executive function
3. 6 Minute Walk test
4. Echocardiography
5. MRI brain and heart
6. Blood and urine tests

Completion date
30/04/2018

Eligibility

Key inclusion criteria
1. Age >=8 years
2. Informed consent with assent in accordance with the institutional policies (UK ethical committee) and European guidelines must be signed by the patient or patient's parent or legally authorised guardian acknowledging written consent to join the study. Patients < 16 years will be requested to give their assent to join the study
3. HbSS diagnosed by standard techniques (HPLC, IEF and MS). Participating institutions must submit documentation of the diagnostic haemoglobin analysis
4. Able to speak and understand English
5. Patient or parent/guardian able to use smartphone app
6. Overnight oximetry showing minimum overnight oxygen saturation of <94%

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Sex
All

Key exclusion criteria
1. Patient already on overnight respiratory support, or has used it in the past
2. Hospital admission for acute sickle complication within the past 1 month
3. Patient with >6 admissions for acute sickle complications within the past 12 months
4. Existing respiratory failure
5. Overnight oximetry showing mean overnight saturation of <90% for >30% of total measured time
6. Severe sleep apnoea (OSA) defined by 4% ODI > 15/hr; Epworth sleepiness score >10
7. Exclusions to APAP therapy:
7.1. Decompensated cardiac failure
7.2. History of severe epistaxis
7.3. Trans-sphenoidal surgery, or trauma that could have left a cranio-nasopharyngeal fistula
7.4. Perforated ear drum
8. Bullous lung disease
9. Bypassed upper airway
10. Pneumothorax
11. Patient at increased risk of aspiration
12 Pneumocephalus has been reported in a patient using nasal Continuous Positive Airway Pressure. Caution should be used when prescribing APAP for susceptible patients such as those with: cerebral spinal fluid (CSF) leaks, abnormalities of the cribriform plate, prior history of head trauma, and/or pneumocephalus
13. Pregnancy
14. Patients on chronic blood transfusion regimes, or has had blood transfusion within past 3 months
15. Any acute or chronic condition which would limit the patient’s ability to complete the study

Date of first enrolment
01/04/2016

Date of final enrolment
30/09/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
United Kingdom
SE1 7EH

Study participating centre
King's College Hospital
United Kingdom
SE5 9RS

Sponsor information

Organisation
University Hospital Southampton (UK)

ROR
https://ror.org/0485axj58

Funder(s)

Funder type
Not defined

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

Funder Name
Great Ormond Street Hospital Charity

Alternative Name(s)
Great Ormond Street Hospital Children's Charity, GOSH Charity, greatormondSt, GOSH

Funding Body Type
Private sector organisation

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

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Data sets will be available after the adult cohort has been published, expected 30/04/2019. For data access, please contact Prof Fenella Kirkham at Fenella.Kirkham@ucl.ac.uk.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	22/01/2018	17/12/2020	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version V6	24/12/2015	01/08/2017	No	No
Statistical Analysis Plan	version V1	31/07/2017	01/08/2017	No	No