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Vascular Function Intervention Trial in sickle cell disease

Submission date
18/01/2012

Recruitment status
No longer recruiting

Registration date
02/02/2012

Overall study status
Completed

Last Edited
17/12/2020

Condition category
Haematological Disorders

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Sickle cell disease (SCD) is the most common inherited disorder worldwide affecting 300,000 births annually. Most cases are in sub-Saharan Africa where poor detection and care result in high childhood mortality, malnutrition, illness and disability in survivors. SCD is caused by abnormal haemoglobin, the compound in red blood cells (RBC) that carries oxygen. Damage to the blood vessels (known as vascular endothelial dysfunction) which results from the effects of the abnormal haemoglobin is thought to underlie many of the symptoms and disability in SCD. In addition, reduced growth is also common in children with SCD, probably from a combination of reduced dietary intake, increased demand and metabolic disturbance.
The aims of this trial are to determine the effects of a Ready-to-Use Supplementary Food (RUSF) on growth in a non-screened population of African children with SCD and to determine whether an RUSF fortified with the naturally occurring amino acids L-arginine and L-citrulline, delivered with daily chloroquine (CQ), compared to the standard RUSF, can improve vascular endothelial function.

Who can participate?
Participants in this trial are children with SCD who are enrolled in the Muhimbili Sickle Cohort, Dar es Salaam Tanzania, and who are aged 8-11 years at enrolment.

What does the study involve?
Children will receive two different formulations of RUSF, in random order, each for 4 months, with a 4-month washout period after each intervention during which participants will not take any supplement. The simple RUSF will be compared to a vascular RUSF, fortified with arginine and citrulline and delivered with daily chloroquine syrup. The simple RUSF will be delivered with a weekly dose of chloroquine syrup, as recommended for anti-malarial prophylaxis in this population group.

What are the possible benefits and risks of participating?
There will be no direct or financial benefits to participation in this study. Participating will allow the investigators to find out if a food supplement and daily chloroquine compared to weekly is of significant benefit to patients with SCD.
There is a very small risk of participants having an allergic reaction to the food supplements. We

will minimize this risk by observing a small test amount of the supplement at the first home visit and delivery of the supplement.
The volume of blood collected is small and only slightly more than is normally collected at the sickle clinics and will not affect the health of the participant.
Some children may find the pressure cuff uncomfortable while it is inflated and there is a possible risk that the participant may experience some pain after its release, although we have never observed this to happen.
As with any drug, there is a small risk that participants may experience some adverse effects associated with the use of chloroquine (weekly or daily doses). The majority of such effects are short-lived and non-serious, but we will be monitoring all these events and parents are asked to report any symptoms or concerns during the weekly clinic visits or to call the SCD patient hotline.

Where is the study run from?
The study is run from Muhimbili National Hospital and Muhimbili University of Health & Allied Sciences, Dar-es-Salaam, Tanzania.

When is study starting and how long is it expected to run for?
The study is due to start in April 2012 and will until November 2013.
Who is funding the study?
Funding for this study is provided by the Wellcome Trust, UK.

Who is the main contact?
Dr. Sharon Cox
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Contact information

Type(s)
Scientific

Contact name
Dr Sharon Cox

Contact details
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT01718054

Secondary identifying numbers
V1_290911

Study information

Scientific Title
Development of a ready-to-use nutraceutical food for patients with sickle cell disease: testing of vascular support components

Acronym
V-FIT

Study objectives
1. That the provision of energy, protein and micronutrients within a ready to use supplementary food (RUSF) will increase linear growth, weight gain and proportion of fat-free mass children with sickle cell disease (SCD).
2. That the provision of supplementary L-arginine and L-citrulline within the matrix of a twice-daily ready to use supplementary food (RUSFv) plus daily chloroquine (CQ) for 4 months, compared to a standard RUSF and weekly anti-malarial prophylaxis CQ to children with sickle cell anaemia (SCA) will:
2.1. Increase plasma arginine concentrations and the ratio of plasma arginine: orninthine
2.2. Decrease or not alter plasma asymetric dimethylated arginine (ADMA) concentrations
2.3. Improve nitric oxide (NO)-dependent vascular function as detected by an increase in maximum flow mediated dilatation (FMDmax)
3. That the provision of daily CQ at a dosage of 2-3mg base/kg/day for 4 months compared to standard anti-malarial prophylactic weekly dose to children with SCA will:
3.1. Decrease the activity of plasma arginase through competitive inhibition
3.2. Decrease levels of plasma inflammatory markers

Please note that as of 22/10/2012, the following changes were made to this record:
1. The anticipated start date was updated from 01/04/2012 to 09/08/2012
2. The anticipated end date was updated from 01/11/2013 to 09/04/2014

22/10/2012: This trial will be recruiting participants until mid-December 2012

Ethics approval required
Old ethics approval format

Ethics approval(s)
London School of Hygiene & Tropical Medicine approved on 12/12/11, ref. 6066

Study design
Random-ordered double-blinded crossover clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please contact Beatrice Kamala, Beatrice.kamala@muhimbili-wellcome.org to request a patient information sheet

Health condition(s) or problem(s) studied
Sickle Cell Disease

Interventions
Both interventions will consist of twice-daily RUSF in single portion packs, comprehensively fortified with vitamins and minerals at approximately 1xRDA (except for folate [1mg/day] and iron [not included in the fortificants]) providing 500kcal/d.

The simple RUSF will be given with placebo base syrup on 6/7 days and chloroquine every 7th day to match the anti-malarial action of chloroquine in the vascular arm and as per Tanzanian guidelines.

The enhanced vascular-RUSF will be additionally fortified with L-arginine and L-citrulline depending on subject weight (<or≥ 25kg, median weight is 24kg in this age range) to achieve mean intakes of 0.2g L-Arg and 0.1g L-Cit/kg/day and maximum intakes of 0.33/0.165g/kg/d. The RUSFv will be given with daily chloroquine syrup to achieve a maximum dose of 3mg base/kg /day.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
1. Compare the effects of the RUSFv compared to the simple RUSF on:
1.1. Plasma arginine concentrations, the ratio of plasma arginine to ornithine & ratio of arginine to ADMA measured at baseline, 4 and 12 months
1.2. NO-dependent endothelial function (vascular function) assessed using flow mediated dilatation (FMDmax) measured at baseline, 4, 8 and 12 months
2. Compare the effects of RUSF compared to no RUSF by comparison of the two intervention periods combined with the two washout periods combined, on: linear growth and weight gain measured at baseline, 4, 8, 12 and 16 months

Secondary outcome measures
1. Haemoglobin concentration measured at baseline, 4, 8, 12 and 16 months
2. Markers of inflammation and vascular activation measured at baseline, 4, 8 and 12 months
3. Markers of haemolysis measured at baseline, 4, 8 and 12 months
4. Frequency of vasoocclusive crisis (VOC) painful episodes: study personnel will administer detailed questionnaires at weekly home visits to assess the frequency of all sickle and non-sickle associated morbidity and health seeking behaviour, with a focus on painful episodes.

Participatory research will be used to determine the likely application and optimal formatting of pain diaries to be completed by patients and families in addition to the standard questionnaire.

Overall study start date
09/08/2012

Completion date
09/04/2014

Eligibility

Key inclusion criteria
1. Aged 8-11 years old at enrolment and resident within urban Dar-es-Salaam
2. Enrolled in MSC and attending routine MNH sickle clinics
3. Haemoglobin phenotype SS (HbSS) confirmed by electrophoresis and High-performance liquid chromatography (HPLC)

Participant type(s)
Patient

Age group
Child

Lower age limit
8 Years

Upper age limit
11 Years

Sex
Both

Target number of participants
120

Total final enrolment
119

Key exclusion criteria
1. >95th percentile for body mass index (BMI) for age using British 1990 growth standards
2. Receiving hydroxyurea (HU) therapy or significant other long-term drug therapy
3. Diagnosis with clinically significant non-SCD related disease including:
3.1. Stage III or above human immunodeficiency virus (HIV) or receiving antiretroviral therapy (ART) therapy regardless of Acquired immune deficiency syndrome (AIDS) stage
3.2. Tuberculosis infection
3.3. Blood transfusion within previous 30 days
4. Previously diagnosed clinical pulmonary hypertension or cardiac dysfunction or clinical signs of pulmonary hypertension (loud pulmonary second heart sound) or heart failure (displaced apex beat, high jugular venous pressure, enlarged liver, peripheral oedema)
5. Low visual acuity at baseline (<6/9 using a modified (for Tanzania) Snellen chart or previously

diagnosed chronic eye disorder likely to suggest retinopathy or macular degeneration
6. Significant hepatic/renal dysfunction assessed by clinical chemistry panel at baseline
7. Epilepsy, psoriasis or currently taking any drugs listed as interacting with chloroquine

Date of first enrolment
09/08/2012

Date of final enrolment
09/04/2014

Locations

Countries of recruitment
Tanzania

Study participating centre
Muhimbili-Wellcome Programme - SCD Study
Dar es Salaam
Tanzania
PO Box 65001

Sponsor information

Organisation
London School of Hygiene and Tropical Medicine (UK)

Sponsor details
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United Kingdom
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Sponsor type
University/education

Website
http://www.lshtm.ac.uk/

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust (UK) (WT094780)

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/04/2018	17/12/2020	Yes	No