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The effect of rice-based, lactose-free F-75 therapeutic formula on diarrhoea in the treatment of children with severe acute malnutrition

Submission date
04/08/2017

Recruitment status
Stopped

Registration date
15/08/2017

Overall study status
Stopped

Last Edited
07/05/2019

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
It is estimated that about 3.9% of children below five years of age in Africa are severely wasted and despite the use of WHO guidelines for inpatient management of severe acute malnutrition, mortality (death) rates remains at 20% or higher in many settings. Poor intestinal function and diarrhoea is a common complication of severe acute malnutrition. Diarrhoea can result in dehydration, salt balance disturbances, prolonged hospitalization, delayed recovery, and death. In line with WHO guidelines, the treatment of severe acute malnutrition patients at Mwanamugimu Nutrition Unit (MNU) is divided in two phases, a stabilization phase where children are given a low protein, liquid formula, F-75, and a rehabilitation phase where children are gradually transitioned to a more energy dense food with higher protein content. This study concerns the stabilization phase and modification of the standard F-75. Studies have indicated that a rice-based rehydration solution or a rice porridge as well as lactose-free formulae may reduce the duration of diarrhoea. In this study F-75 is modified with rice flour or maltodextrin as the main carbohydrate source and the standard level of lactose or no lactose. The aim of this study is to find out whether rice-based, lactose-free F-75 can reduce diarrhoea in hospitalized children with severe acute malnutrition.

Who can participate?
Children aged 6-59 months hospitalized with severe acute malnutrition in the Mwanamugimu nutritional rehabilitation unit at Mulago Hospital in Uganda

What does the study involve?
Participants are treated according to the latest WHO guideline for management of severe acute malnutrition, and are randomly allocated to receive one of four different F-75 formulae with either rice flour or maltodextrin as the main carbohydrate source and either the standard level of lactose or no lactose. The duration of the stabilization phase is typically around one week. In addition, a daily dose of fish oil is given throughout the hospitalization to meet the children's needs. The study ends when the children are discharged from the nutrition unit. Children are

monitored daily by medical doctors and nutritionists. Blood and stool samples are collected at baseline, day 2, transition of feeds and at discharge. Body measurements are taken at the start of the study and discharge and weight is measured daily. Diarrhoea is monitored closely by use of a stool diary to record stool frequency, stool consistency, vomiting and fever. 50 healthy children of the same age and from the same area are also included to collect samples of blood and stool and body measurements.

What are the possible benefits and risks of participating?
Children may benefit from the extra attention and examinations that are part of the study. There are no or minimal risks associated with the procedures and examinations carried out in the study. Blood samples of 2-4 ml are collected. This is well within the safe amounts recommended for blood sampling for research purposes. A data safety monitoring board has been established to follow safety during the study.

Where does the study take place?
Mulago Hospital (Uganda)

When does the study take place?
January 2016 to August 2019

Who is funding the project?
1. The Danish Dairy Research Foundation (Denmark)
2. US Dairy Export Council (USA)
3. University of Copenhagen (Denmark)

Who is the main contact?
Prof. Henrik Friis

Contact information

Type(s)
Scientific

Contact name
Prof Henrik Friis

ORCID ID
http://orcid.org/0000-0002-2848-2940

Contact details
Department of Nutrition, Exercise and Sports
University of Copenhagen
Rolighedsvej 26
Frederiksberg C
Denmark
1958

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
D219

Study information

Scientific Title
The effect of modified F-75 on diarrhoea in the treatment of children with severe acute malnutrition – a randomized controlled 2x2 factorial trial in Uganda

Acronym
LARISAM (lactose-free, rice-based F-75 for SAM children)

Study objectives
1. Lactose-free and rice-based F-75 can reduce the duration, incidence and severity of diarrhoea in children with severe acute malnutrition.
2. Lactose-free and rice-based F-75 can reduce dehydration in children with severe acute malnutrition.
3. Lactose-free and rice-based F-75 can reduce the duration of the stabilization phase in the treatment of children with severe acute malnutrition.
4. Lactose-free and rice-based F-75 can modify blood electrolyte concentrations (P, Mg, K, Na, Cl, bicarbonate) in children with severe acute malnutrition.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Uganda: School of Medicine Research and Ethics committee (SOMREC) at Makerere University, 06/10/2016, ref: 2016-103; amendment approved 10/07/2017
2. Denmark: The National Committee on Health Research Ethics, 18/01/2017

Study design
Randomized controlled double-blind two-by-two factorial 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 use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Severe acute malnutrition (SAM)

Interventions
Four study arms will receive modified F-75 as a replacement of standard F-75. F-75 is a therapeutic food used during stabilization of hospitalized children with severe acute malnutrition. Randomisation will be individual, stratified by diarrhoea status at enrolment, and using varying block size.
1. Maltodextrin-based F-75, standard lactose (standard F-75)
2. Maltodextrin-based F-75, no lactose (<0.02g/100 ml)
3. Rice-based F-75, standard lactose
4. Rice-based F-75, no lactose (<0.02g/100ml)
The amount of energy and the energy distribution (carbohydrate, protein and fat) will be similar in the four therapeutic foods. The amount of modified F-75 is given in accordance with the WHO protocol for treatment of hospitalized children with severe acute malnutrition. In addition, a daily dose of fish oil will be given to all study children to meet their requirements for n-3 LCPUFA during inpatient treatment.

The duration of the stabilization phase is typically around one week. The trial ends when children are discharged from the nutrition unit. Children are monitored daily by medical doctors and nutritionists. Blood and stool samples are collected at baseline, day 2, transition of feeds and at discharge to measure blood electrolytes, stool pH and biomarkers of gut health, infection (at admission only) and fatty acid profile. Anthropometry is measured at admission and discharge and weight is measured daily. Diarrhoea will be monitored closely by use of a stool diary with ongoing registration of stool frequency, stool consistency, vomiting and fever.

50 healthy control children of the same age and from the same area will be included to collect reference samples of blood and stool and body measurements.

Intervention Type
Other

Primary outcome measure
Number of days with diarrhoea during treatment with modified F-75, measured using a validated stool diary daily from admission to transition

Secondary outcome measures
1. Number of days with diarrhoea during hospitalization, measured using a validated stool diary daily from admission to discharge
2. Incidence of diarrhoea, defined as the proportion of children with minimum one day of diarrhoea, measured at transition and discharge
3. Severity of diarrhoea, assessed using the Vesikari scale daily
4. Consumption and feeding patterns:
4.1. Food intake in ml and duration of the meal measured as 3 time categories daily from admission to transition
4.2. Acceptability using a 5-point hedonic scale on day 2 and at transition
5. Number of days of the first stabilization phase and total number of days spent in the stabilization phase if the child deteriorates and resumes stabilization treatment. Duration of the

first stabilization period is defined as: total number of days from admission to the day the child is considered stabilized for the first time. Total number of days spent in stabilization is defined as the total number of days whereby a child is “in the stabilization phase”. It includes the first stabilization phase and any periods when the child may go back to the stabilization phase due to deterioration of health. A child is considered to be stabilized when all these criteria are fulfilled: 1) Return of appetite; the child easily finishes all the prescribed feeds of F-75 and demands for more; 2) Reduced or minimal bilateral pitting oedema (reduced to grade 2 or grade 1); 3) Medical complications resolving; the child may also smile at this stage.
6. Number of days of hospital stay, calculated from the day of admission to discharge. Both days are included in hospitalization duration
7. Plasma electrolyte concentrations (P, Mg, K, Na, Cl, bicarbonate) measured at admission, two days after admission and at transition
8. Degree of dehydration (no, some, severe dehydration and shock), assessed at transition and discharge. Dehydration measured daily throughout hospitalization according to the WHO /Ugandan IMAM guidelines for assessment and treatment of dehydration in severely malnourished children. The highest degree of dehydration in the previous 24 hours is noted
9. Number of new onset severe clinical deteriorations, measured daily during hospitalization, defined as a new onset of any of the WHO danger signs:
9.1. Severe dehydration
9.2. Shock (lethargic or unconscious and has cold peripheries as well as either capillary refill time >3 secs or fast and weak pulse)
9.3. Severe respiratory distress (respiratory rate ≥ 40/50 bpm for children above/below 1 year respectively and severe chest in-drawing, grunting, nasal flaring, central cyanosis and hypoxemia (SPO2<90%)
9.4. Impaired consciousness (modified Glasgow coma scale < 15)
9.5. Cardiac failure (the cardinal signs of cardiac failure includes: tachycardia, tachypnoea, tender hepatomegaly)
9.6. Hypoglycemia (blood glucose less than 3 mmol/l)
9.7. Hypothermia (temperature below 35C, axillary temperature)
9.8. Hyperthermia (temperature above 39.5C, axillary temperature)
9.9. Severe anaemia (Hb below 4g/dl)
9.10. Convulsions
10. Child development, measured using the Malawi Developmental Assessment Tool at discharge

Auxiliary outcomes:
1. Mortality during hospitalization
2. Stool pH and reducing substances, measured using pH strips and Benedict’s solution at admission, day 2 and transition and if lactose intolerance is suspected
3. Gut microbiota, measured using 16S rRNA gene amplicon Illumina based high throughput sequencing at admission, transition and discharge
4. Gut function: plasma citrulline, faecal myeloperoxidase and faecal neopterine measured using mass spectrometry/ELISA test at admission, transition and discharge
5. Body composition, measured using bio-electrical impedance analysis at discharge
6. Fatty acid profile, measured using high-throughput GLC on whole blood dry blood spots at admission, transition and discharge

Overall study start date
01/01/2016

Completion date
31/08/2019

Reason abandoned (if study stopped)
Unforeseeable delays resulting in shortage of funding

Eligibility

Key inclusion criteria
1. Age 6 – 59 months
2. Children with severe acute malnutrition (MUAC < 11.5 cm or weight-for-height z-score < -3 SD or bipedal pitting oedema)
3. Indication for in-patient treatment (oedema above the knees (grade +++)), or failing an appetite test, or medical complications requiring hospitalization
4. Written informed consent obtained

Participant type(s)
Patient

Age group
Child

Lower age limit
6 Months

Upper age limit
59 Months

Sex
Both

Target number of participants
400 patients, 50 healthy controls

Key exclusion criteria
1. Obvious disability and congenital diseases which may affect eating capabilities
2. Weight below 3.0 kg at admission
3. Malignant diseases
4. Patients participating in another study that may interfere with the current study
5. Patients started on F-75 treatment more than 18 hours before recruitment to the study

Date of first enrolment
16/08/2017

Date of final enrolment
31/07/2019

Locations

Countries of recruitment
Uganda

Study participating centre
Mulago National Referral Hospital
Mwanamugimu Nutrition Unit
Department of Pediatrics and Child Health
Kampala
Uganda
PO Box 7051

Sponsor information

Organisation
University of Copenhagen

Sponsor details
Department of Nutrition, Exercise and Sport
Rolighedsvej 26
Frederiksberg C
Denmark
1958

Sponsor type
University/education

ROR
https://ror.org/035b05819

Funder(s)

Funder type
Research organisation

Funder Name
Mejeribrugets ForskningsFond

Alternative Name(s)
Danish Dairy Research Foundation, The Danish Dairy Research Foundation, MFF, DDRF

Funding Body Type
Private sector organisation

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

Location
Denmark

Funder Name
US Dairy Export Council

Funder Name
Københavns Universitet

Alternative Name(s)
university_of_copenhagen, Københavns Universitet - University of Copenhagen, University of Copenhagen (UCPH), Copenhagen University, Københavns Universitet – Københavns Universitet, University of Copenhagen (KU), Denmark, Københavns Universitet – University of Copenaghen (UCPH), koebenhavns_uni, Københavns Uni, University of Copenhagen, KU, UCPH

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Denmark

Results and Publications

Publication and dissemination plan
The protocol will be made publicly available as soon as possible. After completion of the study, the results will be published irrespectively of positive, negative or inconclusive data. Planned main publication in a high-impact peer reviewed journal in August 2020.

Intention to publish date
01/08/2020

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Henrik Friis. The anonymised dataset will be made available at the time of publication.

IPD sharing plan summary
Available on request