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Use of paracetamol in resolving acute kidney injury in severe malaria

Submission date 16/11/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 08/12/2020	**Overall study status** Completed	
Last Edited 01/08/2023	**Condition category** Infections and Infestations	

Plain English summary of protocol

Background and study aims
The global burden of malaria remains very high and there is a very high rate of death among patients presenting with malaria. The rate of death is even higher in sub Saharan Africa where 9 /10 of those deaths occur in children especially those aged below 5 years. Even with the widespread implementation of fast acting antimalarial drugs, death among the children admitted with malaria is unacceptably high (about 1/10) and will not improve without better supportive treatments. Children with malaria complicated by hemoglobinuria (passing dark colored urine) have a higher rate of in hospital and post discharge deaths. In east Africa malaria is a very common cause of admissions and black water fever (passing dark colored urine) is a common feature in severe malaria. Other research studies done have shown that black water fever is associated with acute kidney injury in malarial illnesses.
The aim of this study is to gather enough information on a possible way of controlling Acute Kidney Injury and to check if using paracetamol, which is a cheap, affordable and readily available drug, will be helpful in resolving acute kidney injury in malaria which will help us improve on the management of complications in severe malaria. This will further decrease the rate of death among patients admitted with severe malaria.

Who can participate?
Children aged between 6month and 12 years admitted to the paediatric ward with confirmed severe malaria complicated by passing dark urine (haemoglobinuria)

What does the study involve?
Children will have a rapid structured assessment; conscious level, vital signs (heart rate, oxygen saturation, respiratory rate, axillary temperature, blood pressure), malaria Rapid Diagnostic Test and history of passing dark urine (hemoglobinuria) in the current illness will be carried out to see whether the child is potentially eligible for suspected Acute Kidney Injury. The child will have the usual daily assessments and an extra quick test to determine BUN levels to confirm whether the child is suitable for the study. Participants will be treated following the national guidelines. However, for the purposes of the study participants will be randomly allocated to oral paracetamol (also commonly referred to as Panadol) at 20 mg/kg or no paracetamol. A sample of about 5 ml (about 1 teaspoonful) of venous blood (volume varies - according to age) will be collected and taken for the following investigations: rapid test to determine Blood Urea

Nitrogen (BUN) levels, lactate, glucose, malaria status, HIV test, cross match and a sample of blood will be stored for subsequent parasitological and genetic profiling (for sickle cell). Children will be asked to return 28 days, 90 and 180 from the first of admission. This is for a check-up and some tests.

What are the possible benefits and risks of participating?
There are no direct benefits from this study. However, children will get close observation and be reviewed at the follow-up visit. This will enable us to make important changes to their treatment if needed and treat any illnesses found. Routine medicines and medical tests will be performed during the study and will be paid for by the study. It will also help improve the care of children with haemoglobinuria in future. The study drug (Panadol) and tests are widely used/done in children and are safe. The total amount of blood taken during the study will not harm the health of the children. There are very few risks in this study and children will be monitored throughout their time in hospital.

Where is the study run from?
Mbale regional referral hospital paediatric Acute Care Unit (Uganda)

When is the study starting and how long is it expected to run for?
May 2018 to April 2024

Who is funding the study?
European and Developing Countries Clinical Trials Partnership (EDCTP) (Netherlands)

Who is the main contact
Prof. Peter Olupot-Olupot
ed@mcri.ac.ug

Contact information

Type(s)
Scientific

Contact name
Prof Peter Olupot-Olupot

ORCID ID
http://orcid.org/0000-0002-5757-609X

Contact details
PO Box 1966
Mbale
Uganda
-
+256 (0)772 457 217
ed@mcri.ac.ug

Additional identifiers

EudraCT/CTIS number

Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Version 1; 13/08/2018

Study information

Scientific Title
Paracetamol for Acute Renal Injury in Severe Malaria Trial (PARIST)

Acronym
PARIST

Study objectives
1. To conduct pharmacokinetic studies of paracetamol in patients with acute kidney injury in severe malaria
2. To assess the feasibility of conducting AKI in severe malaria in Eastern Uganda
3. To conduct safety and preliminary effectiveness study for use of paracetamol in ameliorating AKI in severe malaria

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/01/2019; renewal: 19/08/2021, Mbale Regional Referral Hospital Regulatory Ethics Committee (PO Box, 921 Mbale, Uganda; +256 (0)393280584; mrrhrec@gmail.com), ref: MRRHREC- OUT 002/2019

Study design
Single-centre randomized controlled 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 participant information sheet

Health condition(s) or problem(s) studied
Preventing cell-free haemoglobin renal toxicity and ameliorating Acute Kidney Injury (AKI) in children with haemoglobinuric severe malaria

Interventions
A. Paracetamol intervention dose arm: research nurses will administer paracetamol 20 mg/kg orally 6-hourly for 48 h. Patients unable to swallow will receive paracetamol by nasogastric tube. If the patient vomits within 30 min of paracetamol administration, a further dose will be given.
B. Control arm: Patients in the control arm will receive standard of care for temperature control. That is, fever of 37.5°C – 39.4°C will be tepid sponged and fanned. The children whose temperature ≥39.5°C will have paracetamol 10 mg/kg as stated in the standard of care in the Uganda Clinical Guidelines 2016.

Randomization process;
After screening, the patients that qualify will be assigned study numbers which correspond to those assigned in envelopes which are arranged consecutively in sealed opaque envelopes, each assigned across the seal. These numbers are randomly assigned prior to the start of the study by a statistician using the "randomizeR" package of the statistical software R, which allows simple randomization and adaptive assignment through minimization procedure. Minimization allocates patients to best maintain balance in the treatment group by calculating an imbalance score at each randomization. It then assigns with higher probability each patient to the treatment that will reduce the imbalance. The allocation will be on 1:1 ratio to paracetamol (A) and no paracetamol (B).
Those on paracetamol (A) are further randomized in the ratio of 1:1 to A1 or A2 according to different pK sampling schedules.
A1 will be those sampled at time intervals 1, 2, 4, 6, 12, 18 and 24 h while the A2 will be sampled at time intervals 0.5, 1.5, 2.5, 5, 12, 18 and 24 h.
During enrolment, the study staff will pick the cards consecutively and open it. Each envelope will have a card that shows which arm the participant is in (A or B).
Arm B (n = 20), those not receiving paracetamol immediately, but if their temperature is ≥39.5°C they will receive 10 mg/kg; will further be randomised to B1 or B2 in a 1:1 ratio to different sampling schedules as follows; B1 (n = 10), will be sampled at 1, 2, 4, 6 h post randomisation. Thereafter, sampling will continue once every 6 hours for 24 h. B2 (n = 10) will be sampled at 0.5, 1.5, 2.5, 5 h post randomisation. Thereafter, sampling will continue once every 6 hours for 24 h. Study participants randomised to PK sampling will have an extra card which indicates which PK sampling scheduling the participant will follow (A1 vs A2 or B1 vs B2).

Participants are followed up to 28 days post-randomization, day 90 and day 180 for survival and resolution of acute kidney injury.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Paracetamol

Primary outcome measure
Correction of AKI at 48 hours, as indicated by BUN (<20 mmol/L), creatinine level (<80 mmol/L), normal glomerular filtration index (based on Schwartz criteria), plasma creatinine, BUN, urinary-plasma creatinine ratio, serum urea-creatinine ratio, urinary osmolality, urinary-plasma osmolality ratio and urine microscopy.

Secondary outcome measures
1. Survival measured using mortality outcome at 48 h and day 28
2. Resolution of AKI measured using BUN (<20 mmol/L), creatinine level (<80 mmol/L) at day 28, 90 and 180

Overall study start date
01/05/2018

Completion date
30/04/2024

Eligibility

Key inclusion criteria
1. Children aged >6 months to <12 years
2. Positive RDT for P. falciparum malaria at admission
3. One of the following features of severe malaria confirmed haemoglobinuria, impaired consciousness and/or severe respiratory distress
4. Guardian or parent willing and able to provide consent

Participant type(s)
Patient

Age group
Child

Lower age limit
6 Months

Upper age limit
12 Years

Sex
Both

Target number of participants
40

Key exclusion criteria
1. Surgery
2. Acute trauma or burns
3. Known allergy to paracetamol

4. Impaired liver function tests
5. Known chronic renal failure or suspected non-malarial causes of renal impairment
6. Refusal to consent

Date of first enrolment
15/05/2021

Date of final enrolment
15/06/2023

Locations

Countries of recruitment
Uganda

Study participating centre
Mbale Clinical Research Institute
PO Box 1966, Mbale (U) I
Plot 29-33, Pallisa Road
Mbale
Uganda
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Sponsor information

Organisation
European & Developing Countries Clinical Trials Partnership

Sponsor details
PO Box 93015
The Hague
Netherlands
2509 AA
+31 (0)70 344 0880
edctpgrants@edctp.org

Sponsor type
Research organisation

Website
http://www.edctp.org/

ROR
https://ror.org/031jv9v19

Funder(s)

Funder type
Research organisation

Funder Name
European and Developing Countries Clinical Trials Partnership

Alternative Name(s)
Le partenariat Europe-Pays en développement pour les essais cliniques, A Parceria entre a Europa e os Países em Desenvolvimento para a Realização de Ensaios Clínicos, The European & Developing Countries Clinical Trials Partnership, European and Developing Countries Clinical Trials, EDCTP

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
Netherlands

Results and Publications

Publication and dissemination plan
All publications and presentations relating to the study will be authorized by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Principal Investigator, Statistician and Trial Coordinator. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

During the course and following completion of the trial there may be publications, including manuscripts and abstracts for presentation at national and international meetings, as well as the preparation of manuscripts for peer-reviewed publication. In order to avoid disputes regarding authorship, it is important to establish a consensus approach that will provide a framework for all publications derived in full or in part from this clinical trial. The following approach is derived from the Lancet and from the publication policies used in other MRC clinical trials:

All publications are to be approved by the TMG and TSC before submission for publication. In particular, no analyses by randomized group of any outcome (primary, secondary or other) in either the main trial or associated sub-studies will be conducted or presented before the end of

the trial. The TMG and TSC will resolve problems of authorship and maintain the quality of publications.

In line with MRC policy that the results of publicly-funded research should be freely available, manuscripts arising from the trial will, wherever possible, be submitted to peer-reviewed journals which enable Open Access via UK PubMed Central (PMC) within 6 months of the official date of final publication. All conference presentations will be made available as soon as possible after the event. All publications will acknowledge the trial's funding sources.

For all publications, the TMG will nominate a chairperson or approve an individual's request to chair a manuscript writing committee. The chair will usually be the primary or senior author. The chairperson is responsible for identifying fellow authors and for determining with that group the order of authorship that will appear on the manuscript. The TSC will resolve any problems of authorship and maintain the quality of publications.

The TMG will maintain a list of investigators to be presented in an appendix at the end of the paper. This list will include investigators who contributed to the investigation being reported but who are not members of the writing committee. In principle, sub-study reports should include all investigators for the main study, although in some instances where a smaller number of investigators have made any form of contribution, it may be appropriate to abbreviate the listing.

All headline authors in any publication arising from the main study or sub-studies must have a made a significant academic or project management contribution to the work that is being presented. "Significant" must be defined by a written declaration of exactly what the contribution of any individual is believed to have been. In addition to fulfilling the criteria based on contribution, additional features that will be considered in selecting an authorship group will include the recruitment of patients who contributed data to any set of analyses contained in the manuscript, and /or the conduct of analyses (laboratory and statistical), leadership and coordination of the project in the absence of a clear academic contribution.

The presentation or publication of any data collected by the participating investigators on patients entered into this trial is under the direct control of the TMG and TSC. This is true whether the publication or presentation is concerned directly with the results of the trial or is associated with the trial in some other way. However, although individual participating investigators will not have any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any of the data other than under the auspices of and with the approval of the TMG and TSC, they will be encouraged to develop sub-studies or propose analyses subject to the approval by the TMG and TSC. Any requests for access to raw data will be welcomed as long as they are scientifically valid and do not conflict with the integrity of the trial or ongoing analyses by the trial team

Outcome data by randomized group will not be revealed to the participating investigators until the data collection phase and primary full analysis of the trial has been completed. This policy safeguards against possible bias affecting the data collection.

Intention to publish date
01/06/2024

Individual participant data (IPD) sharing plan
The primary participant dataset will be held at Mbale clinical research institute database (www.mcri.ac.ug) and will only be available upon request.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		31/07/2023	01/08/2023	Yes	No