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Evaluating the combined use of non-invasive respiratory support alongside preventative anticonvulsant treatment in children presenting to hospital with cerebral malaria and convulsions

Submission date
18/01/2019

Recruitment status
No longer recruiting

Registration date
05/02/2019

Overall study status
Completed

Last Edited
27/08/2024

Condition category
Infections and Infestations

[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
Worldwide, malaria causes approximately 450,000 deaths annually, and it is estimated that over 90% of severe and fatal malaria cases occur in children less than 5 years of age in sub-Saharan Africa. One of the most severe complications of malaria is cerebral malaria, which occurs when a person with malaria becomes unconscious because of the infection. Fits (seizures) occur commonly in people with cerebral malaria. Children who develop cerebral malaria have a high risk of death, and those that survive have a risk of long-term neurological disability. Children with cerebral malaria who have repeated seizures have an even higher risk of poor outcomes. Because of this, research studies have been conducted to determine if the preventative (prophylactic) use of medications to control seizure activity (anticonvulsants), can improve outcomes in children with cerebral malaria. The largest of these studies found that the use of a prophylactic anticonvulsant called phenobarbitone did reduce seizure frequency in children, but the use of this medicine was associated with a higher risk of death. The excess risk of death was due to cessation of breathing (respiratory arrest), related to the use of this anticonvulsant in a setting where equipment to assist breathing (mechanical ventilation) was unavailable.

Children with cerebral malaria continue to have very poor outcomes. An important question is whether the provision of breathing (ventilatory) support in addition to prophylactic anticonvulsants is effective in terms of preventing respiratory arrest and reducing neurological injury associated with seizures, and whether this strategy can reduce mortality and long-term disability in children with cerebral malaria. Biphasic cuirass ventilation (BCV) is a mode of ventilatory support that provides both negative and positive pressure to the chest wall. This non-invasive system thereby supports both the inspiratory (the negative pressure expands the chest for the in-breath) and expiratory phases (the positive pressure assists with the outbreath) of breathing. The system is portable, does not require insertion of an invasive airway tube (intubation), and can be used across a wide weight and age range. BCV has been used to support

ventilation in children with profound neuromuscular weakness and chest wall disorders at home. If proven to be safe, feasible and effective in children with cerebral malaria, this system of ventilator support could be widely implemented in resource-limited settings.

This research study will explore the potential benefits of BCV, in combination with a newer and safer prophylactic anticonvulsant (levetiracetam), for preventing seizures and ultimately respiratory arrest and thus limiting neurological insult in children with cerebral malaria. The anticonvulsant drug Levetiracetam has been studied in small research trials in Malawi, with the early data suggesting that it reduces seizures and some adverse events in children with cerebral malaria, but overall outcomes remain the same. The aim of this project is to develop a protocol for the use of BCV in combination with prophylactic levetiracetam, within a Phase I trial in children with cerebral malaria admitted to the high dependency ward in Kilifi, Kenya. The Phase I trial will generate feasibility, safety and preliminary efficacy data, which will inform the design of a larger Phase II study to test this intervention.

Who can participate?
Children aged between 3 months and 12 years who are admitted to hospital with severe malaria and impaired consciousness (cerebral malaria), and who have had seizures as part of their illness.

What does the study involve?
This study involves the phased evaluation of non-invasive ventilatory support using biphasic cuirass ventilation (BCV), with or without prophylactic anticonvulsant treatment with levetiracetam. The first 10 children will receive BCV to support ventilation until they recover from their coma. The next 20 children will receive BCV in addition to levetiracetam, given via feeding tube into the stomach, as a preventive strategy to stop seizures.

All children in the study will be carefully monitored throughout the period of coma. Levels of oxygen saturation in the blood (SpO2) and levels of exhaled carbon dioxide (end-tidal CO2) will be monitored both non-invasively (using a finger probe and small tubes that sit beneath the nostrils) and by blood tests. By monitoring changes in SpO2 and CO2 levels, the treating team will be able to optimize ventilation for each patient by adding in low-flow oxygen or high-flow humidified blended air and oxygen, or adjusting the amount of ventilator support delivered by BCV.

All children will receive routine care for severe malaria, which will include intravenous antimalarial medication, antibiotics and fluids. All additional complications of sever malaria such as a fall in the number of red blood cells (anaemia) and low blood sugar levels (hypoglycaemia) will be treated appropriately according to international guidelines.

All monitoring and treatment will continue until patients are ready to be discharged from hospital. Patients will then be followed up to day 28 and day 180.

What are the possible benefits and risks of participating?
Potential benefits to study participants include the close monitoring and regular assessment of all children on the high dependency unit during admission and follow up to day 180 after discharge. As part of being enrolled in a research study, routine medical supplies and treatments will be provided free of charge to participants, so that parents or guardians will not have to buy any treatments. Any medical tests performed during the child’s illness will also be paid for by the study. Participants will be asked back for follow up visit(s), and transport between home and the clinic will be paid for. During the follow up visit(s), the study team will treat any illnesses that are

identified, or arrange referral to an appropriate hospital. The study will be recruiting patients with cerebral malaria who have a high mortality rate, and it is possible that the interventions being delivered in this study will improve patient outcomes.

One potential risk for patients with cerebral malaria is aspiration, where saliva or vomit goes into a child's throat and makes them start to choke. We will monitor very closely for this and we will place a tube from the nose into the stomach of each child to remove stomach contents and reduce this risk. This is done routinely for all children in coma. We will also perform regular suctioning to remove excess saliva from the mouth. We do not think that the use of BCV will increase this risk as it was found to be very small in other studies where BCV has been used (<1%). Another potential risk is that participants will need additional ventilator support to BCV. This will be detected by the close monitoring of oxygen and carbon dioxide levels in the blood, and the additional use of low-flow oxygen or high-flow air/oxygen will be added if necessary. Levetiracetam is an anticonvulsant medication licenced for use in children and with a good safety profile, and the risks associated with its use are low.

Where is the study run from?
Kilifi District Hospital (Kenya)

When is the study starting and how long is it expected to run for?
February 2019 to June 2024

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Professor Kathryn Maitland

Contact information

Type(s)
Public

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Additional identifiers

Protocol serial number
1.1, 209265/Z/17/Z

Study information

Scientific Title
Evaluating the combined use of NOn-invasive Ventilation alongside preventative anticonvulsant treatment In children presenting to hospital with CErebral_Malaria and convulsions: a phase I trial

Acronym
NOVICE_M trial

Study objectives
Non-invasive respiratory support in combination with prophylactic anticonvulsants improves seizure control and supports respiration and may prevent or reduce intracranial hypertension.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Kenyan Medical Research Unit Scientific and Ethics Review Unit, 13/07/2018, ref. KEMRI/RES/7/3/1.
Imperial College Research Ethics Committee, 02/08/2018, ref. I81C4511.

Study design
Single-centre, non-randomised phase I feasibility and safety trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied

Cerebral malaria

Interventions
Thirty children will be allocated in a phased evaluation to receive non-invasive respiratory support with biphasic cuirass ventilation (BCV; Hayek). This will be done sequentially. In the first phase BCV will be used alone (10 patients). In the second and third phases it will be used as a neuroprotective strategy in combination with prophylactic anticonvulsant treatment. In the 2nd phase levetiracetam (LVT) will be given at a standard dose: 40 mg/kg loading dose and 30mg/kg every 12 hours (10 children) for 3 days or until coma resolution (when the child is able to sit unsupported or breast feed if under 6 months). If this reduces seizures to those which are short lived and not clinically-relevant so that 80% do not require additional anticonvulsants and have minimal adverse events (based on the judgement of an independent Data Monitoring Committee), then an additional 10 children will be studied using LVT at this dosage. If this fails to adequately control seizures, the neuroprotective strategy of BCV plus with a higher dose (150%) of levetiracetam will be studied, namely 60 mg/kg loading dose and 45mg/kg every 12 hours given via nasogastric tube for 3 days or until coma resolution.

From the time of enrollment, children will be monitored carefully to determine the efficiency of breathing. This will be done by clinical assessment and by measuring the levels of oxygen saturation in the blood (SpO2) with pulse oximeters, and levels of carbon dioxide (CO2) in the exhaled breath by non-invasive end-tidal capnography (EtCO2) (Capnostream 35 monitor, Medtronic) and venous blood (PCO2) by blood gas analysis. At the first sign of a child's breathing being slowed or inadequate (defined by a respiratory rate below the age-appropriate range or a fall in respiratory rate from baseline, onset of shallow breathing, elevation in EtCO2, or further fall in level of consciousness) a venous blood gas will be checked to confirm the PCO2. If the PCO2 s elevated the BCV ventilation device will be applied to the child's chest and breathing will be supported, with continuous monitoring. Additional oxygen and/or high-flow humidified blended air/oxygen (Airvo2; Fisher and Paykel) will be given if monitoring levels of CO2 indicates that this is needed (EtCo2 greater than 45 mmHg). Respiratory support will be provided until coma resolution and children will be followed at day 28, day 90 and day 180 by phone or face-to-face to verify survival status and for clinical review and neurological assessment (if seen in clinic).

Intervention Type
Mixed

Primary outcome(s)
Current primary outcome measure as of 07/03/2024:

1. Cumulative time with clinically detected epileptogenic seizure activity (witnessed) over 36 hours.

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Previous primary outcome measure:

1. Cumulative time with epileptogenic seizure activity will be determined by continuous EEG monitoring over 36 hours.
2. The number of additional antiepileptic drugs required will be determined at day 28, 90 and 180 by phone or face-to face.
3. The frequency of disability-free survival will be determined at day 28, 90 and 180 by phone or face-to face.

Key secondary outcome(s))
Feasibility will be assessed by the ability to implement and operationalise the use of non-invasive respiratory support with BCV for the duration of a child's coma. This will be measured by:
1. The ability of BCV to safely institute negative pressure ventilation, which will be determined by resolution of the clinical and monitoring (SpO2 and CO2) parameters for which BCV was implemented.
2. Assessing whether children are able to tolerate the use of BCV (judged by children remaining comfortable during transition from coma to a semiconscious state, as assessed by nurses and carers).
3. Whether we are able to clear any secretions by regular suctioning (if this is judged to be a problem).
4. Whether BCV interferes with monitoring the child and the time require by the nursing staff to implement and maintain its use.

Safety endpoints:
1. Episodes of aspiration (determined by sudden decrease in oxygen saturations, and/or denovo presence of coarse chest crepitations, with evidence of gastric reflux/aspirate in the oropharynx).
2. Episodes of hypercarbia (defined as pCO2 level of greater than 45 mmHg).
3. Episodes of bradypnoea (defined as <10, 15 or 20 breaths/minute over 3 minutes for those aged <6m, 6-36m and >36m respectively) and hypoxaemia (oxygen saturation <92%).
4. Development of hypotension (defined as systolic blood pressure <50 mm Hg in children younger than 12 months; <60 mm Hg in children 1-5 years and <70 mm Hg in children olderthan 5 years of age).
5. Use of additional anticonvulsants.
6. Neurological sequelae at day 180.
7. Day 28 and day 180 mortality.
8. Re-admission to hospital through day 180.
9. Serious adverse events and grade 3/4 adverse events through day 180.
10. Grade 3/4 adverse events through day 180.
11. Length of initial hospitalisation.

Completion date
30/06/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 07/03/2024:

1. Aged 3 months to 12-years (up to 40 kg in weight for paediatric dosing of leviteracitam)
2. Hospitalised with:
2.1. Current or recent evidence of P. falciparum malaria (slide or rapid diagnostic test (RDT) positive)
2.2. Blantyre Coma Score 4 or less that persists even after correction for concurrent hypoglycaemia (defined as blood glucose <3 mmol/L)
2.3. History of seizures in this illness

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Previous inclusion criteria:

1. Aged 3 months to 12-years
2. Hospitalised with:
2.1. Current or recent evidence of P. falciparum malaria (slide or rapid diagnostic test (RDT) positive)
2.2. Blantyre Coma Score 2 or less that persists even after correction for concurrent hypoglycaemia (defined as blood glucose <3 mmol/L)
2.3. History of seizures in this illness

Participant type(s)
Health professional

Healthy volunteers allowed
No

Age group
Child

Lower age limit
3 months

Upper age limit
12 years

Sex
All

Key exclusion criteria
1. Known cerebral palsy or significant neuro-development delay (which will affect endpoint assessment)
2. Skin disease or burns preventing use of the BCV
3. Respiratory or cardio-respiratory arrest prior to enrolment
4. A comorbidity which clinician believes has a significant risk of poor outcome e.g. malignancy, end-stage renal failure, major cardiac condition

Date of first enrolment
31/01/2020

Date of final enrolment
30/06/2024

Locations

Countries of recruitment
Kenya

Study participating centre
Kilifi District Hospital
Hospital Road

Kilifi
Kenya
801808

Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Research council

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

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 Kathryn Maitland: K.maitland@imperial.ac.uk MRC Clinical Trials unit at UCL.data supports a controlled access following completion of a request proforma which is approved by the trial management group and does not conflict with on-going analyses. There will be a period of exclusivity for 1 year following the primary publication.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		20/05/2024	27/08/2024	Yes	No
Participant information sheet	Participant information sheet version 2.0	11/11/2025	11/11/2025	No	Yes
Statistical Analysis Plan		06/03/2024	07/03/2024	No	No