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Comparing a comprehensive package of primary care to the standard of care to reduce blindness caused by severe corneal infections in Uganda

Submission date
19/06/2023

Recruitment status
No longer recruiting

Registration date
23/06/2023

Overall study status
Completed

Last Edited
16/10/2023

Condition category
Infections and Infestations

[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

The cornea is your eye's clear, protective outer layer. Infection of the cornea is an important cause of blindness. A scratch in the cornea allows infection to enter and an ulcer to begin. These infections can be very serious with some people losing the sight in the affected eye.

Different types of infectious organisms can cause corneal ulcers. These include bacteria and fungi. In tropical regions about half of all corneal ulcers are caused by fungi. Bacteria and fungi need to be treated with different types of eye drop medicines. Treatments for fungal eye infections are frequently not very effective, in addition access to these treatments in many countries is very limited and can be expensive.

Many people with corneal infection end up with poor vision or other eye problems because of delays in the infection being recognised and treatment being started. With this delay the condition becomes very severe, by which stage there is often nothing that can be done to save the vision or the eye itself.

This study is about testing out a new strategy in the primary health care setting to reduce the delay in diagnosis of cornea infection and the starting of an eye drop treatment, called chlorhexidine, that covers many different types of infections. The person with the infection would then be referred urgently to the regional eye hospital.

Chlorhexidine is an antiseptic. It is very effective at killing bacteria, fungi and other types of infectious organisms. It is used in medical care worldwide in several different ways. For example, it is used to clean skin before surgical operations, in antiseptic creams for skin cuts and as a mouthwash to prevent and treat mouth infections. It has been used in eye care for more than 30 years as an eye-drop preservative, for sterilizing contact lenses, for pre-operative topical antiseptic and for treating corneal infections.

If chlorohexidine eye drops were available at primary health care facilities, it would make this treatment much more easily accessible to many people with corneal infections and allow them to start appropriate treatment early in the course of the infection, as they proceed to an eye

hospital to have a change of getting a good outcome.
This study will test if using this approach of early intervention for people with corneal infection can reduce the risk of getting severe infections and blindness due to corneal infection.

Who can participate?
Patients aged 18 years and over with corneal infection attending the participating centres in Uganda.

What does the study involve?
In half of the health centres, a bottle of chlorhexidine eye drops will be provided to be taken one drop every hour to be started straight away when participants are in the health centre until they are seen in the Eye Unit in Mbarara. In addition, participants will be sent reminder phone messages to remind them to attend the eye clinic for additional treatment.
In half of the health centres, the health workers are also going to give a bottle of chloramphenicol eye drops to be taken one drop every hour to be started straight away when participants are in the health centre until they are seen in the eye hospital at Mbarara.
Once the initial results of the tests for infection are available, the eye doctor will prescribe eye drop treatment that is appropriate to the infection type that is identified. Participants who were already started on chlorhexidine eye drops in the primary health centre may be advised to continue taking these if there is evidence that they are working well.
The researchers will review the response to treatment and document the clinical findings at the following times after starting treatment: 2 days, 1 week, 2 weeks, 3 weeks, 2 months and 3 months.

What are the possible benefits and risks of participating?
The study will involve tests for the type of infection. This helps the doctor to choose the best type of treatment. These tests are not usually available for patients in Uganda.
The costs for the clinical assessment, tests, treatment, and transport to the follow-up visit will be paid for by the study.
By participating in this study, participants will be helping to answer the question about whether or not this early intervention programme can reduce the risk of sight loss in the affected eye.
It is important to recognise that corneal infection is a serious, sight-threatening condition. Many patients, whatever the treatment used, have reduced vision in the affected eye after it has resolved. In some people the affected eye will become blind. Sometimes the infection, despite lots of treatment, can progress to cause a hole to develop in the cornea (perforation) and sometimes it is so severe it is necessary to perform an operation to remove the eye content.
As with most eye drops, there is the risk of local irritation or stinging. This usually only lasts for a short time.
Very rarely, eye drops can provoke a local allergic reaction on the surface of the eye or the eyelids.
The risks to an unborn or breastfed baby from these eye drops use are unknown. Therefore, pregnant and breastfeeding women are excluded from participating in this study.
Chlorhexidine eye drops are used on the surface of the eye as an antiseptic before procedures and also in the treatment of fungal and other eye infections. It has not been associated with any serious side effects. It may cause mild irritation and very rarely a local allergic response. This concentration of chlorhexidine is approved to be used in much larger volumes as a mouthwash. It is considered to be safe and is not associated with any systemic side effects.
The treatments in this study may have rare side effects that are currently not known. If during the course of the study new information becomes available, the researchers will share this.

Where is the study run from?
London School of Hygiene & Tropical Medicine (UK)

When is the study starting and how long is it expected to run for?
August 2018 to August 2025

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
WT 207472/Z/17/Z

Study information

Scientific Title
Cluster randomised controlled trial of a complex intervention package to reduce blindness from severe microbial keratitis in Uganda

Study objectives
A complex intervention package (as described below) can reduce blindness from severe microbial keratitis (MK)

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 26/04/2021, London School of Hygiene and Tropical Medicine Interventions Research Ethics Committee (Keppel Street, London, WC1E 7HT, United Kingdom; +44 (0) 2076368636; ethics@lshtm.ac.uk), ref: 25075

2. approved 28/09/2021, Mbarara University of Science and Technology (MUST) Research Ethics Committee (PO Box 1410, Mbarara, 1410, Uganda; +256 (0)485433795; sec.rec@must.ac.ug), ref: MUST-2021-62

Study design
Prospective single-masked parallel-group two-arm cluster randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Microbial keratitis (MK)

Interventions
A total of 20 primary health centres will be enrolled; 10 clusters in each arm; each cluster serves a population of around 10,000 people (total ~100,000 per arm). The primary health centres will be the units of randomisation. The travel time from the health centre and the direction to the central eye unit will be determined. Health centres will be randomly allocated, in a 1:1 ratio, to each arm using restricted randomisation on the distance to the eye unit, to minimize imbalance between arms. This will be done by an independent statistician

The primary health centres will be randomised to one of the following arms:
Arm I: Offer an early interventional package including a smartphone-based triage system for MK, prompt treatment with g-chlorhexidine digluconate 0.2% eye drops, and early facilitated referral to the eye hospital.
Arm II: Offer “standard of care” for MK.

If individuals present initially with a corneal abrasion but no evidence of a current infection they will be offered chloramphenicol eye ointment in both arms and then reviewed at 3 days.

Patient outcomes will be followed up at 3 months.

Intervention Type
Mixed

Primary outcome(s)
The proportion of people who are blind at 3 months in the affected eye (best spectacle-corrected visual acuity [BSCVA] vision less than 3/60) measured by a trial-certified optometrist

Key secondary outcome(s))
1. Scar/infiltrate size at 3 months, measured by slit-lamp examination by ophthalmologists (trial certified)
2. Perforation and/or therapeutic corneal transplant (TPK) by 3 months, measured by slit-lamp examination by ophthalmologists
3. Diagnostic accuracy in primary care measured compared to the final definitive diagnosis reached at the referral eye hospital using microbiology and in vivo confocal microscopy performed at the referral eye hospital at baseline
4. Time between symptom onset and presenting to primary care facility measured using patient questionnaire at baseline
5. Adherence to and time taken to attend referral at eye hospital measured using the difference between patients’ presentation date to primary care and the presentation to the referral eye hospital
6. Quality of life measured using EQ-5D, WHO/PBD-VF20, WHOQOL-BREF at baseline and at 3 months
7. Cost-effectiveness analysis using EQ5-D and direct cost questionnaire at baseline and at 3 months

Completion date
01/08/2025

Eligibility

Key inclusion criteria
1. Acute MK characterised by:
1.1. Corneal epithelial ulceration >1mm diameter
1.2. Corneal stromal infiltrate
1.3. Acute inflammation: e.g. conjunctival injection, anterior chamber inflammatory cells, hypopyon
2. Informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Unwilling to participate in trial or attend follow-up
2. Aged less than 18 years
3. Pregnancy: self-reported
4. Breast feeding: self-reported
5. No light perception in the affected eye
6. Fellow eye visual acuity <6/60
7. Known allergy to study medication (including preservatives)
8. Previous penetrating keratoplasty in the affected eye
9. Bilateral corneal ulcers
10. Nationals of another country

Date of first enrolment
01/08/2023

Date of final enrolment
01/09/2024

Locations

Countries of recruitment
Uganda

Study participating centre
Mbarara University of Science and Technology (MUST)
PO Box 1410
Mbarara
Uganda
1410

Sponsor information

Organisation
London School of Hygiene & Tropical Medicine

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

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
The datasets generated during and/or analysed during the current study will be available upon request from Prof. Matthew Burton (matthew.burton@lshtm.ac.uk). The full dataset will be available with all patient-identifiable details removed. Data will be available after formal reporting of the study findings in a peer-reviewed scientific publication. Datasets will only be

available to bona fide scientific investigators. Requests should be made to the Chief Investigator in writing detailing the scientific investigator's background and intended use for the data. Consideration will be given to all proposed analyses, with likely envisaged uses including investigators planning on conducting meta-analyses for example. Patient Information Sheets and consent forms specifically referenced making anonymised data available and this has been approved by the relevant ethics committees.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet			19/06/2023	No	Yes