Management of microbial keratitis by private pharmacies and traditional healers in Siraha, Nepal: a study of knowledge, attitude and practice (KAP).

Study Protocol

Version 2.0

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Table of Contents

Contents

Summary

Background

Microbial keratitis (MK), or infection of the cornea frequently leads to sight-loss especially in Asia. MK has been described as a "silent epidemic", which leads to substantial morbidity, related to blindness and other consequences such as pain and stigma. It is the leading cause of unilateral blindness after cataract in tropical regions and is responsible for about 2 million cases of monocular blindness per year. The World Health Organization (WHO) estimated (2017) that 1.3 million individuals are bilaterally blind from corneal opacity globally (excluding trachoma and vitamin A deficiency), accounting for 3.2% of binocular blindness globally. One of the main causes of MK induced blindness is delayed presentation to the eye hospitals where appropriate care can be given. Our recent work in Nepal found that pharmacies and traditional healers are usually the first points of entry for most MK patients after onset of symptoms. Currently, there is little understanding on the knowledge and capacity of these groups and the role they play in the referral care pathway of patients with suspected MK.

Study Design

Using a mixed methods study design, we shall randomly select a representative sample of pharmacies and traditional healers. Interviews will be conducted to determine knowledge and practise of care, treatment and referral. In addition, a purposive sample of pharmacy attendants and traditional healers will be invited for In Depth Interviews and homogeneously composed Focused Group Discussions to discuss their role in the referral care pathway of patients with suspected MK.

Impact

Over the past few years, our group has been conducting formative research in Nepal to understand the epidemiology, presentation journeys and management challenges to support interventional packages to prevent sight loss from MK. The lessons learned from this study will be used to shape a planned community cluster RCT of a complex interventional package of early screening and treatment of suspected MK as a way of preventing severe MK and blindness.

Introduction and Literature Review

Epidemiology

Microbial keratitis (MK), or infection of the cornea, can be caused by a range of pathogens. The causative organisms include bacteria, viruses, protozoa (e.g. acanthamoeba), and fungi (yeasts, moulds and microsporidia). It is characterised by an acute or sub-acute onset of pain, conjunctival hyperaemia and corneal ulceration with a stromal inflammatory cell infiltrate. MK frequently leads to sight-loss from dense corneal scarring, or even loss of the eye, especially when the infection is severe and/or appropriate treatment is delayed.[1]

MK has been described as a "silent epidemic", which leads to substantial morbidity, related to blindness and other consequences such as pain and stigma.[2] It is the leading cause of unilateral blindness after cataract in tropical regions and is responsible for about 2 million cases of monocular blindness per year.[3] The World Health Organization (WHO) estimated (2017) that 1.3 million individuals are bilaterally blind from corneal opacity globally (excluding trachoma and vitamin A deficiency), accounting for 3.2% of binocular blindness globally.[4] In Sub-Saharan Africa (SSA), MK is an important cause of binocular blindness and is responsible for about 15% of monocular blindness in the Nigeria National Survey (personal communication).[5]

Incidence

The incidence of MK varies between high-income countries and Low- and Middle-Income Countries (LMIC). A recent review has described global incidence rates.[6] A summary of the global incidence rates is presented in Table 1. Overall, the incidence of MK is highest in Asian countries (except Hong Kong) and lowest in Europe and North America.[7-9]. Nepal has the highest reported incidence of MK in the world.

Table 1. Incidence of microbial keratitis in population-base studies

Country	Year	Estimate	Source
Africa			
Malawi (Kasisi, Katunga)	1994	210/100,000/year	Courtright[10]
Malawi	2018	10.3/100,000/year	Kalua[11]
Asia			
India (Madurai)	1997	113/100,000/year	Gonzales[12]
Nepal (Bhaktapur)	2001	799/100,000/year	Upadhyay[13]
Hongkong	2002	6.3/100,000/year	Lam[7]
Myanmar	2004	710/100,000/year	WHO / Country Report[14]
Bhutan	2004	339/100,000/year	WHO / Country Report[14]
North America and Europe			
USA	2010	27.6/100,000/year	Jeng[15]
UK	2012	40.3/100,000/year	Ibrahim[9]

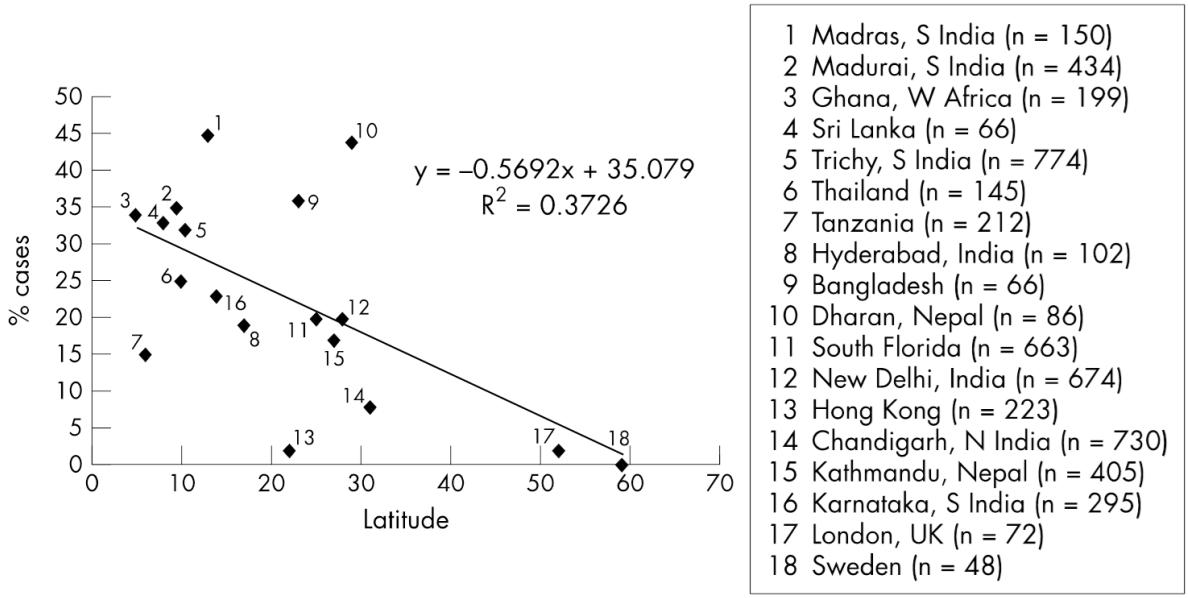
Causes

A wide range of microorganisms can infect the cornea: bacteria, fungi, viruses and protozoa. The pattern of causes seems to be more geographical although urbanisation and seasonal variation has also been reported

to influence specific causes.[16] Our previous work found that majority the cases were caused by fungal infections (64%).[17],[70]

In global epidemiology of MK, three large reviews have looked at the distribution of organisms according to geographical region.[6,18,19] The first review in 2002 looked at the global proportions of fungal keratitis.[20] The authors mapped the proportion of fungal keratitis against latitude and demonstrated that the proportion of filamentous fungi as a cause of MK generally increases the lower the latitude, with the highest proportion being found around the equator (Figure 1).[20-23] In tropical regions filamentous fungi cause about half of MK.[20,24,25]

Figure 1. Distribution of filamentous fungi by Latitude[20]



The second epidemiological review in 2011 described associations between a country's gross national income and types of causative organism.[18] The highest proportion of bacterial corneal ulcers was reported in studies from North America, Australia, Europe and Singapore. The highest proportions of fungal infections were found in studies from India and Nepal.[18] There was a significant correlation between a country's gross national income and type of infection (fungal or bacterial). The higher the income of a country, the higher the proportion of bacterial MK and vice versa.[18] A more recent review (2019) looked at the global incidence and proportions of MK based on large population studies and large case series.[6] The summary of the reports considered in these reviews have been updated and presented in Table 3.

Generally, in temperate climates most corneal infections are bacterial and are frequently related to contact lens use although reports of recent increases in fungal keratitis in the UK have been reported.[13] In the literature of large case series from North America, Europe and South America, the proportion of fungal

keratitis was low ranging from 0-26%.[9,26-30] Conversely, fungal rates from African and Asian studies were high ranging at an average of 50%.[20,31-33]

Specifically, regardless of geographical location, Gram positive organisms (*Streptococcus pneumoniae, Staphylococcus aureus*) and Gram-negative pathogens (*Pseudomonas aeruginosa*) are the most frequent bacterial causes while *Fusarium spp and Aspergillus spp* are the most common fungal causes.[17,20,34-38] However, in temperate climates, Candida spp have been commonly reported. [9,26-30]

Risk factors

There are many potential risk factors that may predispose a person towards developing MK with some risk factors being more specific to settings (region, income status and organism) and some being ubiquitous. Risk factors such as trauma especially with vegetative matter have been associated with fungal keratitis compared to a pre-existing ocular disease for bacterial keratitis.[39,40] Injury with mud is strongly linked to Acanthamoeba keratitis.[40] In addition, agricultural work and foreign body in the eye have been implicated.[39,41,42] Risk factors that are more setting specific include the use of contact lenses, which affects more people in high-income countries as opposed to the use of traditional eye medicines (TEM), which is more of a problem in Low and Middle-Income Countries (LMIC).[10,25,43-45] Other identified risk factors include age (trauma being common in the lower age groups versus ocular surface diseases in older folk), gender (males engaging more in outdoor activities than females) and poverty (MK mostly is more prevalent in among the poor).[39-41] Diabetes Mellitus (DM) has been the most commonly reported systemic risk factor, especially following keratoplasty or corneal trauma.[35,46,47] In a more recent case control study (individually matched for age and gender), the major risk factors for MK were HIV, Diabetes, a farming occupation, poverty and home address being far from the nearest health facility.[50]

Outcomes

A good outcome depends on early appropriate treatment, correct identification of the causative organism, and careful follow-up.[51,52] In LMIC, MK presents major challenges. The outcomes are frequently poor.[25,53,54]. In a recent large cohort from Uganda that followed up MK patients at 3 months, 30% of the participants were blind in the affected eye while 9% had lost their eye due to the infection.[17]

There are several reasons for the poor outcomes: presentation is usually delayed and advanced infections have poor outcomes.[25] Patients may use TEM, which often contains plant matter or inappropriate "conventional" medication (such as a corticosteroid), exacerbating the problem.[10,25,55] Primary health-care staff have little training in recognising, treating and referring MK. It is frequently not possible to clinically distinguish bacterial and fungal MK. Microbiology services are usually unavailable. Fungal keratitis is particularly difficult to treat. Current topical anti-fungal eye drops are not consistently effective and

infection can progress despite prompt treatment.[25,56-60] Anti-fungal drops are rarely available in SSA and often scarce elsewhere.[25] The eye may be lost through progressive deep corneal ulceration and perforation.[25,57]

The Nepal Health System

The total population of Nepal according to Census 2011 was 26.4 million and that of Siraha district was 637328. The projected population growth rate of Siraha district is 1.35% and in reference to this the total population of Siraha district in 2019 is estimated to be 710013.

The national health care system of Nepal consists of several levels (Table 2): National level (Tertiary Referral hospital), Regional level (zonal hospital), District level (district hospital), Village level (health post), ward level (Community Health Worker, Community health volunteer).

Table 2. Nepal Health System Structure

Level	Status	Population	Staffing	Services Provided
Ward	CHW	2500	Health volunteers	Community based preventive health services (awareness, vit A supplement, deworming, etc..)
Village	Health post	5000	CMA, ANM, AHW, NURSE, HA	Preventative, promotive, and curative services
Urban	Primary Health Care centres (PHC)	15000	MEDICAL OFFICER, NURSE, CMA, HA, ANM, LAB TECHNICIAN	Maternal child health and in-patient service, general health, diagnostic services, family planning
District	District Hospital (DH)	65000	PHC PLUS GENERAL PHYSICIAN, SPECIALITY DEPARTMENT	25-50 beds, emergency service, outdoor service and indoor service
Regional	Zonal/community Hospital (Z/CH)	2054326	DH PLUS ICU AND BROAD TEAM OF SPECIALITY DOCTORS	150-250 beds, well equipped services, specialized curative health services
National	Tertiary Referral Hospital	26494504	Z/CH PLUS EXTENDED BED, MORE SURGEONS AND SUB-SPECIALITY DOCTORS	Advanced comprehensive sub speciality care

There are 112 health posts in Siraha district of Nepal. According to the data of the Nepal Living Standard Survey 2010-11, 62% of the population live within thirty minutes of travel time of a health post.

Eye care services are not yet integrated within the general health system of Nepal. However, eye care providers (ophthalmologists, Optometrists, Ophthalmic Assistants [OAs] and eye health workers) work either independently or associated with several eye Hospitals run by NGO's and private owners. Main eye care providers in Nepal are Nepal Netra Jyoti Sangh (NNJS), Lions Club, Tilganga Eye Hospital and Biseshwor Prasad Koirala Lions Club for Ophthalmic Science (BPKLCOS).

According to Rapid Assessment of Avoidable Blindness (RAAB) survey conducted in Nepal in the year 2010 (https://www.iapb.org/news/raab-survey-in-nepal/) to determine the overall prevalence of blindness of the nation, the prevalence of blindness decreased from 0.84% (1981) to 0.35% (2010). The 2010 RAAB survey showed non-trachoma related corneal blindness to be 8.8%.[65]

Management challenges

There are several challenges of management of MK which lead to poor outcomes. Presentation is usually delayed and advanced infections have poor outcomes.[25] Patients may use TEM, which often contains plant matter or inappropriate "conventional" medication (such as a corticosteroid), exacerbating the problem.[10,25,55] Primary health-care staff have little training in recognising, treating and referring MK. It is frequently not possible to clinically distinguish bacterial and fungal MK. Microbiology services are usually unavailable. Fungal keratitis is particularly difficult to treat. Current topical anti-fungal eye drops are not consistently effective and infection can progress despite prompt treatment.[25,56-60] Anti-fungal drops are rarely available in SSA and often scarce elsewhere.[25] The eye may be lost through progressive deep corneal ulceration and perforation.[25,57]

Private Pharmacies

Many regions of South Asia have limited resource for eye health services; this includes the human resources, diagnostics and medicines.[61,62] There is limited access to appropriate treatment and care: people have to travel long distances to major urban centres to access an ophthalmologist. In many parts of Asia, private pharmacies and drug shops usually act as the first line facilities where people present for care. These are usually managed by a nurse dispenser with minimal/little training in managing ocular conditions. In Nepal, it is possible to obtain a range of medicines from pharmacies without a prescription. Our experience is that many eye-drop preparations sold over the counter in our region contain a corticosteroid component which might exacerbate certain types of MK.[63,64]

Our recent work in Nepal mapping the places where people seek eye care services found that the majority of the patients initially presented for care at a pharmacy/drug shop facility after onset of symptoms.[70] In Nepal, this was reported at 47% (LSHTM MSc project). One main finding was that although most patients presented soon after the onset of their symptoms to the primary health facilities, there was poor triage and referral of patients which led to late presentation and poor outcomes.[73]

A subsequent evaluation of the capacity and management of health system in Nepal found that majority of the facilities did not have the basic infrastructure and consumables to aid in the diagnosis and management of MK. Only 27.1% of the primary health workers could correctly identify signs of MK.[65] However, one

limitation of this study is that information was not collected on the knowledge and practise in the private pharmacies which form the bulk of the presentation points of patients with MK.

Traditional Eye Medicine (TEM) and Traditional Healers

Many people in LMIC use TEM. Our work in Nepal found that TEM was common.[66,70] These contribute to severe infections and worse outcomes. The drivers for use of TEM in Nepal were found to be lack of awareness about the disease and faith in the traditional healers.[70] A larger proportion of patients from Nepal (11%) consulted traditional healers.[70] The knowledge and practise for management of MK among traditional healers needs to be explored.

Problem statement and Rationale

Microbial keratitis is a common and serious eye problem that leads to loss of sight and a high morbidity for affected individuals in many parts of Asia. Over the past few years, our group has been conducting formative research in Nepal to understand the epidemiology, presentation journeys and management challenges to support interventional packages to prevent needless blindness from MK.

A major challenge has been delayed presentation to the appropriate level health facility where patients can receive appropriate effective care.[67,68] MK is a time-sensitive disease and once people present late, little can be done to reverse the damage and mitigate a poor outcome.[69] There are various studies that indicate the importance of intervention at the grass root level to decrease the severity of microbial keratitis.[70-73]

Our current work shows that delay was mediated through among other things, poor triage and referral in the health system as well as a use of TEM.[68] The proportion of patients that visited local pharmacies/drug shops was 47%, while the proportion that visited traditional healers was 11%, respectively.[67,68]

In this context, local pharmacy shops and traditional healers play important roles as the primary point of consultation. However, there is a gap in our understanding of the knowledge and practice for treatment of MK among these key stakeholders. Our group plans to implement an early screening and referral interventional cluster randomized trial in Nepal as a prevention strategy of severe MK.

As part of the intervention development process we need to better understand the knowledge and practice of MK management by the private pharmacies and traditional healers, which will help shape the scope of the interventional package that will be rolled out.

Aim

The overall purpose of this research project is to contribute to the development of strategies to reduce blindness from microbial keratitis (MK) by understanding the role pharmacies and Traditional Healers play in the treatment pathway of MK.

Specific objectives

1. To determine the knowledge of private pharmacy workers and traditional healers in Nepal on the management of MK.
2. To describe the current practice for the management of MK among private pharmacies and traditional healers in Nepal.
3. To explore ways to engage local pharmacy and traditional healers to improve referral of patients with suspected MK.

Methodology

Study Design

A mixed methods descriptive cross-sectional study with a KAP questionnaire, in depth interviews (IDIs) and focus group discussions (FGDs) will be carried out in Siraha district in Nepal.

Study location

In Nepal, the study site will be Siraha district, Sagarmatha Zone. This district lies in the eastern part of the country and is mostly sits in the Terai plain belt. The plain belts of terrain are the most populous region. The Sagarmatha zone borders the Indian plain areas of Bihar state in the south; whereas in the north it has difficult and remote hilly areas. It has six districts (including Sirhaha) and the total population is 2.06 millions.[74]

Study population

Pharmacy attendants of Siraha district, Nepal

Traditional Healers of Siraha district, Nepal

Inclusion criteria

- We will include pharmacy attendants of Siraha district, Nepal
- We will also include Traditional Healers of Siraha district, Nepal
- Consent to take part

Sample size

Quantitative KAP Questionnaire

Pharmacies: There are 300 pharmacies registered in Siraha district, from which we will take a sample in order to estimate the proportion of pharmacy attendants who can make a correct diagnosis of MK. These will be selected randomly without any stratification. Based on the findings from our previous work which found that only 27.1% of the health workers in the primary health system could make a diagnosis of MK. Therefore, a sample size of 152 pharmacies should be sufficient to give us a margin of error of 5% with a 95% CI (https://select-statistics.co.uk/calculators/).

Traditional healers: Based on an assumption of 500 traditional healers in Siraha district and about 10% being able to identify MK, a sample size of 109 traditional healers should be sufficient to give us a margin of error of 5% with a 95% CI (https://select-statistics.co.uk/calculators/).

Qualitative Components

This will involve In Depth Interviews (IDIs) and Focused Group Discussions (FGDs), who will be sampled from the pharmacy attendants and traditional healers who are enrolled in the quantitative survey (above). For each group (pharmacists and traditional healers), we will conduct 30 IDIs and 4 homogeneous FGDs with 8-10 participants each. We shall prospectively collect data until data saturation is achieved.

Sampling strategy

A list of pharmacies and traditional healers in the respective districts will be obtained from the registries (drug shop/pharmacy registry and traditional healers registry) of Siraha district Nepal. Using the corresponding numbers on list (1-300) of pharmacies, 152 will be randomly selected using a computer algorithm. From a list of the traditional healers, the same technique shall be applied to randomly select 109 names. The selected pharmacists/healers will be visited and invited to participate in the Knowledge Attitude and Practise (KAP) interviews. The questions will cover knowledge and practise of managing suspected MK cases.

Data collection and tools

We will use both quantitative and qualitative approaches. These shall include semi structured KAP questionnaires, IDIs and FGDs.

KAP Questionnaires: The study team will visit the selected pharmacies and Traditional healers in the district. After initial introductions and establishment of rapport, the team shall proceed to obtain informed consent of the study participants and then administer the KAP questionnaires. These shall cover broad areas of common identification and treatment of suspected MK cases. The questions will be translated into Nepali and Maithili.

IDIs: When administering the KAP questionnaires, participants will be asked if they would be willing to talk about their experiences and suggestions on how to improve care and referral of the patients later. The interviewer will return and conduct a structured individual interview using a topic guide. Data shall be captured with an audio recorder and will be treated as qualitative data. The IDIs will continue until we reach data saturation.

FDGs: From a pool of participants who expressed willingness to speak with us more during the KAP survey, we will conduct 4 FDGs per group (pharmacists/healers) composed of about 8-10 participants in each FDG. The focus of the FDG will be to explore ways in which these groups can become more engaged in the referral care pathway for suspected MK.

Data management and analysis

Quantitative data will be entered into an access database and imported into STATA 16 for analysis. Simple tabulations will be used to summarise descriptive data on knowledge and practise.

Qualitative data will be manually processed. The audio records of the IDIs and FGDs will be transcribed and translated to English. Summaries from transcripts and field notes will be generated for analysis. Working in collaboration with a social anthropologist, we shall manually code the data thematically according our research question with emphasis on the role of pharmacy attendants and traditional healers on the referral care pathway for suspected MK. From having coded thematically, we shall prepare a short summary of the emerging themes which we shall then use in the writing up of our data.

Ethical considerations

We will submit the protocol for review by the relevant Ethics committees:

- The ethics committee of the London School of Hygiene & Tropical Medicine, UK.
- Local ethics of Eastern Regional Eye Care Program (EREC-p) ethics committee, Nepal

Data Management

Data will be collected and managed in the following way to ensure that the anonymity of the participants is protected.

- Only study team staff will be involved in handling participants records.
- Data will be recorded initially onto a paper form which will include several key identifiers which will not be transferred to the electronic database: specifically, individual and pharmacy name. The paper records will remain at the study office in the hospital. This is a secure room only accessible to authorised hospital staff.
- The database will be encrypted on a password protected computer in the study office. This will have the participant unique study ID as the only thing that can link back to the paper forms. The electronic dataset used for analysis will therefore not contain information that could identify the individuals.

Sponsor

The Sponsor of this study is the London School of Hygiene and Tropical Medicine, UK on behalf of the study funder, the Wellcome Trust. On approval the LSHTM will arrange insurance to cover the activities in this study. The copy of the certificate for this will be sent to the local Ethics Committee. The study may be subject to audits by the LSHTM under their remit as sponsor.

This study is supported by funding from the Wellcome Trust. The grant will cover all project related costs.

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Dissemination

The findings will be presented at local/regional meetings. A joint publication is planned to compare the roles of pharmacies and traditional healers in the referral care pathways of suspected MK cases in Africa and Asia.

The lessons learned from this study will be used to shape a planned community cluster RCT of an interventional package of early screening and treatment of suspected MK as a way of preventing severe MK and blindness.

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