"MOXIFLOXACIN VERSUS COMBINATION THERAPY (TOBRAMYCIN + CEFAZOLIN) IN BACTERIAL KERATITIS – A RANDOMIZED CONTROLLED TRIAL"

by

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Under the guidance of

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LIST OF ABBREVIATIONS

AC	-	Anterior chamber
AL	-	Adherent leucoma
CF	-	Counting fingers
DCT	-	Dacryocystectomy
DM	-	Diabetes mellitus
DNA	-	Deoxyribonucleic acid
FCR	-	Favourable clinical response
FQs	-	Fluoroquinolones
GAGs	-	Glycosaaminoglycans
gyr	-	Gyrase
HMCF	-	Hand movements close to face
KOH	-	Potassium hydroxide
MIC	-	Minimum inhibitory concentration
Moxi	-	Moxifloxacin
MRSA	-	Methicillin resistant staphylococcus aureus
NSAID	-	Non steroidal anti inflammatory drug
PL	-	Perception of light
PMN	-	Poly morphonuclear cells
SD	-	Standard deviation
SDA	-	Sabourauds dextrose agar
Staph	-	Staphylococcus
Strept	-	Streptococcus

ABSTRACT

Background and Objectives

Increasing resistance of bacterial keratitis isolates has been shown against second generation fluoroquinolones. Moxifloxacin and Gatifloxacin, are fourth generation FQs, which have been introduced recently. These new ocular antibiotic formulations have improved potency and have been shown to inhibit growth of organisms resistant to second and third generation FQs. Hence the present randomized controlled trial was undertaken to compare the effectiveness of moxifloxacin monotherapy with combination therapy for the treatment of bacterial keratitis.

Methods

The present one year randomized controlled trial was conducted in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010 on 60 patients diagnosed with bacterial keratitis. Patients were randomly allocated into two treatment groups using computer generated randomization Group A (n=30; received monotherapy with Moxifloxacin) and Group B (n=30; received combination therapy with Tobramycin and Cefazolin). After corneal scrapings was obtained assigned study medication was instilled and antibiotics were tapered as per the response.

Results

In this study 37 (61.67%), male predominance was seen with male to female ratio of 1.61:1. Mean age in Group A was 54.37 ± 15.65 years and in

Group B it was 56.37 ± 10.83 years. Positive bacterial culture was obtained in 68.33% cases and distribution of organisms was similar in both groups. There was no statistical difference in the final outcome between the two groups (Group A 96.67%; Group B 90%.; p=0.3006). The mean duration of healing in group A was significantly less (2.03±0.54 v/s 2.31±0.41; p= 0.032). Patients in group B had significantly more severe adverse effects (p= 0.0384).

Conclusion and interpretation

Patients treated with moxifloxacin had shown significantly better results in terms of lesser duration of healing and no adverse effects as compared with fortified antibiotics.

Keywords

Bacterial keratitis; Fortified antibiotics; Fourth generation fluoroquinolones; Moxifloxacin.

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INTRODUCTION

Bacterial keratitis is a serious ocular infectious disease which can lead to significant visual loss.[1] It accounts for approximately 65% to 90% of all microbial corneal infections.[2-5] Any infectious process in the cornea producing a keratitis, mild or severe, requires prompt and vigorous treatment with an effective antimicrobial agent to minimize corneal scarring and visual loss.[1-3,6-8]

The commonly used combination treatment[9,10] regimen includes frequent administration of topical ocular antibacterial agents (e.g cephalosporins and aminoglycosides), often at concentrations higher (fortified) than those currently available in the market.[3,6-8,11,12] Aminoglycosides like tobramycin[9,13] have good gram negative coverage and cephalosporins like cefazolin[9] have good gram positive coverage. Thus, the combination has good broad spectrum coverage of the usual bacteria causing corneal ulcer.

The use of such fortified preparations remains controversial for several reasons.[12] The increased tonicity of concentrated drops may induce reflex tearing, which, in addition to the dilution that occurs secondary to osmosis, may actually decrease corneal tissue penetration.[14] Simultaneous use of multiple antibiotics, with frequent dosing, may result in toxicity and damage to the ocular surface epithelium, thereby impairing recovery.[15,16]

Fortified drops have to be made fresh as they have shorter shelf life.[9] Moreover, each requires special mixing which adds to cost and increases the risk of contamination[14,15,16]

The primary short comings of marketed agents such as aminoglycosides which are currently available for the treatment of ocular infections include hypersensitivity reactions, systemic or ocular toxicity, existence of resistant strains or lack of potency.[3,17]

Thus, introduction of commercially available non fortified broad spectrum topical antibiotics with the ability to achieve concentration greater than the MIC (Minimum inhibitory concentration) for most bacteria was desirable.

With the advent of fluoroquinolones, monotherapy has been established as an alternate paradigm in the treatment of bacterial keratitis.[18,19,20] Fluoroquinolones offer the advantages of good ocular penetration, demonstration of broad spectrum efficacy, excellent safety profiles in ocular infections, and a distinct mode of resistance acquisition.[17]

Recently, increasing resistance of bacterial keratitis isolates has been shown against second generation fluoroquinolones.[21-23] Fourth – generation fluoroquinolones (FQs), namely moxifloxacin and gatifloxacin, have improved potency and have been shown to inhibit growth of organisms resistant to second and third- generation agents.[24,25] They have better corneal and aqueous penetration as compared to second generation fluoroquinolones. Hence they can lead to more effective therapeutic levels with better clinical outcome.[26]

Hence, the present randomized study was undertaken to compare the effectiveness of moxifloxacin monotherapy with conventional combination therapy for the treatment of bacterial keratitis.

OBJECTIVES

The objective of the present study was to find out the effectiveness of Moxifloxacin over combination therapy (Tobramycin + Cefazolin) in the treatment of bacterial keratitis.

REVIEW OF LITERATURE

ANATOMY OF CORNEA[27]

Cornea is a transparent, avascular, watch glass like structure. It is the principle refractive surface of the human eye and forms the anterior one sixth of the outer fibrous coat of eyeball. The adult cornea appears as an ellipsoid being about 12 mm in horizontal meridian and 11 mm in the vertical. However, from the back, the cornea is a circular with a diameter of nearly 11.5 mm, thicker at the periphery (0.67 mm) than at the centre (0.52 mm). The radius of curvature of the cornea varies from the centre to the periphery, being shorter near the centre than the periphery. The radii of curvature of anterior surfaces of the central third of the cornea called "optical zone" are 7.8 mm. Rather wider range of variation from 7 to 8.5 mm is compatible with good visual function.

The cornea has refractive index of 1.376.The concave posterior surface of the cornea faces the aqueous which has lower refractive index 1.336.The refractive power of this surface is –5.8 diopters giving the entire cornea a refractive power of +43 diopters, out of the total 58 diopters refractive power of the eye.

Microscopic structure

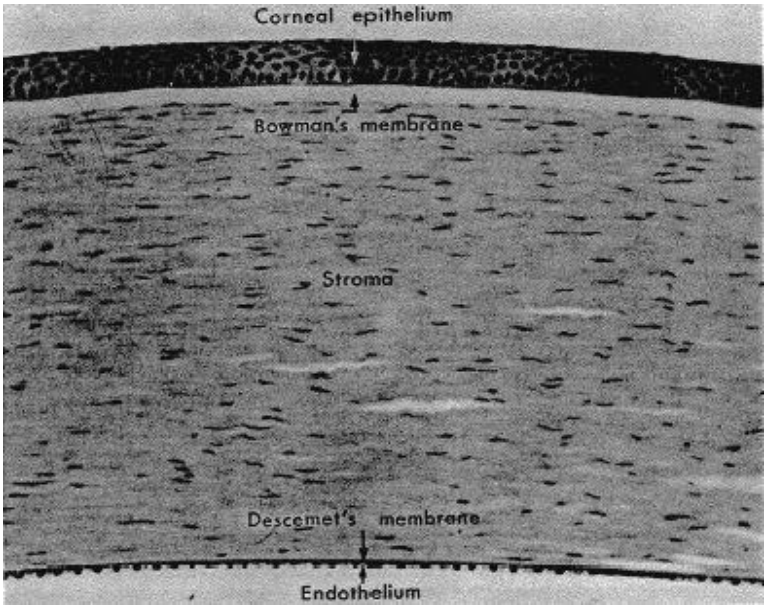


Figure 1. Cross section of human cornea at 160X

Layers of the cornea

Epithelium: Consists of five or six layer of stratified squamous epithelium resting on a very delicate argyrophilic basement membrane. It is about 50 micron in thickness. The deeper layer is basal cells which stand in palisade manner in perfect alignment on a basement membrane.

Bowman's membrane: Measures 8-14 microns in thickness being somewhat thicker in the peripheral third. This is composed of collagen and contains no cells. Towards the periphery, it becomes thinner and arrangement of fibres looser and collagen gradually merges with that of conjuctiva. Collagen fibrils in the bowman's layer are smaller and uniform in thickness and measure between 240 Å and 270 Å. Bowman's membrane once destroyed will not regenerate and thus gives rise to permanent defect.

Stroma: It is 0.5 mm in thickness. It is composed of modified connective tissue of which the constituents have very nearly the same refractive index so that in the perfectly fresh condition, it is difficult to make out any indications of structure. Among the lamellae of the cornea are a considerable number of fixed cells, corneal fibroblasts or keratocytes, wandering macrophages. Occasionally, lymphocytes or polymorphonuclear leucocytes are seen.

Descemet's membrane: It is a strong, homogenous and very resistant membrane. It is 10 to 12 micron thick and sharply defined from the stroma. There is in fact a plane of separation between them which is used in lamellar keratoplasty and sclerocorneal tunnel incisions for cataract surgery. When it is incised, it gapes and curls backwards indicating some elasticity in this layer. In the periphery, it bends form Schwalbe's line to which the trabecular meshwork is attaches anteriorly. When this membrane is destroyed unlike bowman's membrane, it is regenerated by the endothelium.

Endothelium: It is a very precious layer for the anterior segment surgeon. Technique if surgery is modified to see that minimum damage and insult is done to the endothelium. It is the most posterior layer of the cornea and consists of a single layer of flattened epithelial like cells, continuous around the angle of the AC. With slit lamp, endothelium can be visualized. It is the whole site in the whole body where endothelium can be seen and studied under magnification. Specular microscopy helps to evaluate the endothelial status allowing an objective estimation of the endothelial cell loss.

NORMAL WOUND HEALING

Corneal abrasion[28]

An abrasion results from an injury that removes some or all of the layers of epithelium but leaves the Bowman's membrane intact.[40] The wound heals by epithelial sliding and mitotic proliferation. If healing is uncomplicated, no scarring occurs.

After about an hour of lag period, the normal epithelium from the edge of the abraded area flattens and so slides inward to cover the gap. If the entire corneal epithelium is abraded, the gap can be covered by sliding of conjunctival epithelium in 48 to 72 hours. At first the epithelium is thinner than normal, but mitotic cell division restores rapidly the normal thickness. Over a period of weeks to a few months, the conjunctival epithelium takes on completely the morphological characteristic of the corneal epithelium. Mitotic multiplication of the epithelium restores the normal thickness.

Superficial defect[28]

A superficial defect results from an injury that removes epithelium and Bowman's membrane with or without a few anterior layers of stroma. The wound healing takes place exactly as in an abrasion except that mitotic multiplication results in a focus of thicker than normal epithelium called an epithelial facet. An epithelial facet can be seen with the slit lamp as a tiny, focal separation the two anterior most zones of corneal relucency. This type of lesion results most frequently from a small, superficially embedded foreign body.

No attempt is made to repair Bowman's membrane or any superficial stroma that may be involved.

Deep defect[28]

A deep defect results from an injury that removes epithelium, Bowman's membrane and at least the anterior quarter of the stroma. Healing takes place mainly by epithelial sliding and corneal thinning results. The epithelium from the edge of the injured area flattens and slides over the wound, thus attempting to fill the gap promptly.

Mitotic multiplication of the epithelium results in a normal thickness or a slightly thicker than normal epithelium but cannot restore the normal curvature of the anterior corneal surface. Thus a concavity of the anterior corneal surface results in corneal thinning.

Bowman's membrane and corneal stroma never regenerate, when required.

Historical Aspects

Basis of modern outlook of fundamental pathology of cornea was laid by Fuchs, as indeed may be said of most ocular tissues.

The term "Keratitis" was introduced by James Wardrop (1782 – 1869) in his "Essays on the morbid Anatomy of the human eye".[29]

An ulcer is defined (Latin "ulcus" or sore) as a lesion "caused by superficial loss of tissue usually with inflammation."[30]

Definition

Corneal ulcer is defined as a loss of the corneal epithelium with underlying stromal infiltration and suppuration associated with signs of inflammation with or without hypopyon.[31]

Corneal ulcer is a non specific term, and include both non infectious and infectious keratitis cases, although more precise term such as microbial keratitis is gaining acceptance. Microbial keratitis is a common, potentially sight threatening ocular infection caused by viruses, bacteria, fungi or parasites.[28]

Bacterial keratitis is a serious ocular problem which result in corneal scarring and opacification subsequently causing severe visual loss.[1] It accounts for 65% to 90% of all microbial corneal infections.[2-5]

Aetiology

Table 1. Classification of bacterial organisms causing microbial keratitis[32]

Aerobi c bacteria	Anaerobic bacteria
Gram positive cocci	Gram positive cocci
Micrococcaceae	*Peptococcaceae*
Staphylococcus aureus	Peptococcus
Staphylococcus epidermidis	Peptostreptococcus
Streptococcaceae	
Streptococcus pneumoniae	
A and B hemolytic streptococci	
Enterococcus	
Gram positive bacilli	Gram positive bacilli
Bacillaceae	*Propionibacterium acne*
Bacillus cereus	Actinomyces
Bacillus subtilis	Clostridium
Corynebacteria diphtheria	
Corynebacteria xeroses	
Listeria monocytogenes	
Gram negative bacilli	Gram negative bacilli
	Fusobacterium
Pseudomonaceae	
Pseudomonas aeruginosa	Bacteriodes
Acinetobacter	
Azotebacter	
Enterobacteriaceae	
Klebsiella	
Serratia	
Proteus	
Citro bacter	
Enterobacter	
Gram negative diplococcic	*Gram negative cocci*
Neisseria	Veillomella
Gram negative diplobacilli	
	Spirochaetales
Moraxella	Treponema
Gram negative coccobacilli	Leptospina
Hemophilus	
Gram positive filaments	
Mycobacterium (Non tuberculosis)	
Nocardia	

Normal Flora

The conjunctiva and its adnexa are usually sterile at birth and are rapidly colonized by saprophytic bacteria.[33]

According to Mathea, the frequency of different organisms in normal conjunctival flora were found to be Staphylococcus albus in 85%, diptheroids in 50%, Staphylococcus aureus in 20% and Proteus in 3% and gram negative rods in 5% of the cases.[33]

The presence of these micro organisms in the normal, uninfected conjunctival sac, provides a constant reservoir of potentially pathogenic bacteria capable of causing serious ocular infections once the normal protective mechanisms of the cornea are breached.[33] Some organisms such as Neisserria gonorrhea, Neisseria meningitides, Corynebacterium diptheriae, Listeria, and Shigella can directly penetrate an intact epithelium.[28]

Predisposing factors[28]

Exogenous factors

1. Corneal trauma
2. Contact lens use

Endogenous factors

1. Lacrimal disorders such as dry eyes and dacryocystitis.
2. Lid disorders such as blepharitis, entropion, ectropion, lagophthalmos etc
3. Conjunctival infections like trachoma, vernal catarrah, cicatricial pemphigoid

4. Corneal diseases such as bullous keratopathy, corneal abrasions, , chemical injuries, herpetic eye disease, neurotrophic keratitis.
5. Topical drugs

Systemic factors

Extensive burns, alcoholism, debilitating diseases, rheumatoid arthritis, diabetes mellitus, drug addictions, acquired immunodeficiency syndrome.

Pathogenesis[32,34-36]

This involves the following stages.

Stage of infiltration

In this stage corneal ulcer results when the balance between the cornea and its surrounding environment is disrupted and the defence mechanisms are compromised. The organisms adhere to the damaged epithelium, invades the stroma and begins to replicate by binary fission. The host inflammatory response is initiated by the polymorphonuclear cells (PMNs) which arrive via tear film initially and later from the vascular limbus. These PMNs are secreted in response to the corneal insult which secrete various lytic enzymes such as collagenase, elastase and cathepsin causing destruction of the cornea. The PMN response is a two edged sword-both often adding to corneal stromal destruction and helping to contain the infection and promote sterilization of the corneal ulcer.

Stage of ulceration

If the infection is not controlled, the inflammatory reaction progresses relentlessly and results in tissue loss. There may be associated hypopyon which is

usually sterile as the organism does not ordinarily penetrate an intact Descemet's membrane.Progression of such ulcerative process can lead to corneal perforation.

Regressive Stage

This stage is characterized by decrease in ocular symptoms. The infiltrates decrease in size and the ulcer becomes more demarcated. Necrotic areas may slough off, mimicking progression even though the inflammation is regressing.

Healing stage

In the healing stage, the necrotic stroma is replaced by the scar tissue laid down by fibroblasts which are transformed histiocytes and keratocytes. The scar never becomes transparent, although its density decreases with time especially in children and young adults. Vascularization occurs towards the ulcer site, which further promotes healing as a result of influx of fibroblasts and antibodies. When the healing is complete, the vessels regress and become "ghost vessels" which may be visualized by an indirect illumination.

SEQUELAE AND COMPLICATIONS[32,36]

Sequelae can vary in severity from corneal scarring to perforation, endophthalmitis, and loss of the eye.

Corneal Opacification

Depending on the depth of the corneal ulceration, different types of corneal opacities may occur that is, nebular, macular or leucomatous.

Descemetocele

Ulcers due to pneumococci extend rapidly in depth, to involve entire thickness of the cornea sparing the Descemet's membrane.This membrane offers resistance to the inflammatory process, but is unable to withstand the intraocular pressure and therefore herniates through the corneal ulcer as a transparent membrane called as descemetocele or keratocele.

Perforation

On perforation aqueous escapes and the intraocular pressure falls to the atmospheric levels. Subsequently, the lens iris diaphragm moves forward and adheres to back of the cornea. Due to decreased intraocular pressure, the pain is alleviated; extension of the ulcer decreases and the process of scar formation is initiated.

When perforation is small, the iris is plugged to the back of the cornea and adhesions from the iris gets organized and the scar tissue is formed which is called as *"pseudocornea"*. The plastered iris at the back of the cornea, allows anterior chamber to form. When perforation is large, the iris prolapses out through the perforation; in long standing cases of prolapsed fibrin and exudates deposition occurs on the surface. Thus, adherence of iris tissue to the back of cornea, subsequent to a perforated corneal ulcer, is called as a *corneo-iridic scar*.

Ectatic Cicatrix

Due to the presence of anterior synechiae and plugging of the iris, adherent leucoma forms, often leading to secondary glaucoma. The cicatricial

tissue is too weak to support this raised intra ocular pressure and hence cicatrix becomes ectatic. An ectatic cicatrix into which the iris is incarcerated is called *anterior staphyloma*.

Corneal Fistula

If perforation occurs near the pupillary margin.

Hemorrhage

The sudden decrease in the intraocular pressure dilates the intraocular blood vessels, which may rupture causing an intraocular hemorrhage. It may even lead to expulsive hemorrhage.

Endophthalmitis

Organisms, may gain access to the interior of the eye as a result of perforation and cause purulent iridocyclitis, endophthalmitis and even panophthalmitis.

SPECIFIC ORGANISMS

Staphylococcus organisms[28]

The presence or absence of coagulase enzyme divides the Staphylococci into two broad groups. The coagulase positive and coagulase negative Staphylococci.

Streptococcus pneumococci

Important cause of bacterial keratitis in cases of chronic dacryocystitis.[28]

Gram positive aerobic bacilli

Bacillus Cereus have been associated with keratitis following foreign body injury.[37]

Pseudomonas species

It is the most common Gram negative and highly virulent organism causing corneal ulcers. Pseudomonas species has also been increasingly isolated more so in daily or extended wear soft contact lens wearers.[38]

Anaerobes

Anaerobes and higher order bacterias cause ulcers following corneal injuries with contaminated soil.[39] Actinomyces species, a filamentous bacteria is an important cause of canaliculitis.[28]

Nocardia species inhabits the soil and cause indolent ulceration.[40] Mycobacterium fortuitum also inhabits the soil and causes indolent ulcerations with "cracked windshield" appearance.[41,42]

Non-spore forming Anaerobic Organisms

Non-spore forming anaerobic organisms should be suspected as a cause of keratitis following human or animal bites. They are associated with extensive necrosis of the tissue, gas formation in tissue or foul discharge. The most frequently isolated anaerobes are Peptostreptococcus, Peptococcus, Propionibacterium, Bacteroides and Fusobacterium species.[39]

Non-tuberculous Mycobacteria

Non-tuberculous mycobacteria, including Mycobacterium fortuitum, M. chelonae and M avium intracellular are emerging as causes of indolent keratitis especially after surgical procedures such as laser-in-situ keratomileusis.[42]

GENERAL CLINCIAL FEATURES[28,34,36]

Most patients with bacterial keratitis manifest with decreased visual acuity, photophobia, pain, redness and swelling. Discharge is usually absent in keratitis unless it is associated with purulent conjunctivitis.

Slit lamp examination reveals a non-specific conjunctival response (mainly papillary response) and conjunctival chemosis, if a significant iritis is present, a circumlimbal ciliary flush may be seen. The corneal epithelium become ulcerated and the stroma exhibits variable degree of gray white infiltration. The cornea will be edematous, with visible folds in descemet's membrane. Fine keratic precipitates are found on the endothelium. Anterior chamber reaction exhibits variable degrees of cells and flare. A hypopyon may be present which in bacterial keratitis, is typically sterile .It is relatively more common in ulcers caused by Streptococcus pneumoniae and Pseudomonas.

SPECIFIC CLINICAL FEATURES[28,32,34]

Staphylococcus

They are typically localized round or oval ulcers with distinct borders surrounded by grayish white zone of infiltration. The ulcer develops more in depth than in width and may cause intrastromal abscess which may lead to perforation. Corneal ulcers produced by non-aureus strain tends to be more indolent with less infiltration and anterior chamber reaction.

Streptococcus pneumoniae

Pneumococcal ulcers tends to remain localized or may have a tendency to spread in one direction, usually centrally (Ulcer serpens). Fibrin deposition may be seen on endothelial side of the ulcer and a deep stromal abscess may form, with intervening stroma being relatively clear. There is marked anterior chamber reaction with hypopyon formation. Perforation is more common with pneumococcal ulcers.

Pseudomonas species

It is the most common gram negative and highest virulent organism causing corneal ulcers clinically. It causes a rapidly spreading central or paracentral ulcer and is associated with dense stromal infiltration. The surrounding cornea is edematous which gives a characteristic ‘ground-glass’ appearance .If untreated, the ulcer spreads circumferentially to form a ring ulcer within 48 to 96 hours .There may be, soupy melting of the cornea with greenish

mucopurulent discharge with eventual perforation within two to five days of onset of infection.

Other Gram negative rods like Klebsiella, Escherichia coli and Proteus cause indolent ulcer commonly seen in cases of trauma, malnourished debilitated patients and alcoholic patients.

LABORATORY DIAGNOSIS

A complete laboratory workup is very essential owing to considerable overlap in the clinical appearance of corneal ulcers due to various microorganisms.[43]

The first step is to obtain samples from eyelids and conjunctiva using calcium alginate swabs moistened with nutrient broth of both the eyes (infected and non-infected).[43]

Corneal scraping from the ulcer area is performed, under local anaesthesia; Ulcer is scraped from the leading edge, under magnification (binocular loupe, slit lamp, operating microscope) using a blunt cataract knife, Beaver blade No. 64, Bard parker blade No. 15.[31,44,45] A prospective comparative evaluation of Bard parker blade No. 15 and calcium alginate swab for collecting the corneal material, showed that there is no significant difference in microbial yield between the two methods[46] contrary to that reported earlier.[47]

Material is "C-streaked" on culture plates. These include fresh blood agar, chocolate agar and sabourauds agar media. The scraped material is also smeared on two glass slides, one for KOH wet mount and the other for Gram's

stain.[31,44,45,48] If the patient is already on treatment then stop treatment 12 hours prior to culture to enhance recovery of organism. Beyond its diagnostic value, corneal scraping may accelerate disease resolution by enhancing antibiotic penetration and therapeutic debridement of necrotic tissue.[28,36]

In case of contact lens Keratitis, contact lens, case and solution should also be sent for microbiologic examination.[40]

Microbial cultures are considered significant when there is growth of the same organism on two or more media, confluent growth at site of inoculation on one solid medium, growth in one medium with consistent direct microscopy findings or growth of the same organism on repeated corneal scraping.[31,44,45,48]

If infectious keratitis is suspected clinically and twice repeated microscopic evaluation of smears and culture results are negative and no clinical improvement is noted on the initial broad spectrum antibiotic therapy, corneal biopsy is recommended. The biopsied tissue is bisected, half being sent to microbiology laboratory for homogenization and culture, and the remaining half is placed in 10% buffered formalin to be transported to a pathology laboratory.[43]

Morphology of corneal pathogens[49]

- *Staphylococcus***:** consists of gram positive cocci arranged in grape like clusters.
- *Streptococcus***:** it consists of gram positive cocci arranged in chains or pairs.
- *Haemophilus:* it consists of gram –negative , rod –shaped cells

- *Pseudomonas:* consists of non fermentative gram negative rods.
- *Enterococci:* consists of gram positive cocci arranged in chains or pairs.

Colony characterstics of various corneal pathogens[49]

- *Staphylococcus aureus:* typically small colonies, often less than 1mm diameter.
- *Streptococcus pneumonia:* frequently cultured on blood agar.Some species can break down erythrocytes to produce a clear zone around the colonies.
- *Haemophilus influenzae:* these organisms grow on enriched chocolate agar.
- *Pseudomonas aeruginosa*: several species secrete soluble pigments,some of which are only fluorescent and may be seen with the aid of ultraviolet lamp.
- *Enterococci*: the colonies are similar to Streptococcus.

TREATMENT

The objective of therapy in bacterial keratitis is to rapidly eliminate the infective organism, reduce the inflammatory response, prevent structural damage to the cornea, and promote healing of the epithelial surface.[28]

Until the results of the definitive cultures are available, Gram's stain is a quick and helpful tool for initiating a rational antibiotic therapy. Gram's stain

may identify pathogen in upto 75% of the mono bacterial keratitis and 37% of the polybacterial cases.[28,32] If the gram stain is equivocal or there is uncertainty in interpretation of diagnostic smears, broad spectrum antibiotic coverage should be initiated in the initial treatment of all cases of severe suppurative microbial keratitis.[12,28] The initial management of cases of bacterial keratitis includes the use of medical therapy.

Medical management

A study,[43] identified two different approaches in the initial treatment of microbial keratitis. The 'Shotgun therapy' in which the choice of a combination of fortified antibiotics, used as intensive initial therapy based on local epidemiological information regarding likely infecting organisms and the 'Specific therapy', in which intensive treatment with a single antibiotic is directed by the results of the microbiological investigation. With shotgun therapy, complete antibiotic cover is not possible and treatment toxicity is more likely, whereas specific therapy risks disease progression if microbiological investigations are incomplete or misleading. A compromise approach is often adopted in which shotgun therapy is continued until clear evidence of the infecting agent and its antimicrobial sensitivities emerges to direct specific therapy.

- Combination therapy
- Monotherapy

Combination therapy

A combination therapy consists of a cephalosporin, which acts against the gram-positive cocci and some of the gram negative rods and an aminoglycoside which acts against the gram negative organisms.[50] Combined fortified five percent cefazolin sodium and 1.3% tobramycin sulphate are given in hourly dosage for the initial 48 hours.[32]

Monotherapy[68]

The newer fluoroquinolone drugs with their broad spectrum efficacy like ciprofloxacin 0.3%, moxifloxacin 0.5%, gatifloxacin 0.3% or ofloxacin 0.3% can be given as monotherapy and is effective against many corneal pathogens. They are also effective against aminoglycoside resistant strain Pseudomonas, methicillin resistant Staphylococcus and potent against Neisseria keratitis.[51]

Patient is put on intensive antibiotic therapy during the initial phase of sterilization. As the infection comes under control, the antibiotic frequency is gradually tapered. Systemic antibiotics are started along with topical antibiotics in cases of severe keratitis with scleral melting, impending perforation and frank perforation which have propensity for intraocular spread.[50]

A careful slit lamp examination at each visit is an essential feature to determine the progress of the disease. Alternative antibiotic regimen should be considered in patient with no clinical response or patients who have developed toxicity to initial treatment.[43]

ADJUNCTIVE THERAPY[36,43]

- Topical cycloplegic agents (Atropine, homatropine, Cyclopentolate etc) administered to relieve ciliary spasm, alleviate pain and prevent the synechiae formation.
- Antiglaucoma drugs: (topical β- adrenergic blocker or oral carbonic anhydrase inhibitors). They have a significant role in cases with descemetocele or impending perforation.
- Therapeutic soft contact lens: may be a useful adjunct to assist epithelial healing. Antibiotics should continue over the lens. Caution should be exercised as infection may occasionaly complicate therapeutic contact lens.
- Collagenase inhibitors like ethylene diamine tetra acetic acid (EDTA) (0.05% eye drops), Acetylcysteine 20% or heparin 2% have been shown to be effective. However they are seldom used.
- Analgesics to relieve pain.

SURGICAL MANAGEMENT[36,43]

Various modalities of treatment available are:

- Removal of epithelium and anterior lamellar keratectomy.
- Conjunctival flaps: may be helpful in non healing ulcers and impending perforation.
- Tissue adhesives: Isobutyl cyanoacrylate glue can be used to seal perforation upto 3mm in diameter.

- Penetrating keratoplasty: the indications are perforation, descemetocele, and post infectious corneal scar.

PHARMACOTHERAPY

Fluoroquinolones[52,53] are a new group of antibiotics; their mechanism of action is inhibition of bacterial DNA gyrase. They are bactericidal[52] having a broad spectrum of activity against most gram negative and most gram positive organisms with variable activity against streptococcus and anaerobic species.

Second generation fluoroquinolones

They were used as a monotherapy in the treatment of bacterial keratitis. Studies have shown that monotherapy with ciprofloxacin 0.3% and ofloxacin 0.3% are equal in efficacy to the above described conventional therapy in the treatment of bacterial keratitis.[18,19,54-57] Antibiotic resistance of staphylococcus aureus[57] and pseudomonas aeruginosa[58] keratitis isolates to second generation fluoroquinolones (FQs) has increased the interest in the fourth generation fluoroquinolone for future coverage of bacterial keratitis.

Fourth generation fluoroquinolones

Recently fourth generation FQ – Moxifloxacin and gatifloxacin have been introduced. These new ocular antibiotic formulations have improved potency and have been shown to inhibit growth of organisms resistant to second and third generation agents. Moxifloxacin exhibits the broad spectrum bactericidal activity.[59-61] It has also been shown to have superior activity compared with ciprofloxacin against quinolone resistant strains of staph aureus.[62]

Mechanism of action of fourth generation FQs[24,25]

Fourth generation FQs inhibit both bacterial DNA gyrase and DNA topoisomerase IV by forming drug-enzyme-DNA complexes. This prevents uncoiling of the replicated strands of DNA, resulting in the inhibition of DNA replication and death of the bacterium. The DNA gyrase is the target in organisms, such as M. tuberculosis, H. pylori and T. pallidum which represents a group of bacteria with genomes that lack a gene encoding topoisomerase IV. In gram negative organisms DNA gyrase is more sensitive than topoisomerase IV to FQs and is considered to be the primary target. The general target in gram positive organisms is topoisomerase IV. The gyrase in these organisms is less sensitive to FQs than in gram negative bacteria. Since fourth generation FQs acts on both enzymes and they have broader antibiotic spectrum.

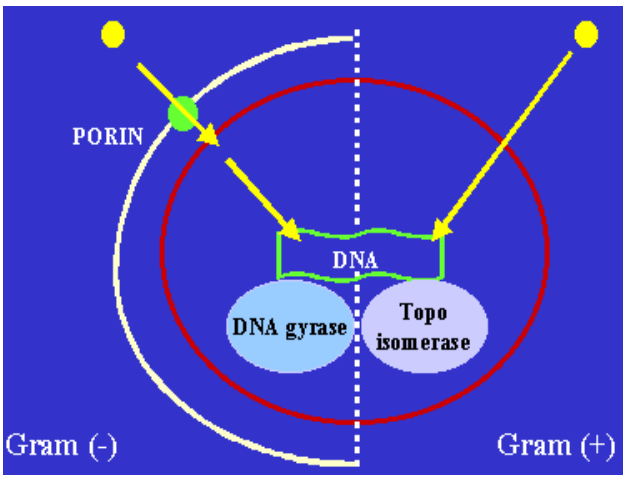


Fig. 2. Fluoroquinolones - Mechanism of action

Mechanism of resistance of fourth generation FQs[24,25]

Change in enzyme targets: Resistance in gram negative bacteria occurs typically as a result of alterations in DNA gyrase either in the GyrA or GyrB subunit, the former being more common. Resistance in gram positive bacteria occurs typically as a result of alterations in topoisomerase IV either in the ParC or ParE subunit, the former being more common. Topoisomerase mutations have been studied in gram negative bacteria and are believed to play a secondary role in development of resistance as ParC or ParE mutations typically confer resistance only in the presence of concomitant DNA gyrase mutations.

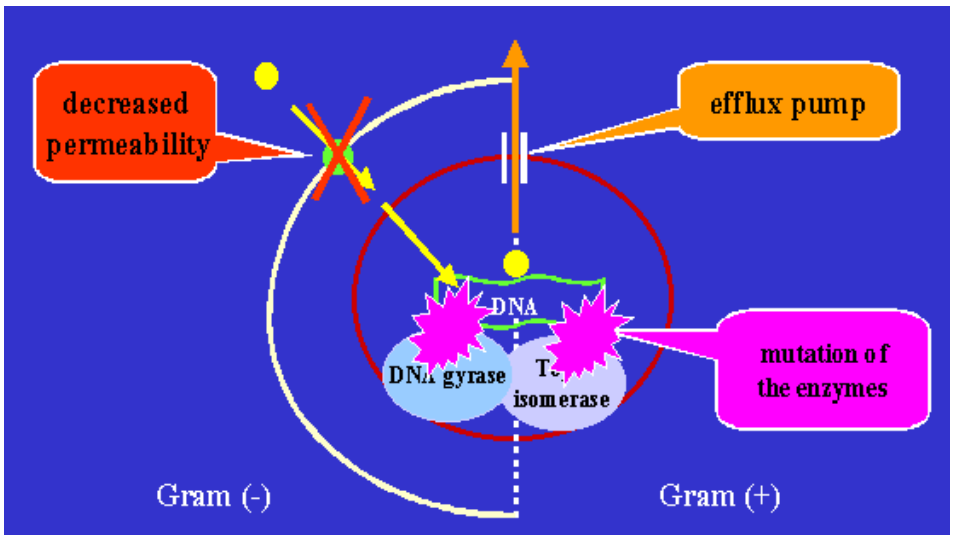


Fig. 3. Fluoroquinolones - Resistance

Production of gyrase protection protein: A plasmid mediated gyrase protecting protein primarily found in gram negative bacteria protects DNA gyrase from FQs. This has been described with Klebsiella pneumoniae.

Decreasing cell permeability: In gram negative organisms decreased levels of porins in outer membrane reduces the accumulation of FQs in cytoplasm.

Efflux pumps: Bacterial efflux pump contribute to bacterial resistance by preventing the accumulation of lethal level of the FQs. However, moxifloxacin has a bulky C_7 side chain which prevents the efflux of the antibiotic from the organism.

Thus fourth generation FQs have less chance of developing bacterial resistance. However, mutations that confer resistance to second or third generation FQs also lower susceptibility to fourth generation of FQs.

Pharmacokinetics and pharmacodynamics of fourth generation FQs

Studies have shown that fourth generation FQs achieve higher concentration in tear film, aqueous humour, vitreous and for prolonged duration, with moxifloxacin being better than gatifloxacin. Also these levels are several folds higher than the MICs of most ocular isolates causing keratitis. Moxifloxacin in addition is lipophilic and has good solubility at physiological pH which gives it good penetration across the cornea. Fourth generation FQs do not cause significant change in the corneal epithelial or endothelial characteristics.[24-26]

These antibiotics are available commercially. Gatifloxacin is available as 0.3% formulation with pH near 6.0 with (0.005%) benzalkonium chloride as the preservative while moxifloxacin is available in preservative free solutions it is commercially available as 0.5% solution pH 6.8. These solutions are stable and having long shelf life.[63,64]

Moxifloxacin exhibits a broad spectrum of bactericidal activity[59-61] against both gram positive and gram negative bacterial pathogens, including

staphylococci, S. pneumoniae, members of the family enterobacteriaceae, P. aeruginosa, H. influenza and Moraxella species. Moxifloxacin has also been shown to have superior activity compared with ciprofloxacin against quinolone resistant strains of S. aureus.[62]

Since the introduction of fluoroquinolones in 1991 in ophthalmology, they have been used widely. Due to their efficacy and broad spectrum action they were used in the treatment of bacterial keratitis as monotherapy.

Studies related to use of 2nd generation FQs in bacterial keratitis

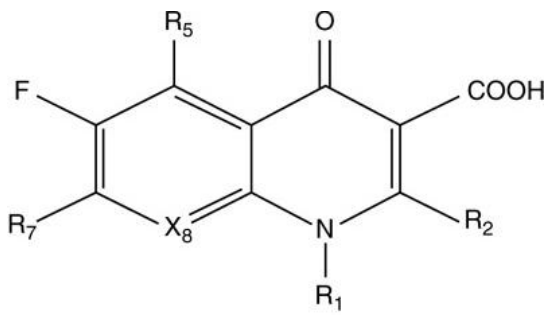


Fig 4: Chemical structure of Fluoroquinolone

A non randomized, multicentre prospective case series[18] compared the safety and efficacy of ciprofloxacin 0.3% ointment with conventional therapy in the treatment of culture positive bacterial corneal ulcer. Out of total 253 eligible patients, 145 (57%) patients were treated with ciprofloxacin ointment 0.3% instilled every one to two hours for the initial two days and then every four hours for 12 days. The rest received conventional therapy with cefazolin and tobramycin. Clinical success with the initial treatment occurred in 135 patients (93%) in the ciprofloxacin ointment group and in 28 patients (70%) in the non enrolled group. No serious adverse event attributable to ciprofloxacin ointment

occurred, although 32 (13%) of 253 patients developed a transient white crystalline corneal precipitate. The study concluded that ciprofloxacin ophthalmic ointment is an effective and safe topical antimicrobial agent for the treatment of bacterial keratitis caused by susceptible microorganisms .

In a similar study[55] the authors did not find any remarkable difference between the control group (cefazolin 50 mg/ml and fortified gentamycin sulphate 9.1mg/ml) and the ciprofloxacin treated group regarding patient age, risk factors, need for hospitalization and virulence of organism isolated. The average time to healing in culture positive ciprofloxacin treated patients was 34 ± 33 days Vs 45±71 days in the control group and this difference was not statistically significant. The study concluded that ciprofloxacin appears to be an effective single agent in the treatment of ulcerative keratitis.

A prospective multicenter study[19] was conducted to compare ofloxacin 0.3% solution with a combination of fortified antibiotics (1.5 % tobramycin and 10% cefazolin) in 248 enrolled patients with an eye with suspected bacterial keratitis. A positive bacterial culture was obtained in 140 (56%) of the 248 enrolled patients. The time to healing was similar among the 73 patients receiving ofloxacin and 67 patients receiving fortified antibiotics.Patients receiving ofloxacin reported substantially less burning and stinging on instillation than the patients receiving fortified antibiotics . The study concluded that, the efficacy of the ofloxacin solution in treating bacterial keratitis is equivalent to that of the fortified cefazolin and tobramycin solutions. The reduced frequency of ocular toxic effects and the relative ease of preparation of the ofloxacin were additional considerations.

Another study[57] found no statistically significant treatment differences in the treatment of 324 bacterial corneal ulcer patients between ciprofloxacin (91.5%) and standard therapy (fortified tobramycin 1.3% and cefazolin 5%) (86.2%) in terms of all overall clinical efficacy, resolution in terms of clinical signs and symptoms or the time to cure . The incidence of treatment failure was less in the ciprofloxacin group (8.5%) compared with the standard treatment group (13.8%). Significantly fewer patients treated with ciprofloxacin reported discomfort than did patients treated with the standard therapy regimen.

Another study[54] showed no significant treatment difference between FQ and fortified therapy in terms of final visual outcome. However, serious complications such as corneal perforation, evisceration or enucleation of the affected eye were more common with the FQ therapy (16.7%) compared with the fortified therapy (2.4%, p=0.02).The study concluded that monotherapy with FQ eyedrops for the treatment of the bacterial corneal ulcers led to shorter duration of intensive therapy and shorter hospital stay compared with the combined the fortified therapy .This finding may have been resulted from quicker clinical response of healing as a result of less toxicity found in the patients treated with FQ. However, as some serious complications were encountered more commonly in the FQ group, they advised cautious use of FQ_s in large, deep ulcers and in the elderly.

A study[56] enrolled 217 bacterial corneal ulcer patients of which 112 were treated with ofloxacin and 105 were treated with ciprofloxacin. Complete corneal re-epithelialization occurred in 85%of those treated with ofloxacin and in 77% of those treated with ciprofloxacin .The average time to corneal ulcer healing was

13.7 days in those treated with ofloxacin and 14.4 days in those treated with ciprofloxacin .Both treatments were well tolerated with no patient discontinuing the study because of side effects. The authors concluded that ofloxacin 0.3% and ciprofloxacin 0.3% ophthalmic solutions were effective and safe in the treatment of patients with culture positive bacterial keratitis.

According to the above studies advantages of these second generation FQs monotherapy include:[18,19,54-57]

- Commercially available formulations, hence easy to dispense.
- Less contamination, longer shelf life.
- Better acceptance by patients, hence better compliance.
- Shorter time to healing of corneal ulcer hence faster rate of recovery.
- Shorter duration of intensive therapy.
- Shorter hospital stay, less cost.

Cautious use of second generation of FQs particularly ofloxacin has been advised due to possible increased risk of enucleation ,evisceration and perforations when they have been used as monotherapy.[9,54,65]

Studies showing increased resistance to second generation fluoroquinolone

A retrospective study[22] on 1558 corneal isolates showed that, 478 (30.7%) were not sensitive to ciprofloxacin. Among the isolates, 355 (32.5%) of the 1091 gram positive cocci were not sensitive to ciprofloxacin, and 2 (10%) of the 20 gram positive bacilli, 22 (13.3%) of the 165 gram negative organisms, and 99 (35.1%) of the 282 Actinomycetes and related organisms were not sensitive to

ciprofloxacin. Results showed a trend of significantly increasing ciprofloxacin insensitivity in bacteria between 1992 and 1997 (p=0.011).This was the first report of significantly increasing ciprofloxacin insensitivity among corneal pathogens.

A retrospective observational case series[23] of 1053 ocular isolates from 825 cases were subjected to in vitro susceptibility testing to ciprofloxacin and ofloxacin by the Kirby-Bauer disk diffusion method. Resistance of Staphylococcus aureus to ciprofloxacin significantly increased annually from 5.8% in 1993 to 35.0% in 1997 and for ofloxacin from 4.7% to 35.0%over the same period . Streptococcus species and coagulase negative Staphylococcus species showed significant resistance to both FQ_S but no change in resistance over the study period. The gram- negative organisms showed good susceptibility to the FQs. The study concluded that, there was significant increased resistance of Staphylococcus aureus to the FQ_S from 1993 to 1997.In addition, gaps in FQ coverage for Streptococcus and coagulase negative Staphylococcus species was of concern for the use of monotherapy in treating bacterial keratitis.

Recently fourth generation FQ_S have been introduced such as gatifloxacin and moxifloxacin. They may be of more rational choices as shown by the following studies.

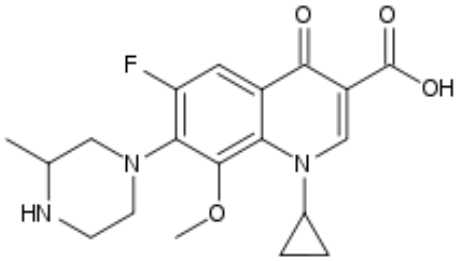


Fig 5: Gatifloxacin : Chemical structure.

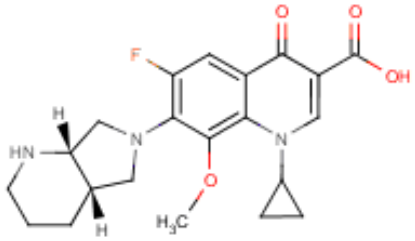


Fig 6: Moxifloxacin : Chemical structure

Studies regarding in vitro activity of fourth generation FQs

A study[66] was conducted to compare the in vitro activity of moxifloxacin with that of 15 antibacterial agents against 513 gram positive microorganisms. The MIC 90 (mg/L) of moxifloxacin was 0.06 for quinolone susceptible Staphlococcus aureus and Staphlococcus epidermidis, 0.12 for Streptococcus pyogenes and Streptococcus agalactiae; 0.25 for Streptococcus pneumoniae, Streptococcus mitis, Streptococcus bovis, Streptococcus anginosus and Actinomyces pyogenes; 0.5 for Streptococcus sanguis and Listeria monocytogenes, two for Cornybacterium jekeium and Bifidobacterium bivius. Moxifloxacin and Trovafloxacin demonstrated comparably high activity towards Gram positive cocci; moxifloxacin and clinafloxacin were most active against

Gram positive bacilli. They concluded moxifloxacin showed better results than other antimicrobials against gram positive isolates.

In a study[67] authors compared the in-vitro susceptibility patterns and minimum inhibitory concentration (MIC_S) of gatifloxacin (GAT), and moxifloxacin (MOX) to ciprofloxacin (CIP), ofloxacin (OFX) and levofloxacin (LEV) using bacterial keratitis isolates. In retrospect, the MIC_S of 177 bacterial keratitis isolates were determined to CIP, OFX, LEV, GAT and MOX using E tests. A relative susceptibility analysis was performed for each bacterial group. The MICs were compared statistically. The study concluded that,

- In most isolates there were no susceptibility differences among five FQs
- The fourth generation FQs did demonstrate increased susceptibility for Staphylococcus aureus isolates that were resistant to CIP, LEV and OFX
- CIP demonstated the lowest MIC_S for gram negative bacteria
- The MIC_S for fourth generation FQs were statistically lower than the second generation FQs for all gram positive bacteria tested
- Comparing the two fourth generation FQs, MOX demonstrated lower MICs for most gram positive bacteria ;whereas GAT demonstrated lower MICs for most gram negative bacteria. Based on these the study concluded that fourth generation FQs may offer some advantages over those currently available for treatment of bacterial keratitis. Clinical studies are required to confirm these results.

Animal studies of use of 4th generation FQs

An experimental study[68] was conducted to evaluate the aqueous penetration of the fourth generation FQs moxifloxacin and gatifloxacin. Forty eyes of 20 New Zealand white rabbits were divided into two experimental groups. In experiment 1: rabbits (20 eyes), a commercial preparation of topical gatifloxacin 0.3% was administered to nine eyes and moxifloxacin 0.5% to nine eyes; two eyes were served as control. Eyes were dosed according to keratitis protocol; that is, every 15 minutes for four hours. Experiment II rabbits (20 eyes) were dosed according to cataract prophylaxis protocol; that is four times a day for 10 days. In the keratitits dosing protocol, the mean concentration of moxifloxacin in the aqueous (n=9) was 11.057 microg/mL ,which was significantly higher than the mean concentration of gatifloxacin (n=8) was 7.570 microg/mL .In the cataract prophylaxis dosing protocol, the mean aqueous concentration of moxifloxacin (n=6) was 1.745 microg/mL. The mean concentration of gatifloxacin (n=6) was 1.207 microg/mL .The difference was not statistically significant (P=0.359). Higher mean level (x 1.46) of aqueous penetration were achieved with moxifloxacin than with gatifloxacin in the keratitis dosing model. There was no statistically significant difference between the two drugs in the cataract prophylaxis dosing model. Both antibiotics had aqueous levels in excess of the minimum inhibitory concentration for most pathogenic organisms in both models.

In another experimental study[69] on a rabbit keratitis model to qualitatively compare the effectiveness of moxifloxacin, levofloxacin, ciprofloxacin for the treatment of Staphylococus aureus isolates of diverse antibiotic susceptibilities.

Early treatment of rabbit eyes infected with ofloxacin – sensitive MRSA demonstrated that moxifloxacin, levofloxacin, ciprofloxacin reduced the number of Staphylococus aureus equally by approximately 5-log (Colony forming unit) CFU/cornea as compared to the untreated control group. Late treatment of infected rabbit eyes with moxifloxacin or levofloxacin, ciprofloxacin produced approximately 5, 4 or 2.5–log reduction in CFU/cornea, respectively relative to the control group. Early treatment of rabbit eyes infected with ofloxacin – resistant MRSA with moxifloxacin or levofloxacin, or ciprofloxacin produced approximately 4.5, 3.5, or 0.5-log reductions in CFU/cornea, respectively, relative to the untreated eyes. Late treatment of the infected rabbit eyes with either levofloxacin, or ciprofloxacin did not produce significant reductions in CFU relative to the untreated control. During late treatment, only moxifloxacin was able to significantly reduce the CFU/cornea as compared to the untreated group. Moxifloxacin was shown to be the most effective therapy demonstrating its activity in both the early and later treatment schedules.

Clinical studies on use of fourth generation FQs

A double masked clinical study[70] in which 52 patients undergoing cataract surgery were given preoperative topical gatifloxacin 0.3% (Zymar), moxifloxacin 0.5% (Vigamox), or ciprofloxacin 0.3% (Ciloxan). The patients were instructed to use their antibiotic drops 4 times a day for 3 days before surgery. On the day of surgery, patients were given their assigned antibiotics every 15 minutes for 3 doses,1 hour before their procedure. Mean aqueous concentration of gatifloxacin in 16 eyes was 0.63 microg/mL (standard deviation {SD}0.30); moxifloxacin in 14 eyes was 1.31 microg/mL (SD, 0.46), and the mean concentration of

ciprofloxacin in 22 eyes was 0.15 microg/mL (SD, 0.11). Thus both moxifloxacin ($p<0.001$) and gatifloxacin ($p<0.005$) penetrated the aqueous humour at significantly higher levels than ciprofloxacin. Moxifloxacin penetrated into the aqueous humour at significantly higher levels than gatifloxacin ($p<0.05$). The anterior chamber levels of moxifloxacin and gatifloxacin may be due to the difference in antibiotic concentration.

In a double masked randomized fellow eye comparison study[71] gatifloxacin 0.3% was instilled in one eye and moxifloxacin 0.5% in the other eye either four times a day for seven days or hourly for 10 hours. Before and after dosing, all eyes were examined with a slit lamp and the cell layers in the central cornea were evaluated by confocal microscopy. There was no statistically significant increase in the incidence or severity of superficial punctate keratitis following use of gatifloxacin 0.3% or moxifloxacin 0.5% when instilled four times a day for seven days or hourly for 10 hours. Hourly use of gatifloxacin 0.3% for 10 hours resulted in mild but statistically significant increase in conjunctival hyperemia ($p=0.029$). Use of moxifloxacin 0.5% resulted in a small but statistically significant deterioration of the corneal epithelial surface as assessed by confocal microscopy ($p=0.045$). The incidence of subject discomfort with study drop instillation was comparable for the two antibiotics ($p=0.67$). Thus the use of the ophthalmic solution of the gatifloxacin 0.3% or moxifloxacin 0.5% did not result in clinically significant epithelial toxicity in healthy human corneas after dosing regimens of four times a day for seven days or hourly for 10 hours dosing regimens.

A prospective, randomized clinical trial[72] which showed that gatifloxacin exhibited a significantly better action than ciprofloxacin against gram positive cocci in vitro ($p<0.001$) and percentage of ulcers caused by these pathogens that healed in the gatifloxacin group was significantly better than in the ciprofloxacin group ($p=0.009$). Mean time taken for healing of ulcer and the efficacy against gram negative bacteria did not differ in the two group significantly. In view of this the study concluded that the gatifloxacin may be a preferred alternative to ciprofloxacin as the first line monotherapy in the treatment of bacterial keratitis.

In a study[73] authors compared five independent, multi-centered, double masked, parallel, controlled studies to determine the safety of moxifloxacin 0.5% in paediatric and non- paediatric patients with bacterial conjunctivitis. They were treated with moxifloxacin 0.5% twice or thrice a day. A total of 1978 (918 paediatric and 1060 non-paediatric) were evaluated. The most frequent adverse event was transient ocular discomfort (2.8%) which was similar to that observed with the vehicle. No treatment related changes in ocular signs or visual acuity were observed. The study concluded that moxifloxacin 0.5% without the preservative benzalkonium chloride is safe and well tolerated.

Thus a review of literature, makes it clear that fourth generation fluoroquinolones have proven advantages above the earlier generation, as regards to its in vitro action as well as its action in bacterial keratitis models. Its clinical efficacy and safety in the treatment of bacterial keratitis is yet to be understood completely.

METHODOLOGY

The present study was conducted in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010.

Study design

One year randomized controlled trial.

Source of Data

Patients with suspected Bacterial corneal ulcer attending Out Patient and In patient Department at Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum attached to Jawaharlal Nehru Medical College, Belgaum.

Study Period

One year from January 2010 to December 2010.

Sample Size

Out of 87 cases screened, 60 patients with suspected bacterial corneal ulcer were deemed eligible to participate in the study, and divided into two groups using computer generated randomization.

Sampling procedure

Based on the 80% average of last two years hospital statistics of cases with corneal ulcer. Hospital statistics show 75 cases of corneal ulcer on an average for the past two years and 80% of the same is calculated as 60 patients.

Selection criteria

Inclusion criteria

- All cases of clinically suspected bacterial corneal ulcer.
- Ability to complete three week follow up.
- All antibiotic resistant cases showing clinical improvement in ulcer healing.

Exclusion criteria

- Fungal ulcer.
- Acanthamoeba.
- Viral keratitis.
- Trophic ulcer associated with herpes zoster.
- Mooren ulcer.
- Chronic exposure keratitis
- Hypersensitivity to any of trial drug.
- Not willing to participate in the study.

Randomization

Patients were randomly allocated into one of the two groups using computer generated randomization that is Group A (n=30; received monotherapy with Moxifloxacin) and Group B (n=30; received combination therapy with Tobramycin + Cefazolin). After the enrollment patients were treated according to the group assigned.

Procedure

Prior to the commencement of study ethical clearance was obtained from Institutional Ethics Committee. Based on the selection criteria, patients with suspected bacterial corneal ulcer attending out patient department at Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were screened for eligibility. The selected patients were briefed about the study nature and a written informed consent (Annexure I) was obtained. Patients were randomly allocated into two groups namely, Group A and Group B. Data was collected and findings were recorded on predesigned and pretested proforma (Annexure II).

Ulceration was defined as a loss of the corneal epithelium with underlying stromal infiltration and suppuration associated with signs of inflammation with or without hypopyon.[31] A detailed history was taken with special reference to;

- Socio-demographic information of the patient
- Clinical information including duration of symptoms, previous treatment, predisposing ocular conditions and associated risk factors.

- The visual acuity was measured by the Snellen's chart.

Complete initial ocular examination was carried out under slit lamp biomicroscope .The size of the ulcer was measured after staining with wet sterile fluorescein paper strip using the variable slit on the biomicroscope and recorded in millimeters, with special attention paid to the characteristics of ulcer in terms of:

- Site, size, margins, floor and depth of ulcer.
- Size and depth of the stromal infiltrate.
- Presence or absence of hypopyon and its measurement.
- AC reaction.
- Associated uveitis.
- Associated risk factors such as blepharitis, dacryocystitis, dry eyes etc.

After detailed ocular examination, grading of the corneal ulcer was done using the criteria of Jones.[74]

Feature	**Non severe**	**Severe**
Suppuration Area Depth	 ≤ 6 mm Superficial two-thirds	 > 6 mm Deeper third
Rate of progression	Slow, moderate	Rapid
Depth of ulcer	Superficial two-thirds	Deeper one-third
Scleral suppuration	Not present	May be involved
Perforation	Unlikely to occur	Present, imminent

Severe - when three or more of the criteria are met.

Clinical procedure

Corneal scraping was performed under strict aseptic conditions using a sterile 15 No.(number) Bard Parker Blade.[31,44,45] The procedure was performed under magnification of a slit lamp following instillation of 4% lignocaine hydrochloride. Scraping was taken from the base and progressive edge of the ulcer. Material obtained from scraping was inoculated onto the culture media in a "C-streaked" pattern. These media were blood agar, chocolate agar and sabourauds dextrose agar.

The scraping was repeated several times using a fresh blade for each scrape. The scraped material was also smeared on two glass slides, one stained with Gram's stain and the other with 10% Potassium hydroxide (KOH) wet mount, for direct microscopic evaluation.[31,44,45] Smear reports were obtained from the laboratory as early as possible. Samples with a negative KOH wet mount result were considered to be bacterial in nature.

Laboratory procedures

Bacterial cultures were incubated aerobically at 37^0 C. Cultures on blood agar and chocolate agar were evaluated at 24 hours and 48 hours and then discarded if no growth was seen. For fungal cultures materials were inoculated on to Sabourauds dextrose agar (SDA) and incubated at room temperature, examined daily and discarded at two weeks if no growth was present.

Microbial cultures were considered significant only if growth of the same organism was isolated on both solid media, or there was semi-confluent growth at

the site of inoculation (at least two "C" streaks) on one media with the identification of morphological characteristics of similar organism on Gram stain.[31,44,45,48] The specific identification of bacterial pathogens was based on microscopic morphology, staining characteristics and biochemical properties using standard laboratory criteria. After taking corneal scrapings patient was advised to put one drop of the respective study treatment. Antibiotic sensitivity was done using Kirby-Bauer disk diffusion method.

For patients who were on prior antibiotic therapy, their antibiotics were stopped for a duration of 12-24 hours, and then their corneal scrapings were undertaken.

If the ulcer failed to respond to the initial therapy or showed signs of progression at the end of 72 hours, the study medication was discontinued and an alternate therapy was instituted. These outcomes were considered as treatment failure.

The patency of the nasolacrimal duct was evaluated by syringing in all cases, and patients with nasolacrimal duct obstruction underwent dacryocystectomy.

Documentation of the corneal ulcer was done by taking anterior segment photographs and using detailed schematic drawings.

Study medications

(Initially, it was thought that we would use commercially available 0.3% Tobramycin. However, fortified Tobramycin (1.3%) was used due to its proven

efficacy.) Cefazolin (5%) drops were freshly prepared by mixing sterile water to a vial of cefazolin 500 mg (powder for injection) to make up a 10ml solution, and given to the patient. Drops were discarded after 7 days or any change in color whichever came early[75,76]

Fortified Tobramycin (1.3%) was prepared by injecting 2 ml of tobramycin (40 mg/ml) injection in a 5 ml bottle of commercially available 0.3% tobramycin drops. Drops were discarded after 14 days or any change in color whichever came early.[76]

Moxifloxacin 0.5% commercially available eye drops were used.

Frequency of drug administration[51]

The patients were advised to put one drop of Moxifloxacin each hour round the clock for the initial 48 hours. In the combination group, both the drops were instilled, alternately, hourly, with a gap of five minute between the two drugs.

If a favourable clinical response was observed at Day 3, the medication was tapered. On the third day, one drop was instilled every hour by day and every two hours at night. For days four and five, one drop was instilled every two hours by day, and every four hours at night. For days six and seven, one drop was used every four hours. After Day seven, the drops were tapered to every six hours, and stopped when clinically appropriate.

Adjunct medications were prescribed such as cycloplegics (homatropine bromide 2%), antiglaucoma medications and oral NSAIDs.

Daily evaluation of the ulcer was done till, hospitalized. Then, the follow up was done on weekly basis till the total healing of the ulcer. At each follow up, detailed examination including visual acuity testing and detailed slit lamp biomicroscopic examination was done .The size of the ulcer and infiltrate was noted. The ulcer status was defined as one of the following:[77]

Table 2. Ulcer status

Ulcer status	Definition
Healing ulcer	Ulcer/infiltrate decreasing in size but not completely re-epithelialized
Treatment failure No change in ulcer worsening ulcer	 Ulcer/infiltrate of same size at the end of 72 hours Ulcer/infiltrate increasing in size or evidence of complications like spread of infection, endophthalmitis, ulcer perforation and adverse drug reaction
Healed ulcer	Complete re-epithelialization with no fluorescein staining of cornea

Treatment was discontinued if the ulcer seemed to be healed early. All patients were followed up regularly till the final outcome.

Criteria for favourable clinical response :[78]

1. Blunting of ulcer margin
2. Improvement in signs of inflammation

3. Reduction in infiltrate size and oedema
4. Reduction in AC reaction
5. Decreased pain and other symptoms by patient.

Statistical analysis

The data obtained was tabulated on Microsoft excel spreadsheet and analyzed. The data was expressed in terms of rates, ratios and percentages and analyzed by chi-square test and test of proportion. A probability value ('p' value) of < 0.05 was considered as statistically significant.

RESULTS

The present one year randomized controlled trial was conducted in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010.

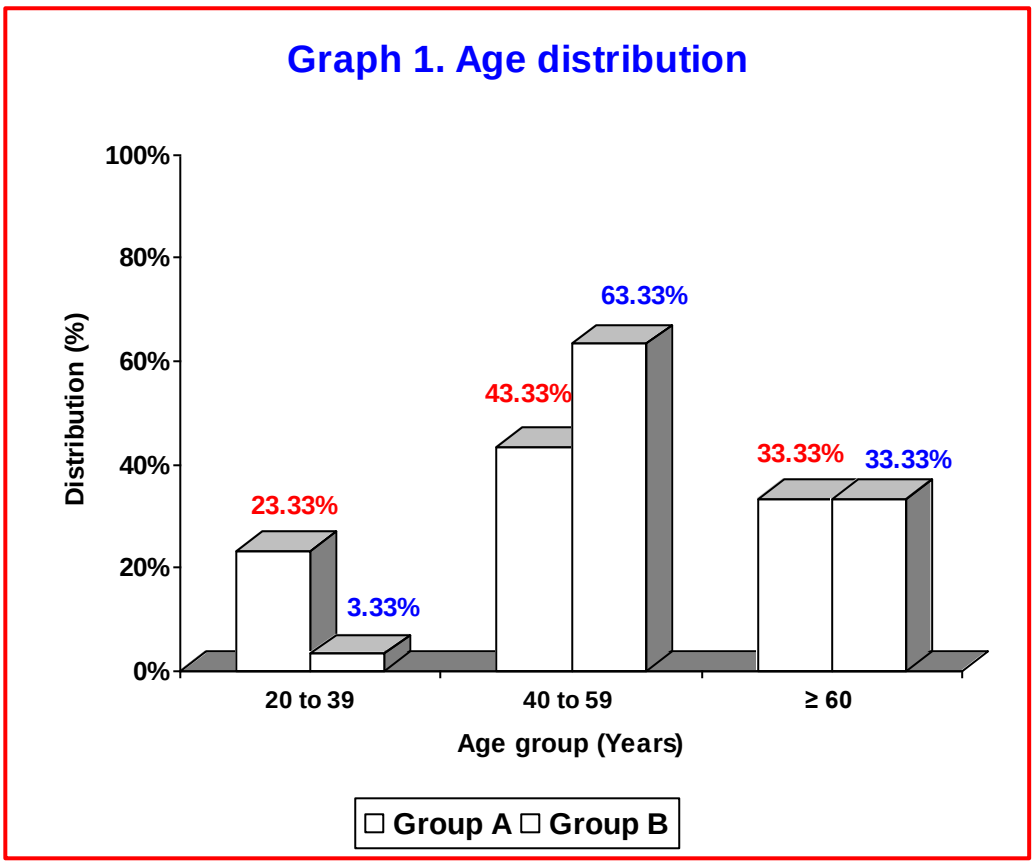
Out of 87 cases screened, 60 patients with suspected bacterial corneal ulcer were deemed eligible to participate in the study. These subjects were randomly allocated into one of the two groups using computer generated randomization that is Group A (n=30; received monotherapy with Moxifloxacin) and Group B (n=30; received combination therapy with Tobramycin and Cefazolin).

The data obtained was tabulated on Microsoft excel spreadsheet and analysed as below.

Table 3. Age distribution

Age group (Years)	Group A (n=30)		Group B (n=30)		Total (n=60)	
	No	%	No	%	No	%
20 to 39	7	23.33	1	3.33	8	13.33
40 to 59	13	43.33	19	63.33	32	53.33
≥ 60	10	33.33	10	33.33	20	33.33
Total	**30**	**100**	**30**	**100**	**60**	**100.00**

x^2=5.625 DF=2; p=0.0601

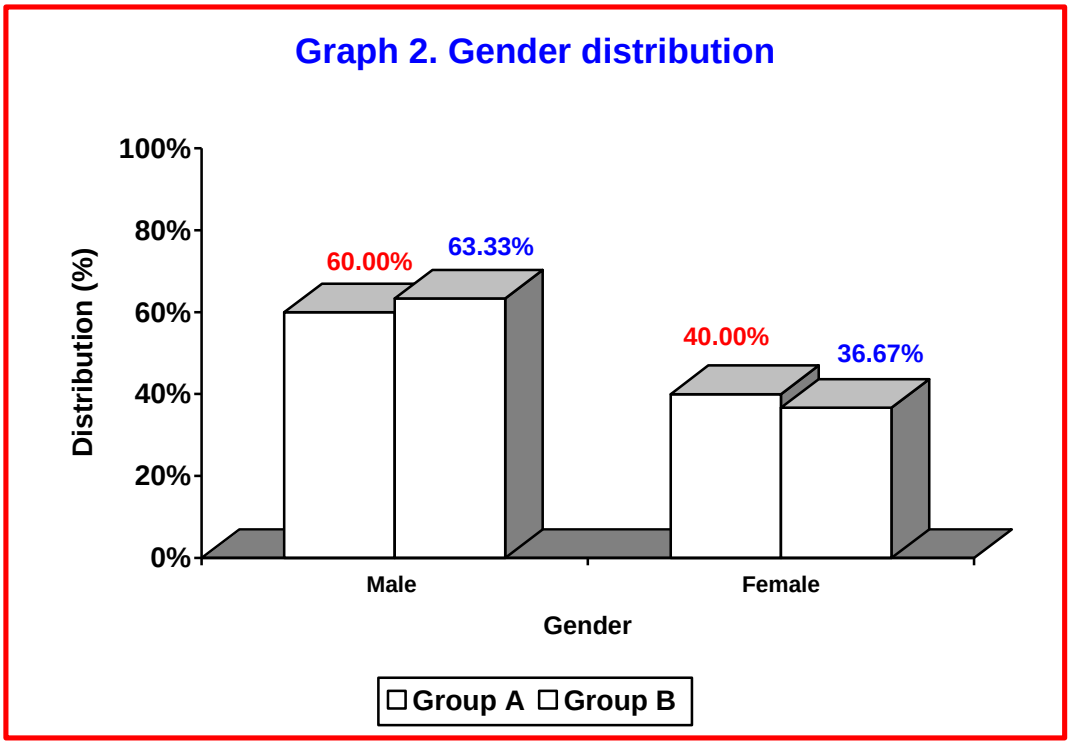


Majority of cases in our study, 32 (53.33%) belonged to the age group of 40–59 years, 20(33.33%) were more than 60 years of age and 8 (13.33%) belonged to the age group of 20 to 39years. Mean age in Group A was 54.37 ± 15.65 years and in Group B was 56.37 ± 10.83 years. However most of the patients (78.33%) had age more than 50 years which was clinically larger as compared to the percentage of age less than 50 years. The two groups were similar with respect to age distribution (p=0.0601)

Table 4. Gender distribution

Gender	Group A (n=30)		Group B (n=30)		Total (n=60)	
	No	**%**	**No**	**%**	**No**	**%**
Male	18	60%.	19	63.33%.	37	61.67
Female	12	40%	11	36.67%	23	38.33
Total	**30**	**100**	**30**	**100**	**60**	**100.00**

x^2=0.0705 DF= 1 p= 0.7906

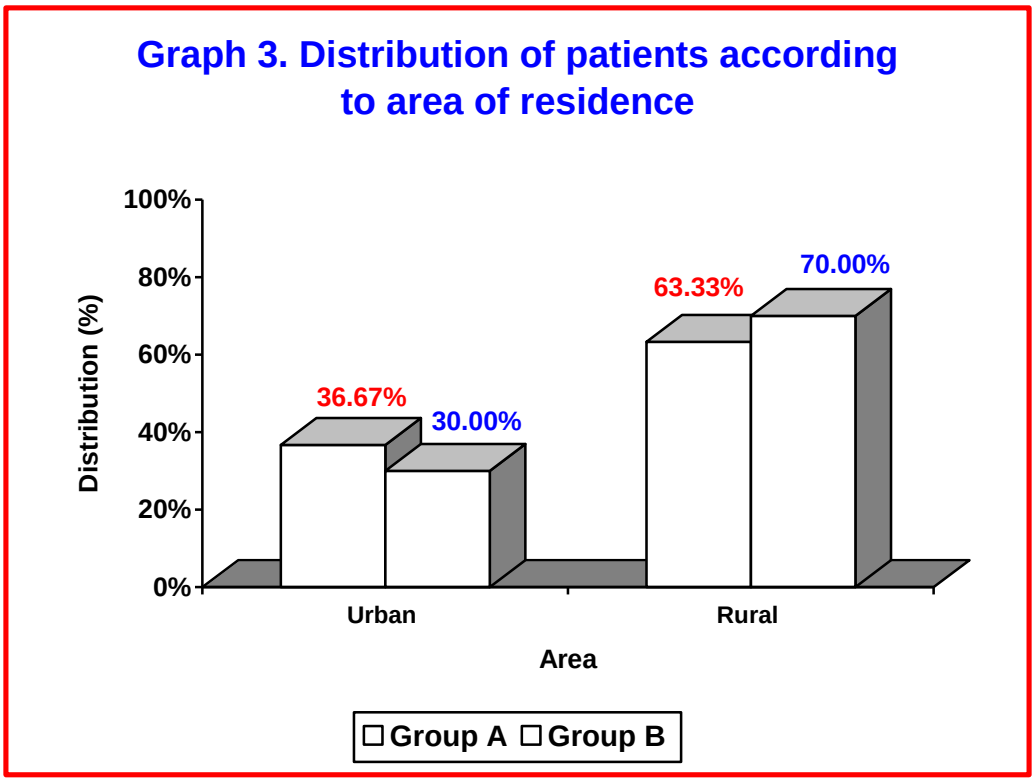


In this study 37 (61.67%) were males. Male predominance was seen with male to female ratio of 1.61:1 Gender distribution was statistically similar (p=0.7906) in between the two groups.

Table 5. Distribution of patients according to area of residence

Area	Group A (n=30)		Group B (n=30)		Total (n=60)	
	No	%	No	%	No	%
Urban	11	36.67	9	30.00	20	33.33
Rural	19	63.33	21	70.00	40	66.67
Total	**30**	**100**	**30**	**100**	**60**	**100.00**

x^2=0.30 DF= 1 p= 0.5839

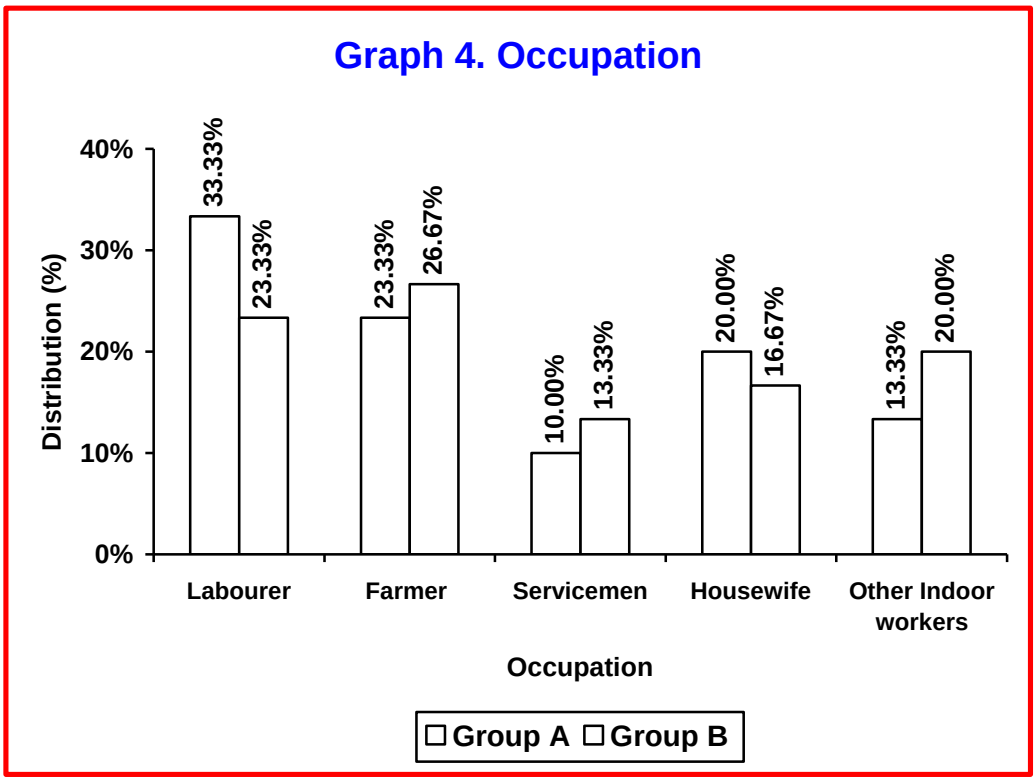


Majority of the patients were from rural population 40 (66.67%). Only 20 (33.33%) patients were from urban population. The distribution between the two groups was statistically similar (p=0.5839).

Table 6. Occupation

Occupation	Group A (n=30)		Group B (n=30)		Total (n=60)	
	No	%	No	%	No	%
Labourer	10	33.33	7	23.33	17	28.33
Farmer	7	23.33	8	26.67	15	25.00
Servicemen	3	10.00	4	13.33	7	11.67
Housewife	6	20.00	5	16.67	11	18.33
Other Indoor workers	4	13.33	6	20.00	10	16.67
Total	**30**	**100.00**	**30**	**100.00**	**60**	**100.00**

x^2=1.2298 DF=1 p= 0.8732



Out of the 60 cases, 17(28.33%) patients were labourers, farmers were 15(25%), followed by housewifes 11(18.3%), servicemen 7 (11.6%) and other indoor workers 10 (16.6%). In this study, the bulk of the study subjects was formed by labourers and farmers 32 (53.3%). No significant association (p=0.4916) was found for the distribution of keratitis between farmers and labourers. The distribution in both the groups was comparable (p=0.8732)

Table 7. Risk factors - Ocular trauma

Ocular Trauma	Group A (n=30)		Group B (n=30)		Total (n=60)	
	No	**%**	**No**	**%**	**No**	**%**
Present	19	63.33	16	53.33	35	58.33
Absent	11	36.67	14	46.67	25	41.67
Total	**30**	**100**	**30**	**100**	**60**	**100**

p=0.2161 (Test of proportion)

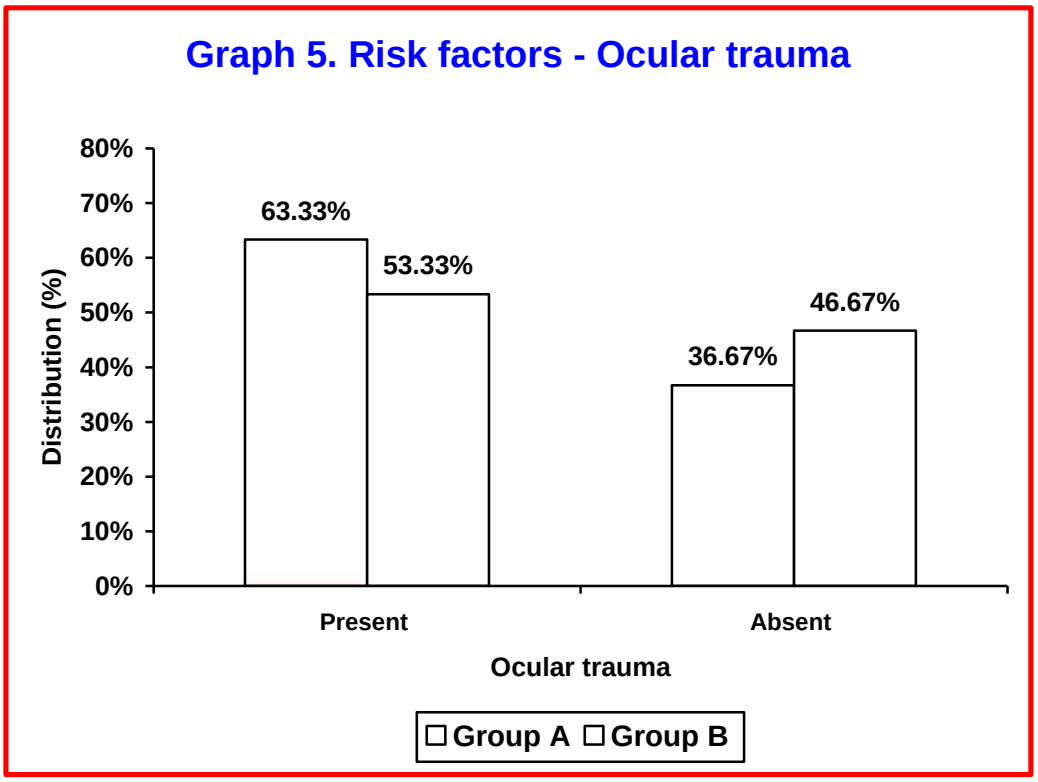
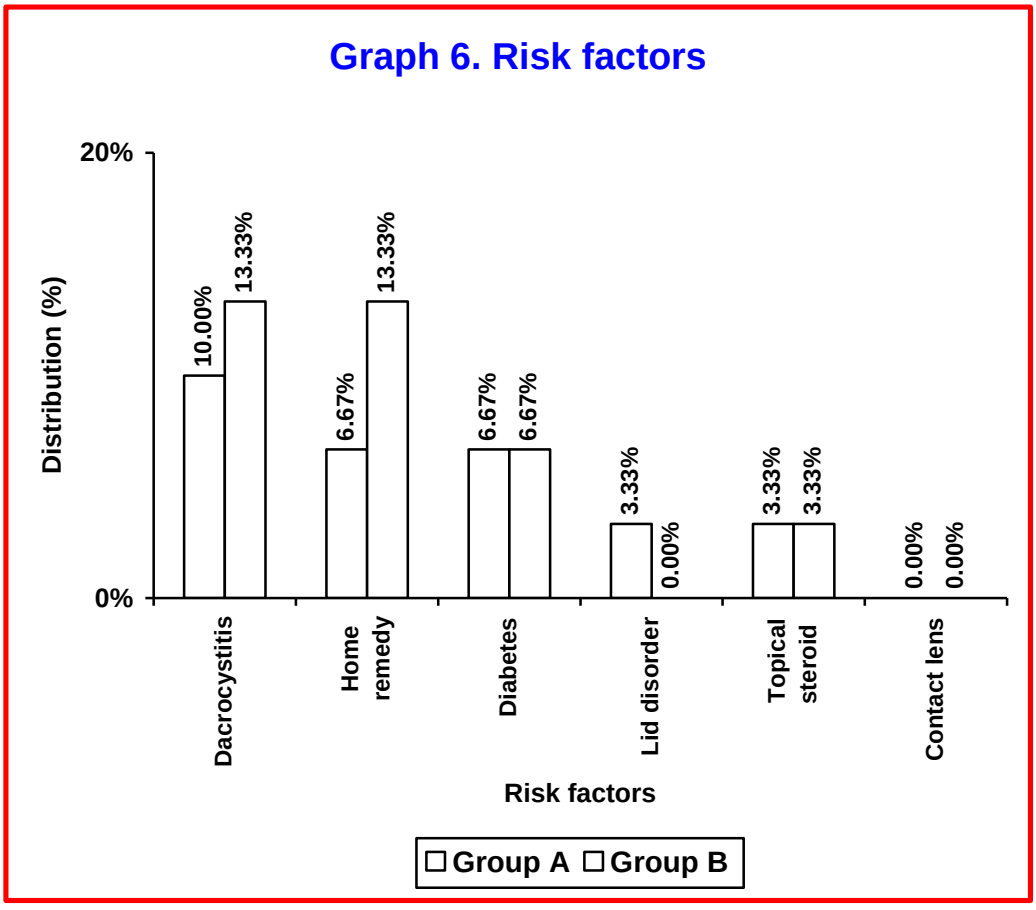


Table 8. Other risk factors

Risk factors	Group A (n=30)		Group B (n=30)		Total (n=60)		'p' value
	No	%	No	%	No	%	
Dacrocystitis	3	10.00	4	13.33	7	11.67	0.3438
Home remedy	2	6.67	4	13.33	6	10.00	0.1947
Diabetes	2	6.67	2	6.67	4	6.67	0.50
Lid disorder	1	3.33	0	0.00	1	1.67	0.1566
Topical steroid	1	3.33	1	3.33	2	3.33	0.50
Contact lens	0	0.00	0	0.00	0	0.00	-

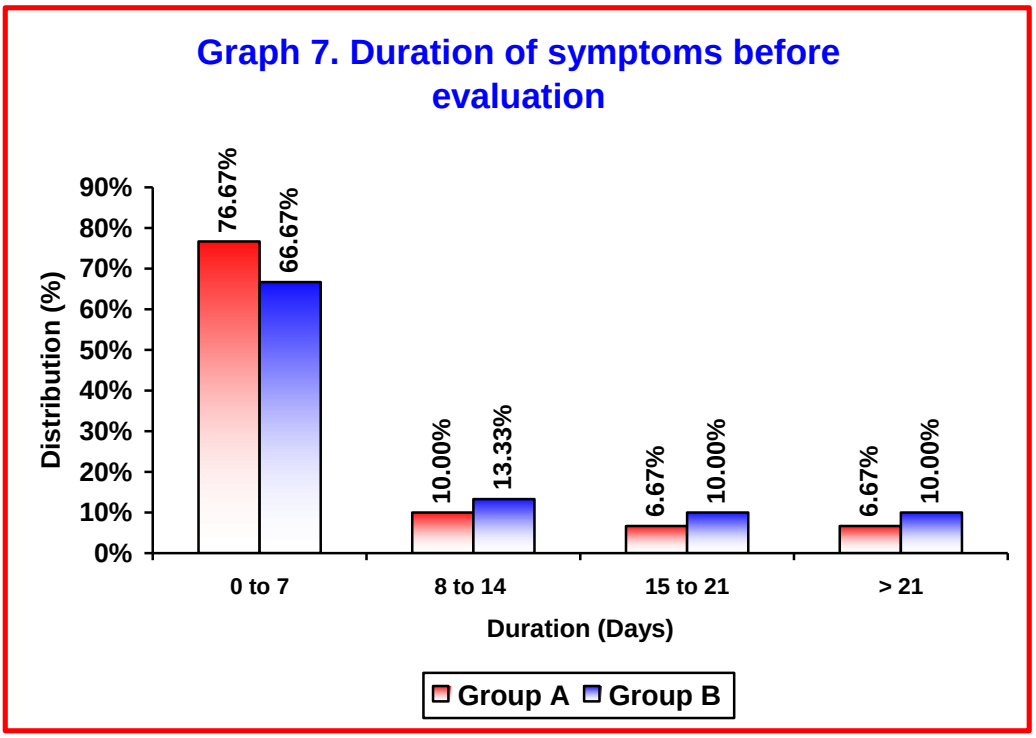


Of 60 cases studied, 35 (58.33%) cases gave history of ocular trauma which was the most common risk factor. The distribution in both groups was comparable (0.2161). Dacryocystitis was found to be present in 7 cases (11.67%). Home remedy was used by 6 (10%).Two patients (3.3%) patients were on topical steroids at the time of presentation. The differences in between the two groups with respect to other risk factors like dacryocystitis (p= 0.3438), home remedy (p=0.1947), diabetes (p=0.50), lid disorder (p= 0.1566) and topical steroid (p=0.5) were found to be insignificant (Test of proportion ;p> 0.05).

Table 9. Duration of symptoms before evaluation

Duration (Days)	Group A (n=30)		Group B (n=30)		Total (n=60)	
	No	%	No	%	No	%
0 to 7	23	76.67	20	66.67	43	71.67
8 to 14	3	10.00	4	13.33	7	11.67
15 to 21	2	6.67	3	10.00	5	8.33
> 21	2	6.67	3	10.00	5	8.33
Total	**30**	**100.00**	**30**	**100.00**	**60**	**100.00**

x^2=0.7522 DF=3 p=0.8609



Majority of patients in both the groups presented during first week of the onset of symptoms 43 (71.67%), while 7 (11.67%) subjects presented during the second week and remaining 10 (16.66%) presented after more than two weeks duration. Both groups were similar with respect to the distribution of duration of symptoms (p=0.8609)

Table 10. Visual acuity at initial presentation

Visual acuity	Total cases (n=60)	
	Number	**Percent**
6/5 to 6/9	6	10.00
6/12 to 6/24	10	16.67
6/36 to 6/60	16	26.67
CF to HMCF, PL +	28	46.67
No PL	0	0
Total	**60**	**100.00**

In the present study majority of the patients 28/60 (46.67%) presented with an visual acuity of CF to HMCF, PL +. While 16/60 (26.67%) presented with 6/36 to 6/60, another 10 patients (16.67%) presented with vision between 6/12 to 6/24 and 6 (10%) had vision ranging from 6/5 to 6/9.

Table 11. Ulcer characteristics at time of presentation

Characteristics	Group A (n=30)		Group B (n=30)		Total (n=60)	
	No	**%**	**No**	**%**	**No**	**%**
Location						
Central	16	53.33	18	60.00	34	56.66
Peripheral	10	33.33	10	33.33	20	33.33
Limbal	4	13.33	2	6.67	6	10.00
Severity						
Non Severe	16	53.33	18	60.00	34	56.66
Severe	14	46.67	12	40.00	26	43.33
Vascularization	12	40.00	8	26.67	20	33.33
Hypopyon	16	53.33	12	40.00	28	46.66

$p>0.05$

In this study majority of ulcers were centrally located 34(56.67%) whereas 20 (33.3%) showed peripherally located ulcer. Of the 60 cases, 34(56.67%) had non severe and 26 (43.33%) had severe ulceration at the time of presentation. Hypopyon was present in 28 (46.66%) cases. Vascularization was present in 20 (33.33%). The differences in between the two groups with respect to location ($p=0.6756$), severity ($p=0.6023$) and vascularization of the ulcers ($p=0.2733$), and the presence of hypopyon($p= 0.3006$) were insignificant ($p>0.05$).

Table 12. Lacrimal patency test

Lacrimal passage	Group A (n=30)		Group B (n=30)		Total (n=60)	
	No	**%**	**No**	**%**	**No**	**%**
Obstructed	3	10.00	4	13.33	7	11.67
Patent	27	90.00	26	86.97	53	88.33
Total	**30**	**100**	**30**	**100**	**60**	**100.00**

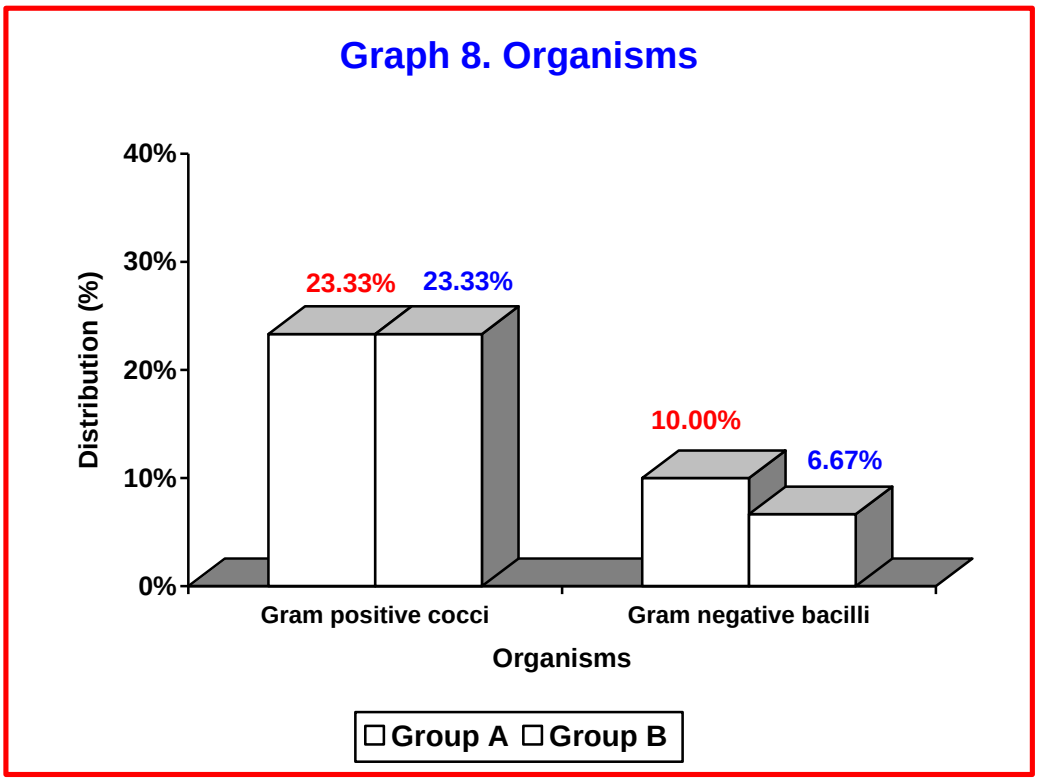
x^2=0.1617 DF=1 p= 0.6876

In the present study, 7/60 cases (11.67%) showed lacrimal passage obstruction. All of these patients underwent dacryocystectomy. The incidence of dacryocystitis in the two groups was comparable (p=0.6876).

Table 13. Gram stain

Gram stain	Group A (n=30)		Group B (n=30)		Total (n=60)	
	No	**%**	**No**	**%**	**No**	**%**
Gram positive cocci	7	23.33	7	23.33	14	23.33
Gram negative bacilli	3	10.00	2	6.67	5	8.33
No organism	20	66.67	21	70.00	41	68.33
Total	**30**	**100**	**30**	**100**	**60**	**100.00**

x^2= 0.2244 DF =2 p=0.8939



Out of the total 19 cases (31.6%), detected on gram staining, 14 (23.33%) were found to be Gram positive cocci and 5 (8.33%) were Gram negative bacilli. There was no statistical difference in the distribution between the two groups (p=0.8939).

Table 14. Culture Isolation

Characteristics	Group A (n=21)		Group B (n=20)		Total (n=41)	
	No	**%**	**No**	**%**	**No**	**%**
Gram positive organism	***19***	***90.48***	***17***	***85.00***	***36***	***87.80***
Staph epidermidis	7	36.84	6	35.29	13	31.70
Staph aureus	5	26.32	2	11.76	7	17
Strept. Pneumoniae	3	15.79	4	23.53	7	17
Strept viridans	3	15.79	4	23.53	7	17
Bacillus	1	5.26	1	5.88	2	4.87
Gram negative organism	***2***	***9.52***	***3***	***15.00***	***5***	***12.1***
Pseudomonas	2	100.00	2	66.67	4	9.75
E Coli	0	0.00	1	33.33	1	2.43

x^2=0.2869 DF=1 p= 0.5922

In the present study, 41 (68.33%) of the patients were culture positive. Out of the total 41 cases detected on culture, 36(87.80%) were found to be Gram positive and 5 (12.1%) were Gram negative. Among Gram positive most commonly isolated organism was Staphylococcus epidermidis13 (31.70%) and among Gram negative most commonly isolated organism was Pseudomonas species 4(9.75%) .The distribution of organisms was similar in both (p=0.5922) groups..

Table 15. Antibiotic resistance

Drug	Resistance (n=41)	
	No	**%**
Moxifloxacin	0	0.0
Tobramycin	1	2.43
Cefazolin	2	4.86

All isolated organisms were tested for antibiotic sensitivity. The results for cefazolin, tobramycin and moxifloxacin are given in the above table. Of the strains tested 2 (4.86%) were resistant to cefazolin and 1 (2.43%) was resistant to tobramycin. All isolates were sensitive to moxifloxacin.

Table 16. Clinical response at day 3

Duration of presentation (Days)	Group A (n=30)			Group B (n=30)		
	Total	**Improved**	**Percent**	**Total**	**Improved**	**Percent**
0 to 7	23	23	76.67	20	20	66.67
8 to 14	3	3	10.00	4	3	10
15 to 21	2	1	3.33	3	2	6.67
> 21	2	2	6.67	3	2	6.67
Total	**30**	**29**	**96.67**	**30**	**27**	**90.00**

Favourable response, was seen in 29(96.67%) cases in Group A and 27 (90%) in Group B. All cases in both groups which presented during the first week of onset of symptoms showed a favourable clinical response at day 3. Out of the subjects who presented during the second week of onset, all improved in Group A and only one case out of four in group B showed deterioration. Those who had presented after more than two weeks, one case was a treatment failure in Group A and two were failures in Group B. Subjects who presented within two weeks of onset of symptoms showed a significantly better clinical response in both groups than those who presented later. ($p=0.0085$ for Group A and $p=0.0332$ for Group B). However, the clinical response at Day 3 in these subjects were similar in both groups, with respect to the duration till presentation. ($p=0.2931$ for subjects presenting within 2 weeks and $p=0.7782$ for those presenting after 2 weeks).

Table 17. Outcome with respect to severity

Outcome		Group A (n=30)		Group B (n=30)	
		Number	**Percent**	**Number**	**Percent**
Severe	Improved	15	93.77	16	88.8
	Not imp	1	6.22	2	11.11
	Total	16	100	18	100
Non severe	Improved	14	100	11	91.66
	Not imp	0	00	1	8.34
	Total	14	100	12	100

Severe ulcer - x^2= 0.01 DF = 1 p=0.9149

Non severe ulcer - x^2 = 0.0062 DF = 1 p=0.9373

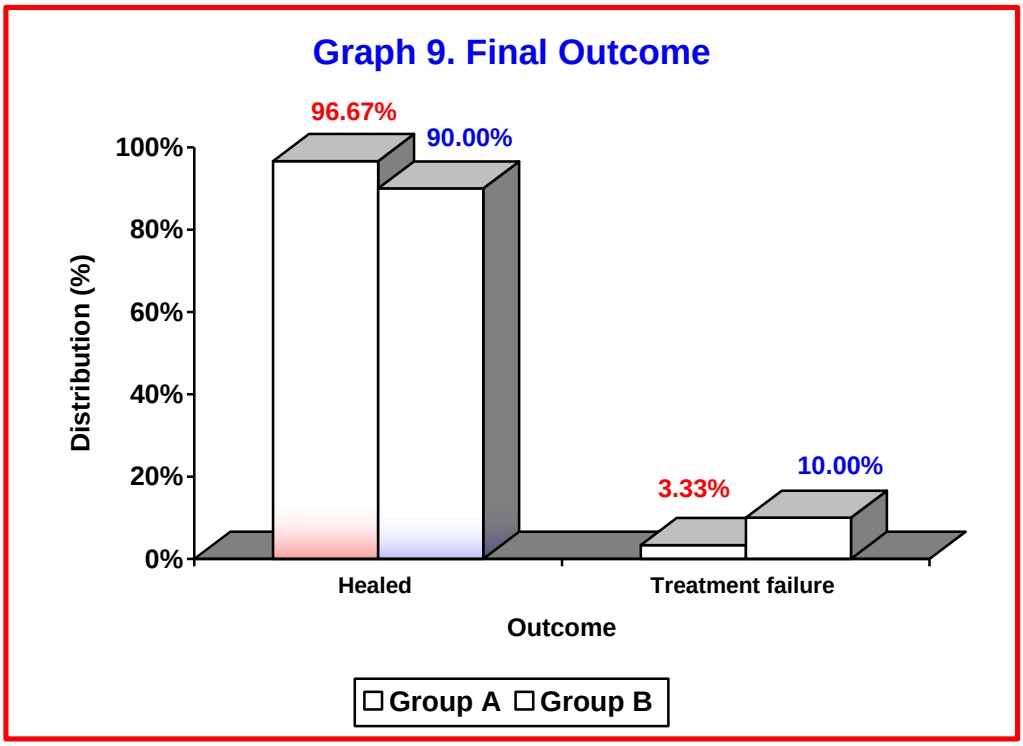
Severe ulcers: 15/16 (93.77%) cases treated in Group A showed improvement and in Group B, 16/18 cases (88.8%) showed improvement .The outcome of severe ulcers in both groups was similar (p= 0.9149).

Non severe ulcers: all 14 cases in Group A and 11/12(91.67%) in Group B, showed improvement. The outcome of non severe ulcers in both groups was similar (0.9373).

Table 18. Final Outcome

Outcome	Group A (n=30)		Group B (n=30)	
	Number	**Percent**	**Number**	**Percent**
Healed	29	96.67	27	90.00
Treatment failure	1	3.33	3	10.00
Total	**30**	**100**	**30**	**100**

x^2=1.0714 DF=1 p= 0.3006

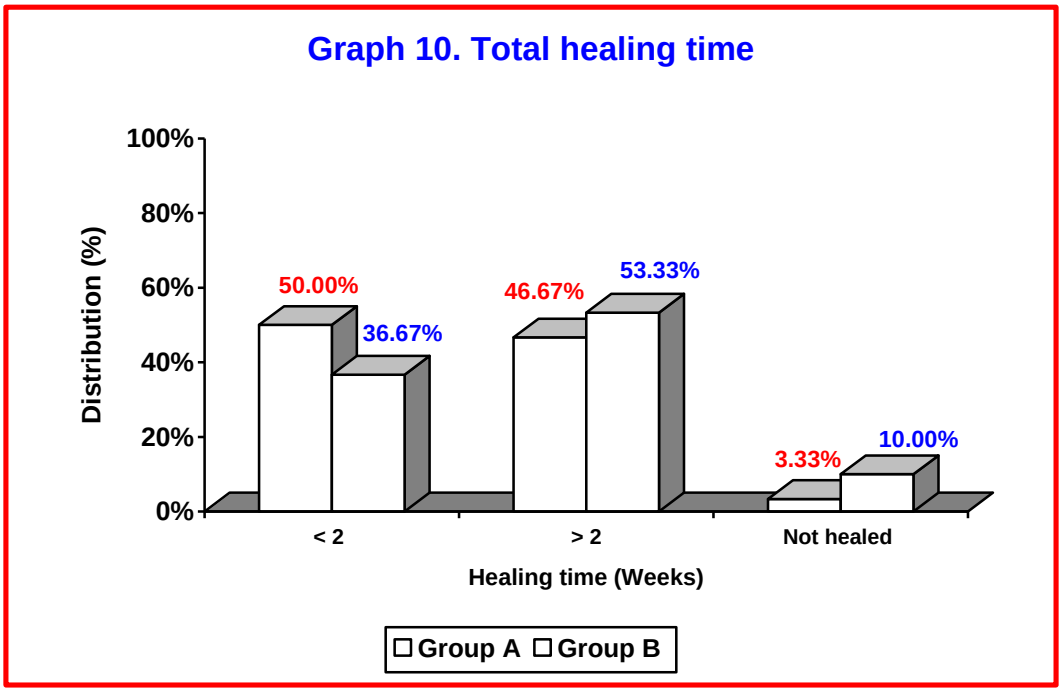


29 (96.67%) cases healed in Group A and 27 (90%) healed in group B. There was no statistical difference in the final outcomes between the two groups (p=0.3006).

Table 19. Total healing time

Total healing time	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
< 2 weeks	15	50.00	11	36.67
> 2 weeks	14	46.67	16	53.33
Not healed	1	3.33	3	10.00
Total	**30**	**100**	**30**	**100**

p= 0.032 (Unpaired 't' test)

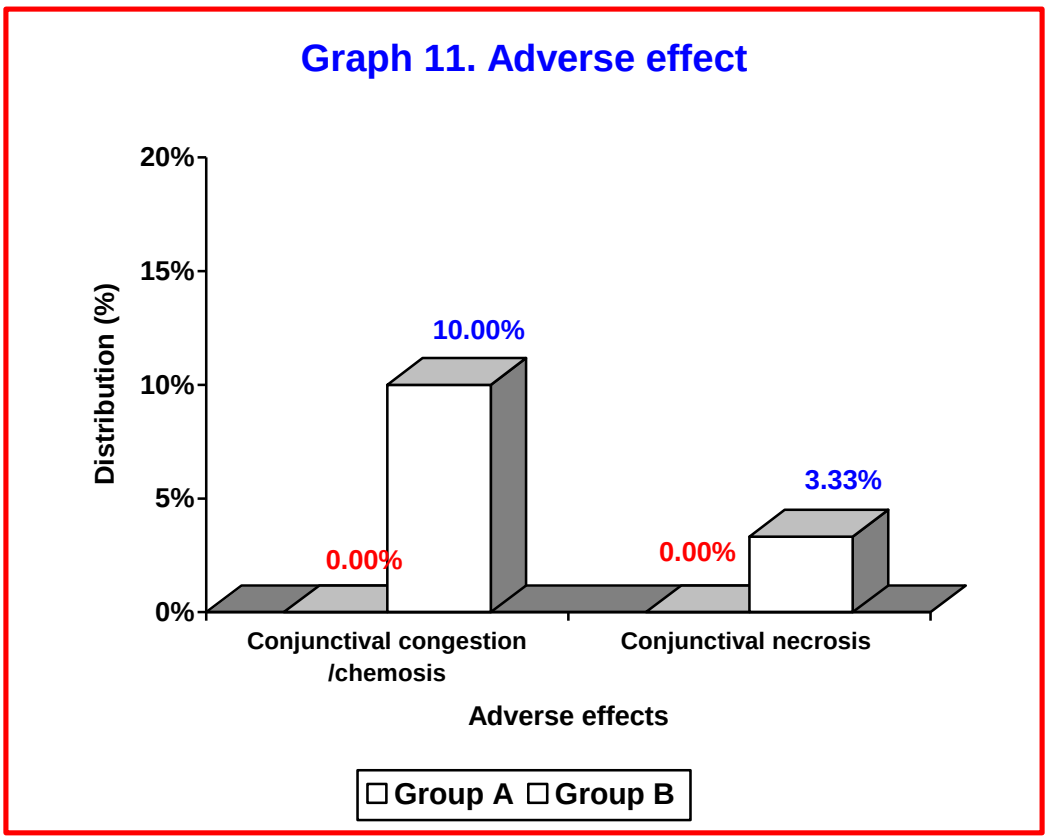


In Group A, 15 (50%) cases showed complete healing in less than 2 week and 14 (46.67%) took more than two weeks to heal. In Group B, 11(36.67%) cases showed complete healing in less than 2 week and 16 (53.33%) cases healed in more than two weeks duration .Mean duration of healing was 2.03 ± 0.54 week in Group A; and 2.31 ± 0.41 in Group B. The difference was statistically significant (p=0.032) healing duration was less in patients treated with monotherapy than with fortified group.

Table 20. Adverse effect

Outcome	Group A (n=30)		Group B (n=30)	
	Number	**Percent**	**Number**	**Percent**
Conjuctival congestion/Chemosis	0	0.00	3	10.00%
Conjunctival necrosis	0	0.00	1	3.33%
None	30	100%	26	86.6%
Total	**30**	**100.00**	**30**	**100.00**

x^2=4.290 DF=1 p= 0.0384



In Group A none of the patients had severe adverse effects like conjunctival chemosis, necrosis whereas the same was seen among 3 (10%) cases in Group B. Conjunctival necrosis was seen in a single case in Group B. The higher rate of adverse sequeale in the Group B was statistically significant (p=0.0384) as compared to Group A.

Table 21.Vision of affected eye during last follow up

Vision	Total cases (n=60)	
	Number	**Percent**
6/5 to 6/9	14	23.33
6/12 to 6/24	12	20.00
6/36 to 6/60	8	13.33
CF to HMCF,PL+	26	43.33
No PL	0	0.00
Total	**60**	**100**

At the last follow up, 26 (43.33%) subjects had a vision of less than 6/60. 23.33% subjects had a vision between 6/5 and 6/9, 20% between 6/12 and 6/24, and 13.33% between 6/36 and 6/60.

DISCUSSION

Bacterial keratitis is a serious sight threatening disease and an important cause of corneal blindness in India.[1] The initial treatment is usually started with broad spectrum antibiotics.[9] Till date the treatment of choice was fortified antibiotics (Cephalosporins and aminoglycosides like Tobramycin or Amikacin) or monotherapy with second generation fluoroquinolones.[18,19]

However use of such fortified preparations remains controversial for several reasons:

- The increased tonicity of concentrated drops which, may actually decrease corneal tissue penetration.[14]

- Use of multiple antibiotics, with frequent dosing results in toxicity and damage to the ocular surface epithelium, thereby impairing recovery.[15,16]

- These Drops have to be made fresh as they have shorter shelf life.[11] Moreover each requires special mixing which adds to cost and increases the risk of contamination.[14-16]

Thus, introduction of commercially available non fortified broad spectrum topical antibiotics with the ability to achieve concentration greater than the MIC (Minimum inhibitory concentration) for most bacteria was desirable. Various studies have shown the safety and efficacy of 2nd and 3rd generation FQs in the treatment of bacterial keratitis. These studies have shown that monotherapy has various advantages as it enjoys better compliance, better penetration, wide

spectrum of action, easy commercial availability and hence easier to dispense at peripheral centres.[18,19,54-57]

Antibiotic resistance of bacterial keratitis isolates has been shown against second generation fluoroquinolones. Topical preparations of the fourth generation FQs - Moxifloxacin and Gatifloxacin have been introduced for ocular use. These antibiotics have a broader spectrum of action with activity against Gram positive, Gram negative and some anaerobic bacteria. They have very low MIC values for organisms isolated from corneal ulcer specimens. In addition they act on DNA gyrase as well as DNA topoisomerase IV; which makes development of resistance to these antibiotics unlikely. Moxifloxacin in addition has a bulky C_7 side chain which prevents reflux of the antibiotic by the reflux pumps in the bacterial cell wall .All these properties make them ideal first line agents for treatment of bacterial corneal ulcers.[24,25]

Hence the present randomized controlled trial was undertaken to compare the effectiveness of moxifloxacin monotherapy with conventional combination therapy for the treatment of bacterial keratitis.

Out of 87 cases screened, 60 patients with suspected bacterial corneal ulcer were deemed eligible to participate in the study. These subjects were randomly allocated into one of the two groups using computer generated randomization that is Group A (n=30; received monotherapy with Moxifloxacin) and Group B (n=30; received combination therapy with fortified Tobramycin and Cefazolin).

Bacterial keratitis was seen most commonly between the age group of 40 to 59 years 32 (53.33%), 20 subjects (33.33%) were aged above 60 years. Only 8(13.33%) were below 40 years of age. Both groups were statistically similar with respect to age distribution (p=0.0601). The mean age of patients in group A was 54.37 ± 15.65 years and in Group B it was 56.37± 10.83 years. However most of the patients (78.33%) had age more than 50 years

Similar findings have been reported in a study conducted by Upadhyay MP et[79] with 50 % of the patients presented with more than 50 years of age.

In this study, the cases of males 37 (61.67%) were numerically larger as compared to females 23(38.33%) with male to female ratio of 1.61 to 1. The gender distribution among both groups was comparable with no significant difference (p=0.7906)

Similar results were seen in a study conducted by Srinivasan et al[31] in which 61.52% were males and 38.47% females, with male to female ratio 1.6:1 Earlier studies also show a male:female ratio ranging from 1:1 to 3:2.[80-82] . Male predominance was seen presumably because they are more physically active and undertake more outdoor activities and hence predisposed for external injury and so were at a higher risk of external injury.

Among all, the number of patients from rural population 40 (66.67%) was clinically higher than the patients from urban population 20 (33.33%). The distribution of urban and rural populations between the two groups was statistically similar (p=0.5839).

Bharathi et al[44] in their study on 1043 patients found 54 % patients from rural population and 45.93% from urban.

Out of 60 cases, 17 (28.33%) patients were labourers. Farmers 15 (25%) followed by housewifes 11 (18.33%), servicemen 7 (11.67%) and 10 (16.67%) subjects were those with other indoor occupations. No significant association (p=0.4916) was found for the distribution of keratitis between farmers and labourers. The distribution in both the groups was comparable (p=0.8732). Majority 32 (53.3%) of the patients were agricultural workers and daily wage earners, an occupation profile similar to South Indian study 66.8%[31] as well as a study by Upadhyay (53.1%).[79]

Ocular trauma 35 (58.33%) was the most common risk factor. The distribution in both groups was comparable (0.2161). Of the other risk factors, the most common cause was chronic dacryocystitis which was present in 7 (11.67%) cases. In this study, 6 (10%) patients were on home remedy at time of their presentation .The most common was the application of castor oil, although patients applied various other materials as well. Inspite of using home remedy they had shown favourable response which could be due to their early referral and prompt initiation of the proper treatment. Others, such as topical steroids 2 (3.33%) and systemic illness like diabetes 4 (6.67%), were likely to compromise cornea sufficiently to allow development of an ulcer. One case had a pre-existing lid disorder 1 (1.67%) in the form of an entropion. The differences in between the two groups with respect to other risk factors like dacryocystitis (p=0.3438), home remedy (p=0.1947), diabetes (p=0.50), lid disorder (p=0.1566) and topical steroid (p=0.500) were found to be insignificant (p>0.05).

Other studies by Upadhyaya[79] and Srinivasan[31] had also shown ocular trauma as the most common risk factor with 65.4% and 52.8% respectively; and chronic dacryocystitis to be 5% and 2.2% respectively.

Srinivasan[31] in his study on 162 patients, found 32 (19.8%) patients were using herbal medicines and had put some kind of oil into the eye.

Contact lens usage has been accused to be the most common cause of bacterial keratitis in most studies, as seen in 50% of cases in the study by Bourcier et al[82] and in 22% of cases seen in the study by Green M et al.[81] But none of the patients in this study presented with history of contact lens wear. The difference in our study as compared to others is probably due to the poor socio economic class of people that usually are seen at our hospital.

Majority, 43(71.67%) of the patients in both the groups presented, during first week following the onset of symptoms while 7 (11.67%) presented during the second week and remaining 10 (16.67%) presented after more than two weeks duration. The distribution of the duration of presentations between the two groups was statistically similar (p=0.8609).

These findings were in correlation with the study Srinivasan M et al[31] where 60.8% presented during first week, 18.7% in second week and 19.7% in more than two week duration.

In this study, 28 (46.6%) patients presented with an initial visual acuity of CF to HMCF, PL +, while 16 (26.67%) presented with 6/36 to 6/60, and another 6(10%) had vision ranging from 6/5 to 6/9.

Gangopadhyay[54] in his study found 47.8% patients with visual acuity ranging from 3/60 to HMCF.

Common bacterial organisms which cause keratitis usually affect the central two-thirds of the cornea. Centrally located ulcers were more commonly seen in both groups, 34 (56.67%) whereas 20 (33.33%) showed peripherally located ulcer. Of the 60 cases, 34 (56.67%) had non severe corneal ulcers and 26 (43.33%) had severe ulceration at the time of presentation. Hypopyon was present in 28 (46.66%) cases. Vascularization was present in 20 (33.33%) cases. The differences in between the two groups with respect to location (p=0.6756), severity (p=0.6023) and vascularization (p=0.2733) of the ulcers, and the presence of hypopyon (p=0.3006) were insignificant.

In a study by Gangopadhyay,[54] 64.5% ulcers were central in location. There were 47.8% non severe and 52.2% severe ulcers.

On the basis of sample data chronic dacryocystitis was found in 7 (11.67%) subjects. The rate of dacryocystitis was a little higher as compared to a study in Madurai,[31] with 5% prevalence of chronic dacryocystitis. This could be due to the majority of rural population and less awareness of the disease. The distribution in the two groups was comparable (p=0.6876). All of these patients underwent dacryocystectomy. Streptococcus pneumoniae was isolated in three cases.

In the present study, 19 (31.6%) organisms could be detected on Gram staining. Our findings correlated with study by MC Leod SD[83]wherein Gram

positivity was seen in 26.8% of cases. Constantinou et al[51] on 229 patients found Gram stain positivity in 36% of the cases.

Out of the total 19 cases detected on Gram Stain, 14 (23.33%) were found to be Gram positive cocci and 5(8.33%) were Gram negative bacilli. There was no statistical difference in the distribution between the two groups (p=0.8939).

Culture positivity was seen in 41/60 (68.33%) of cases in this study, which was similar to a study conducted by Basak et al[84] on1198 patients with culture positivity in 67.7% of patients. Other studies in Ghana[48] and South India,[31,44] had shown 57.3%, 68.4% and 70.6% culture positivity respectively.

Out of the 41 cases detected on culture, 36(87.80%) were found to be Gram positive and 5(12.1%) were Gram negative. Among Gram positive most commonly isolated organism was Staphylococcus epidermidis 13 (31.7%), followed by Staphylococcus aureus, Streptococcus pneumoniae and Streptococcus viridans, each 7 (17%). Bacillus was detected in two cases (4.87%). Among Gram negative organisms, the most commonly isolated organism was Pseudomonas species, detected in 4 (9.75%) subjects. The distribution of organisms was similar in both groups (p=0.5922).The spectrum of organisms isolated in this study was similar to other studies.[81,82]

All isolated organisms were tested for antibiotic sensitivity. Of all the organisms tested in this study, 2 (4.86%) were resistant to cefazolin, one (2.43%) was resistant to tobramycin. All isolates were sensitive to moxifloxacin.

Constantinou[51] in his study on 229 patients, found culture positivity in 83% cases and all were susceptible to moxifloxacin. However, there have been few case reports that have shown occurrence of resistance to fourth generation fluoroqinolones.[85]

A favourable clinical response was seen 29/30 (96.67%) cases in Group A and 27/30 (90%) in Group B. All cases in both groups which presented during the first week of onset of symptoms showed a FCR at Day 3. Out of the subjects who presented during the second week of onset, all improved in Group A and only one case, out of four in group B showed deterioration. Those who had presented after more than two weeks, one case was a treatment failure in Group A and two were failures in Group B. An association was seen between the duration of symptoms before presentation and the clinical response. Subjects who presented within two weeks of onset of symptoms showed a significantly better clinical response in both groups than those who presented later. ($p=0.0085$ for Group A and $p=0.0332$ for Group B). However, the clinical response at Day 3 in these subjects were similar in both groups, with respect to the duration till presentation. ($p=0.2931$ for subjects presenting within 2 weeks and $p=0.7782$ for those presenting after 2 weeks).

Out of 16 severe ulcers in Group A, 15(93.77%) showed improvement. In group B, 16(88.8%) out of 18 showed improvement. The outcome of severe ulcers was similar in both groups ($p=0.9149$). Among the non-severe ulcers, all 14 cases in Group A and 11(91.67%) out of 12 in Group B showed improvement. The outcome of non-severe ulcers in both groups was similar ($p=0.9373$).

The patients were kept on regular follow up and the response to treatment was noted at each visit in terms of the change in the corneal ulcer or infiltrate diameter and presence of any complications or adverse drug reactions. Outcomes measured included healing of corneal ulcer as well as time to cure. Overall twenty nine (96.67%) cases healed in Group A and 27 (90%) healed in group B. There was no difference in the final outcome between the two groups (p=0.3006).

Out of the 3(10%) treatment failures in Group B, one case was shifted to moxifloxacin therapy, and after one week of treatment it healed with a scar. This was a classical case of poor compliance. The patient was not using the drops properly as explained, and when shifted to monotherapy, the compliance improved and subsequently the ulcer was healed with a scar.

In the second case, there was marked suppuration, dense stromal infiltration and no improvement was seen with the drug. The patient underwent therapeutic keratoplasty for the same.

Other two cases, one in Group B and other in Group A, showed marked corneal thinning which later went on to perforation and healed with an adherent leucoma.

Complete healing in less than 2 weeks was observed in 15(50%) cases in Group A and 11(36.67%) in Group B. 14(46.67%) cases healed in more than two weeks duration in Group A and 16(53.33%) in Group B. The mean duration of healing was 2.03 ± 0.54 weeks in the Group A and 2.31 ± 0.41 weeks in the Group B. The difference in healing rates between the two groups was statistically significant (p=0.032).

Similar results was obtained in a study conducted[86] found that the time required for complete healing of ulcer was 15.0 ± 3.86 days with monotherapy and 15.46 ± 3.86 days in the fortified group.

Conjunctival congestion and chemosis were seen in 3(10%) cases in Group B and conjunctival necrosis was seen in a single case (3.33%) in the same group. None of the serious adverse effects were observed in Group A. The incidence of ocular side effects for patients receiving Group B medication was significantly greater clinically and statistically than in patients treated with Group A (p=0.0384). However, burning sensation and irritation was seen in 8 cases among Group A and 7 in Group B. None of the drugs showed the occurrence of corneal precipitates as shown by previous studies with ciprofloxacin and few studies in which ofloxacin drops were used topically.[18,19]

Toxicity with conventional therapy has been reported in other studies as well. Hyndiuk et al[57] found 3.7% incidence of ocular hyperemia, 2.4% of ocular prurutis and 13.3% of non-specific ocular discomfort in the form of burning and stinging. O'Brien et al[19] found eight of nine patients with severe ocular side effects when treated with conventional therapy. A five times greater incidence of adverse effects with conventional therapy as compared to treatment with Ofloxacin therapy has been noted in another study.[20] Conjunctival necrosis as an adverse effect of topical fortified aminoglycoside therapy has been reported elsewhere as well.[87]

At the end of last follow up, majority of the cases (43.33%) had visual acuity between CF to HMCF, 8 (13.33%) cases had visual acuity between 6/36 to

6/60. Kunimoto DY et al[88] in their study reported that 55% of patients had visual acuity between CF to HMCF. This finding was more or less similar to that of the present study. Thus, the present study reveals poor visual outcome in patients who have decreased visual acuity at their initial presentation. Therefore, initial visual acuity at presentation is a significant risk factor for the final visual outcome.

Previous studies[22,23] had shown increasing resistance to second generation FQs by the bacterial isolates from corneal ulcer. Moxifloxacin have lower MICs for most gram positive and gram negative organisms when compared with fortified medications as well as second generation FQs.[25] Also they have very good corneal permeability and achieve aqueous concentrations which are several folds higher than the MIC values.[89]

Overall, the findings of the present study showed that patients treated with moxifloxacin had significantly better results in terms of lesser duration of healing and no adverse effects as compared to group B which received combination therapy.

A small sample size of only 60 patients was an important limitation of this study. Another was observer bias as it was unmasked clinical trial. However, to minimize the observer bias, the clinical study was designed such that the primary outcome was a definite endpoint that is, healing of corneal ulcer which was defined as complete re epithelization as seen after fluorescein staining.

CONCLUSION

The results of the present study showed that the clinical response in bacterial keratitis, in terms of improvement in ulcer characteristics, for those treated with Moxifloxacin monotherapy was similar to those treated with combination therapy irrespective of the severity of the ulcer.

Overall, patients who presented early, had a significantly better clinical outcome as compared to those who presented late.

The final outcome, in terms of healing, was not significantly different for ulcers treated with Moxifloxacin and with Combination therapy.

However, the mean duration of healing, was significantly less for ulcers treated with Moxifloxacin monotherapy, as compared to those treated with combination therapy.

Adverse effects observed with Combination therapy, in terms of congestion, chemosis and conjunctival necrosis, were significantly more as compared to Moxifloxacin therapy.

One may infer that a single commercially available treatment greatly simplifies the therapy for patients and clinicians alike, also reduces hospital stay of the patient whereas the absence of drug toxicity both clarifies interpretation of the clinical response and improves patient comfort.

SUMMARY

At present, the standard treatment for a case of bacterial keratitis is either the use of fortified antibiotics or monotherapy with second generation fluoroquinolones. Recently, increasing resistance of bacterial keratitis isolates has been seen against the latter. Moxifloxacin and Gatifloxacin are the fourth generation FQs, which have been introduced. These new ocular antibiotic formulations have improved potency and have been shown to inhibit growth of organisms resistant to second and third generation FQs. These drugs have many advantages as compared to earlier generation FQs and fortified medications in the treatment of bacterial keratitis. Hence, the present randomized controlled trial was undertaken to compare the effectiveness of moxifloxacin monotherapy with combination therapy for the treatment of bacterial keratitis.

The present one year randomized controlled trial was conducted in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010. 87 patients, who presented with corneal ulcer to the out-patient department, were screened for eligibility. Based on the inclusion and exclusion criteria of the study, 60 subjects were deemed eligible. These patients were randomly allocated into one of the two treatment groups using computer generated randomization - that is Group A (n=30; received monotherapy with Moxifloxacin) and Group B (n=30; received combination therapy with Tobramycin and Cefazolin). After corneal scrapings were obtained, the assigned study medications were instilled, and antibiotics were gradually tapered as per the response.

In this study male predominance was seen (61.67%) with male to female ratio of 1.61:1. The most common age in both the groups was 40 to 59 years. Mean age in Group A was 54.37 ± 15.65 years and in Group B it was 56.37 ± 10.83 years. Most of the patients were from rural area (66.67%). No significant association (p=0.4916) was found for incidence of keratitis between farmers and labourers. There was no statistically significant difference between the two groups with regard to the basic demographic characteristics.

Ocular trauma was the most common risk factor (58.33%). Most of the patients in both the groups presented during first week of onset (71.67%) and most of the ulcers were centrally located in both the groups. The incidence of dacryocystitis in the two groups was comparable. On gram staining, 31.6% of the patients were positive and most common organisms were Gram positive cocci (23.33%). Culture was positive in 68.33% of the patients and most commonly isolated organism was Staphylococcus epidermidis (31.70%). All isolates were sensitive to Moxifloxacin. Subjects who presented within two weeks of onset of symptoms showed a significantly better clinical response in both groups than those who presented later. There was no statistical difference in the final outcome between the two groups (Group A 96.67%; Group B 90%.; p=0.3006). The mean duration of healing in group A was significantly less compared to group B (2.03 ± 0.54 v/s 2.31 ± 0.41; p= 0.032). Patients in group B had significantly more severe adverse effects (p= 0.0384).

The findings of the present study showed that patients treated with moxifloxacin had relatively better results in terms of duration of healing. In

addition, less adverse effects were seen in patients treated with moxifloxacin therapy, compared to those treated with combination therapy.

Hence, we conclude that topical moxifloxacin therapy is safe and effective for the management of bacterial keratitis.

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ANNEXURE I - CONSENT FORM

Mr/Mrs/Ms _____

You are invited to participate in our research study titled **"**A one year randomized control study to determine the clinical efficacy and safety of moxifloxacin vs conventional dual therapy(cefazolin and tobramycin)in treatment of bacterial keratitis in patients attending the Ophthalmology OPD at KLES Dr. Prabhakar Kore Hospital and MRC, Belgaum.**"** conducted by Dr. Manisha Sharma, Post Graduate student in M.S. Ophthalmology, under the guidance of Dr. Arvind. L Tenagi Professor in the Department of Ophthalmology, J. N. Medical College, Belgaum.

Respected Sir/Madam, we request you to enroll yourself in our study as you are eligible for participation. Your participation in research is voluntary. If you decide to participate you are free to withdraw at any time.

Purpose of the Study

The purpose of research is to determine the clinical efficacy and safety of moxifloxacin in treatment of bacterial keratitis

Procedure Involved

If you agree to enroll yourself in this study, you will be asked your present, past and family history. You will be clinically examined and relevant investigations will be done. Then you will be asked to undergo either of the two treatment procedures based entirely on computer generated randomization. You

will be asked to follow up on specified dates when your progress would be monitored, documented and if necessary photographed.

Risks and Benefits

There are no major risks involved, however some complications may occur primarily due to the disease process itself, but not related to the medications used. Your participation may benefit you and others with the same condition in future, by helping us learn more about the disease process. No financial incentives are promised for being a part of the study.

Alternatives

If you are not willing to participate you will be treated according to the existing protocol & it will not affect your relationship with this hospital.

Costs for participating in this research

There will not be any extra cost incurred by you. You will, however, have to pay for the investigations and medications which are part of the existing management protocol for the condition. There is no commitment for any reimbursement or any other compensation.

Privacy and Confidentiality

Your privacy is guaranteed. However, your medical records can be directly accessed and reviewed by authorized individuals or by the ethics committee. Records, which could reveal your identity, will be kept confidential.

Personal data will remain anonymous if data is being published or written as a dissertation.

Authorization to Publish Results

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity.

Compensation

In the event of injury related to the study, treatment will be made available through KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. There is no compensation or payment for such medical treatment by law. The doctors and the staff will provide facilities and medical attention to you.

Questions

If you have any questions about the research you may please contact:

1. Investigator, Dr. Manisha Sharma, Post Graduate student, Department of Ophthalmology, JNMC, Belgaum. Contact No. 9620022240

2. Guide, Dr. Arvind L. Tenagi, Professor, Department of Ophthalmology, JNMC, Belgaum. Contact No. 9844009667

3. Dr. V. D. Patil, Principal, JNMC, Belgaum and Chairman, Institutional Ethics Committee. Contact No. (0831) 2471350

CONSENT FOR PARTICIPATION IN RESEARCH TRIAL

I, Mr./Ms./Mrs _____ voluntarily agree for the participation as a subject of this study. By signing this consent form, I am not giving up any of my legal rights. I may withdraw from the study at anytime. I am signing the consent form after having read or been read for me in my own vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject : _____

Witness Name :_____

Signature of Witness:_____

Investigators Name: _____

Signature of Investigator : _____

Date:

Place:

Name of Guide: _____

Signature of guide: _____

ANNEXURE II – PROFORMA

MOXIFLOXACIN VERSUS COMBINATION THERAPY (TOBRAMYCIN + CEFAZOLIN IN BACTERIAL KERATITIS: A RANDOMIZED CONTROLLED TRIAL.

1. PATIENT OPD NO. ☐ PATIENT IP NO. : ☐

2. NAME:_____

3. AGE: ☐ yrs SEX: ☐ (1-male, 2-female)

4. OCCUPATION:_____

5. DATE OF ADMISSION:_____DATE OF DISCHARGE :___

6. ADDRESS :

_____

_____

7. TELEPHONE No.(s)_____

8. SOCIO-ECONOMIC STATUS: ☐

   1- UPPER
   2- MIDDLE
   3- LOWER

9. IS THE PATIENT ELIGIBLE FOR STUDY: ☐ 1-YES 2-NO

10. HAS INFORMED CONSENT BEEN GIVEN? ☐ 1-YES 2-NO

11. PROVISIONAL DIAGNOSIS:

12. COMPLAINTS:

	RIGHT EYE	LEFT EYE	DURATION
			Less than 1 week = 1 1 week to 2 weeks = 2 2 weeks to 4 weeks = 3 >4 weeks = 4
1. PAIN 1- YES 2- NO (If 1, then, 1=mild, 2=moderate, 3=severe)	☐	☐	☐
2. PHOTOPHOBIA 1- YES 2- NO	☐	☐	☐
3. WATERING 1- YES 2- NO	☐	☐	☐
4. REDNESS 1- YES 2- NO	☐	☐	☐
5. HEADACHE 1- YES 2- NO	☐	☐	☐
6. DISCHARGE 1- YES 2- NO (If 1, then 1=serous, 2=mucopurulent, 3=purulent)	☐	☐	☐
7. DIMINUTIC VISION 1- YES 2- NO	☐	☐	☐

8. INJURY TO EYE ☐ ☐ ☐

1- YES

2- NO

(If 1, then, 1=Agricultural, ☐ ☐ ☐

2=Industrial 3=domestic, 4=others)

13. NATURE OF HISTORY:

PREVIOUS HISTORY OF APPLICATIONS OF (1- YES , 2- NO)

1. ANTIBIOTIC ☐
2. ANTIBIOTIC + STEROID ☐
3. CYCLOPEGIC ☐
4. HOME REMEDY ☐
   (INDIGENOUS MEDICATION)
5. BANDAGE CONTACT LENS ☐

14. HISTORY OF RISK FACTORS (1- YES, 2- NO)

1. TRAUMA ☐
2. CONTACT LENS WEAR ☐
3. DIABETES ☐
4. DACRYOCYSTITIS ☐
5. ALCOHOL ☐
6. IMMUNE SUPPRESSOR ☐

15. PAST HISTORY :

PAST HISTORY OF ☐ (1- DIABETES, 2- HYPERTENSION, 3- BOTH, 4- ANY OTHER MEDICAL DISORDER,5- NONE)

IF 4 SPECIFY : _____

16. PERSONAL HISTORY:

PERSONAL HISTORY OF ☐ (1- SMOKING, 2-ALCOHOLISM, 3- BOTH ,4- NONE)

17. GENERAL PHYSICAL EXAMINATION

PALLOR ☐ (1- PRESENT, 2- ABSENT)

OEDEMA ☐ (1- PRESENT, 2- ABSENT)

LYMPHADENOPATHY ☐ (1- PRESENT, 2- ABSENT)

PULSE: _____/ MINUTE

BLOOD PRESSURE: _____mmHg

TEMPERATURE: _____(1- AFEBRILE, 2- FEBRILE)

18. SYSTEMIC EXAMINATION

CVS: ☐ (1-Normal, 2-Abnormal, If Abnormal, specify : _____

RS: ☐ (1-Normal, 2-Abnormal, If Abnormal, specify : _____

CNS: ☐ (1-Normal, 2-Abnormal, If Abnormal, specify : _____

PER ABDOMEN: ☐ (1-Normal, 2-Abnormal, If Abnormal, specify :

19. OCULAR EXAMAINATION:

HEAD POSTURE ☐ (1- ERECT, 2- TILTED)

FACIAL SYMMETRY ☐ (1- SYMMETRICAL, 2- ASYMMETRICAL)

VISUAL AXIS ☐ (1- PARALLEL, 2- DEVIATED)

	RIGHT EYE	**LEFT EYE**
• **Extraocular Movements** (1- NORMAL, 2- RESTRICTED)		
Uniocular	☐	☐
Binocular		
• **Visual Acuity**		
Distant Vision	☐	☐
1- 6/5 to 6/9		
2- 6/12 to 6/24		
3- 6/36 to 6/60		
4-CF to Hand movement (HM), -Projection of light (PL/PR)		
5-NPL (No PL)		
• **Adnexa** (1-Normal; 2-Abnormal, if abnormal specify : _____)	☐	☐
• **Sclera** (1-Normal; 2-Congested)	☐	☐
• **Conjunctiva**		
Normal (1=yes; 2=no)	☐	☐
Conjunctival congestion (1=yes; 2=no)	☐	☐
Circum corneal congestion (1=yes; 2=no)	☐	☐
Chemosis (1=yes; 2=no)	☐	
Others	☐	☐

- **Cornea**

(1-Normal; 2-Abnormal) ☐ ☐

Corneal ulcer

- Location (1=Central; 2=Peripheral) ☐ ☐
- Shape ☐ ☐
- Size
- Margin (1=well defined; 2=feathery,3= ill defined) ☐ ☐
- Edges (1=sloping;2=punched out; 3=undermined) ☐ ☐
- Depth - (1=Superficial;2=Mid Stromal; 3=Deep Stromal) ☐ ☐
- Floor (1=Fibrotic; 2=slough) ☐ ☐
- Infiltration (1=yes; 2=no) ☐ ☐

  If 1, then, specify

  Size ☐ ☐

  Depth (1=Superficial;2=Mid Stromal; 3=Deep Stromal) ☐ ☐
- Vascularisation – (1=yes; 2=no) ☐ ☐

  If 1, then, (1=superficial; 2=deep; 3=both)
- Immune ring (1=yes; 2=no) ☐ ☐
- Pigmentation (1=yes; 2=no) ☐ ☐

- Satellite lesion (1=yes; 2=no) ☐ ☐
- Descemetocele (1=yes; 2=no) ☐ ☐
- Perforation (1=yes; 2=no) ☐ ☐
- Keratic precipitates (1=present; 2=absent) ☐ ☐
- Aqueous flare/ cells (1=yes; 2=no) ☐ ☐

If 1, then specify the grade: ☐ ☐

- Scarring (1=yes; 2=No) ☐ ☐

(If 1, then, 1=nebular; 2=macular, 3=leucomatous)

- **Anterior Chamber**
- Depth : ☐ ☐

(1-Normal depth ; 2-Shallow, 3- Deep, 4-Absent, 5- Irregular)

- Hypopyon (1=yes; 2=no): ☐ ☐

If 1, then specify,

Level (1=<2mm; 2=2-4mm; 3=>4mm) ☐ ☐

Mobility (1=mobile; 2=immobile) ☐ ☐

- Hyphema (1=yes; 2=no): ☐ ☐
- **Iris**

(1=Details visible 2=Details not visible) ☐ ☐

If 1 specify,1=Normal colour and pattern; 2=Abnormal) ☐ ☐

If 2, then, 1=synechiae; 2=staphyloma; 3=others ☐ ☐

- **Pupil** ☐ ☐

(1-Round,regular,reacting; 2-Abnormal)

If 2, then specify

- **Lens**

(1=Clear; 2=Cataractous; 3=details not made out)

If 2, then, 1=immature; 2=mature; 3=hypermature ☐ ☐

20. LACRIMAL PATENCY TEST

1. Patent ☐ ☐
2. Blocked

21. INVESTIGATIONS: (1- Normal, 2- Abnormal)

- Blood Sugar ☐

22. OCULAR INVESTIGATIONS:

A. Fluorescein staining ☐ ☐

1- Staining

2- Not staining

3- Pooling

B. Corneal scraping

a. Stain (1- positive, 2- negative)

- Gram ☐
- KOH wet mount ☐

b. Culture (1- positive, 2- negative)

- Blood Agar ☐
- Chocolate Agar ☐
- Sabouraud's Slope agar ☐

C. Antibiotic sensitivity test

23. TREATMENT GIVEN

	Drug	frequency	Duration
Group A	Moxifloxacin 0.5%		
Group B	Tobramycin 1.3% + Cefazolin 5%		

24. FOLLOW UP CRITERIA:

- After 1 week
- After 2 weeks
- After 3 weeks
- After 4 weeks

25. FOLLOW UP

- **Visual Acuity**

(1=Increased; 2=Decreased; 3=Same) ☐ ☐ ☐ ☐

- **Sclera**

(1-Normal; 2-Congested) ☐ ☐ ☐ ☐

- **Conjunctiva**

Normal (1=yes; 2=no) ☐ ☐ ☐ ☐

Conjunctival congestion (1=yes; 2=no) ☐ ☐ ☐ ☐

Circum corneal congestion (1=yes; 2=no) ☐ ☐ ☐ ☐

Chemosis (1=yes; 2=no) ☐ ☐ ☐ ☐

- **Cornea**

Corneal ulcer

- Size

(1=Increased; 2=Decreased; 3=Same) ☐ ☐ ☐ ☐

- Margin (1=well defined;

2=feathery,3= ill defined) ☐ ☐ ☐ ☐

- Edges (1=sloping;2=punched out;

3=undermined) ☐ ☐ ☐ ☐

- Depth - (1=Superficial;2=Mid Stromal; 3=Deep Stromal) ☐ ☐ ☐ ☐
  (1=Increased; 2=Decreased; 3=Same) ☐ ☐ ☐ ☐
- Floor (1=Fibrotic; 2=slough) ☐ ☐ ☐ ☐
- Infiltration (1=yes; 2=no) ☐ ☐ ☐ ☐
  If 1, then,
  (1=Increased; 2=Decreased; 3=Same) ☐ ☐ ☐ ☐
- Vascularisation ☐ ☐ ☐ ☐
  (1=Increased; 2=Decreased; 3=Same)

- Immune ring (1=yes; 2=no) ☐ ☐ ☐ ☐
- Pigmentation (1=yes; 2=no) ☐ ☐ ☐ ☐
- Satellite lesion (1=yes; 2=no) ☐ ☐ ☐ ☐
- Descemetocele (1=yes; 2=no) ☐ ☐ ☐ ☐
  (1=Increased; 2=Decreased; 3=Same) ☐ ☐ ☐ ☐
- Perforation (1=yes; 2=no) ☐ ☐ ☐ ☐
- Keratic precipitates (1=present; 2=absent) ☐ ☐ ☐ ☐
- Aqueous flare/cells (1=yes; 2=no) ☐ ☐ ☐ ☐
  If 1, then specify the grade: ☐ ☐ ☐ ☐
- Scarring (1=yes; 2=No) ☐ ☐ ☐ ☐
  (If 1, then, 1=Increased; 2=Decreased; 3=Same) ☐ ☐ ☐ ☐

Others: _____

- **Anterior Chamber**

- Depth :
(1-Normal depth ; 2-Shallow, 3- Deep, 4-Absent, 5- Irregular)

- Hypopyon (1=yes; 2=no):
If 1, then specify,
(1=Increased; 2=Decreased; 3=Same)

- Hyphema (1=yes; 2=no)
If 1, then specify,
(1=Increased; 2=Decreased; 3=Same)

Others: _____

- **Iris**

(1=Details visible 2=Details not visible)
If 1 specify,1=Normal colour and pattern; 2=Abnormal)
If 2, then, 1=synechiae; 2=staphyloma; 3=others

- **Pupil**

(1-Round,regular,reacting; 2-Abnormal)
If 2, then specify

- **Lens**

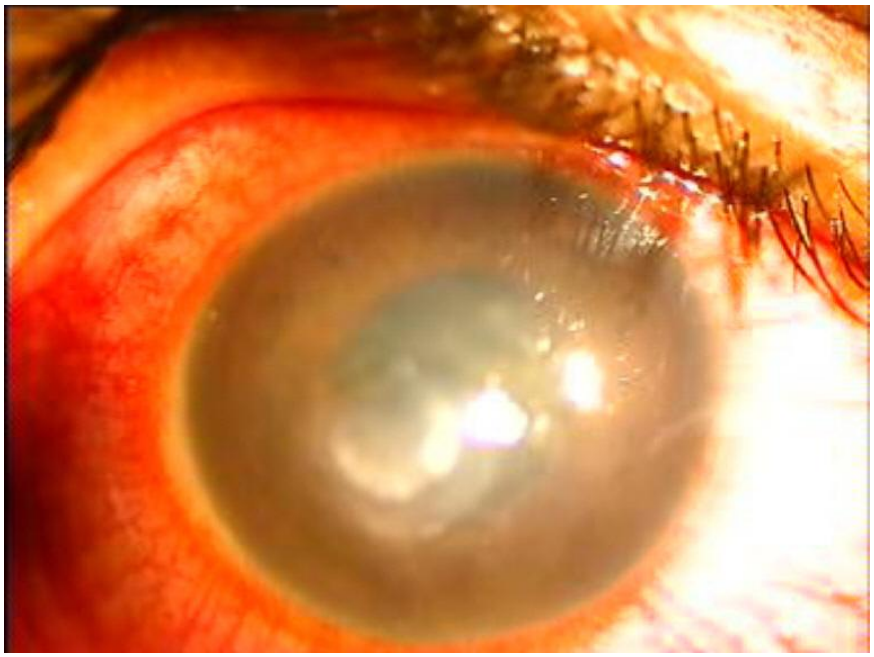
(1=Clear; 2=Cataractous; 3=details not made out)
If 2, then, 1=immature; 2=mature; 3=hypermature

26. ADJUNCTIVE THERAPY

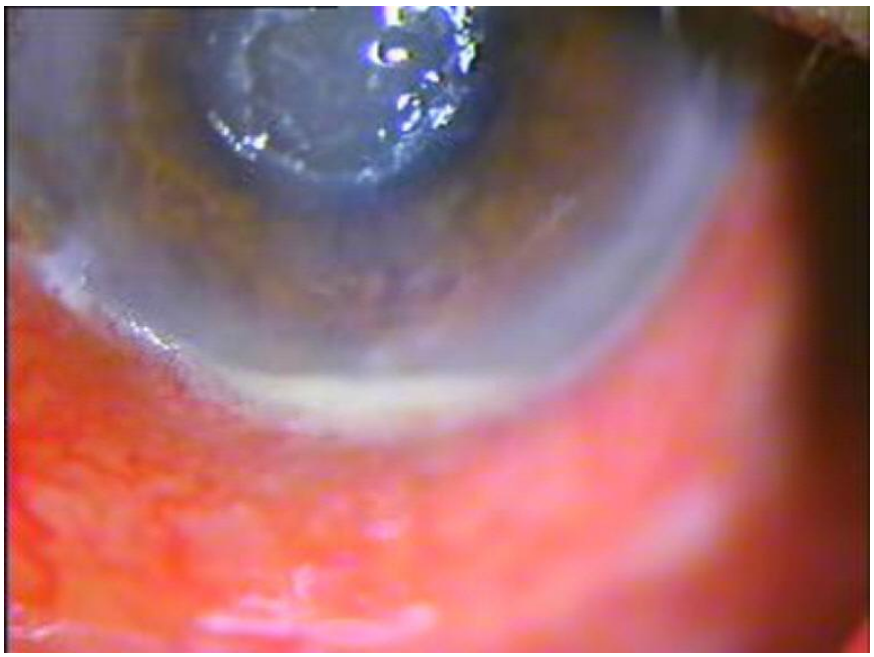
27. END RESULTS

- Healed ☐
- No response ☐
- Worsening ☐
- Perforated ☐
- Adherent leucoma ☐
- Eviscerated ☐
- Lost to follow up ☐

ANNEXURE III – PHOTOGRAPHS

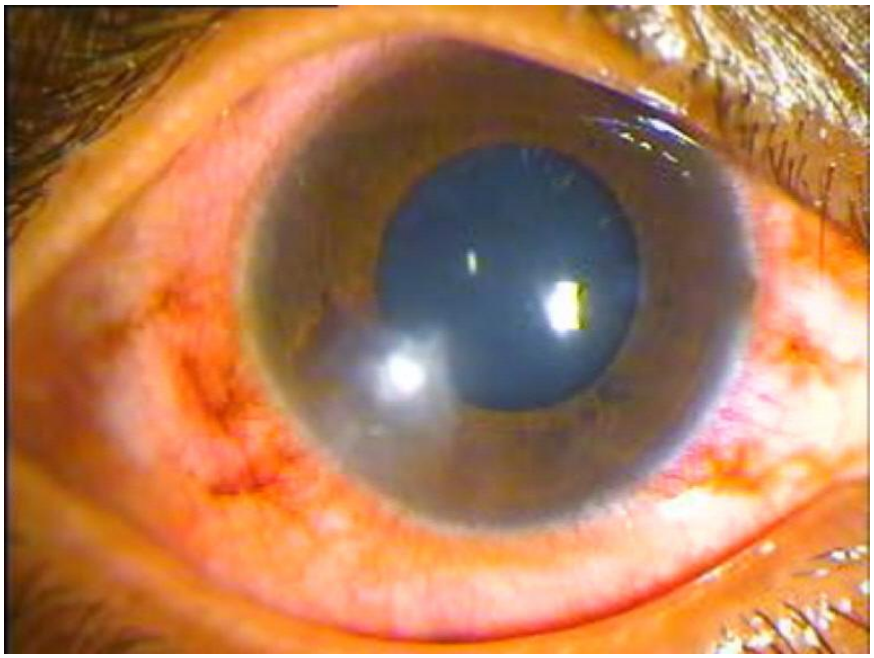


Photograph 1. Central corneal ulcer with marked infiltration

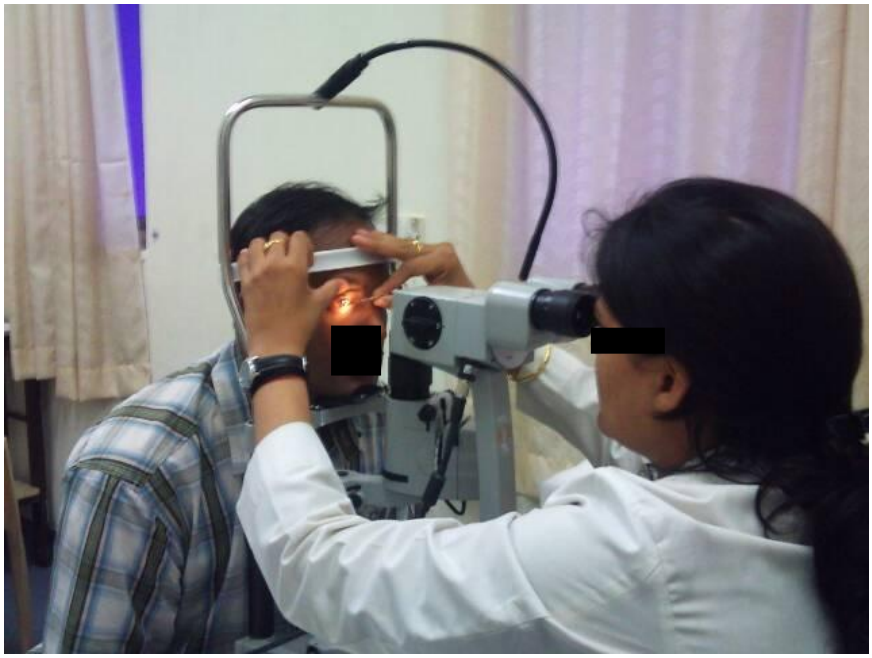


Photograph 2. Central corneal ulcer with hypopyon with chemosis

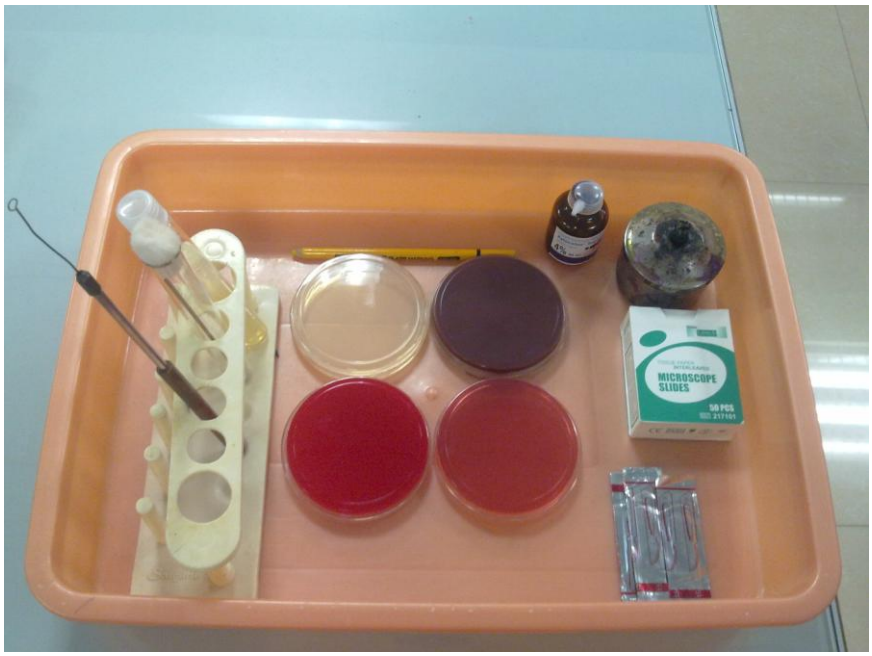
Photograph 3. Corneal ulcer with stromal thinning



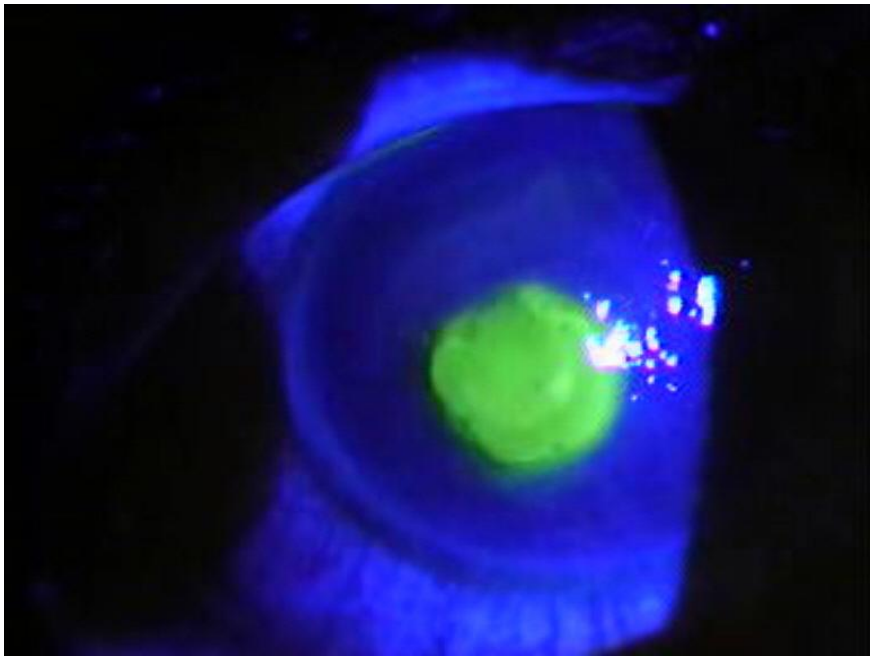
Photograph 4. Peripheral corneal ulcer



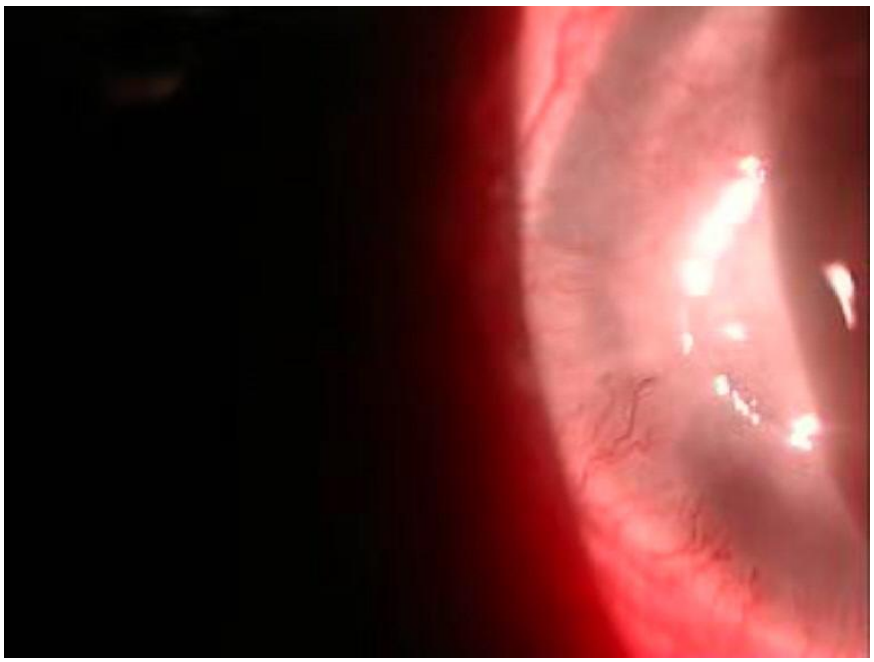
Photograph 5. Patient undergoing corneal scraping



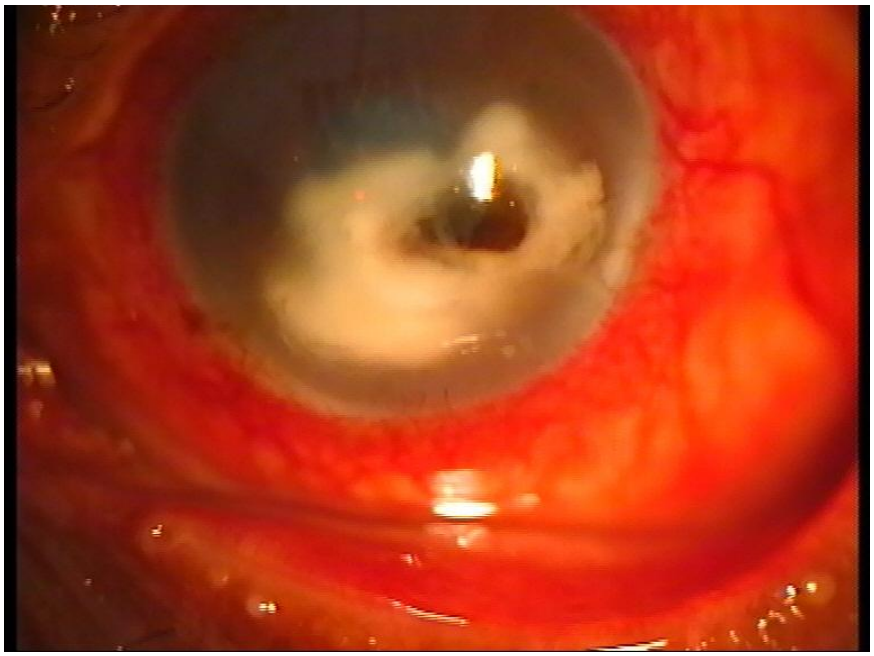
Photograph 6. Laboratory armamentarium



Photograph 7. Epithelial defect with fluorescein staining



Photograph 8. Corneal ulcer with both superficial and deep vascularisation



Photograph 9. Perforated corneal ulcer

ANNEXURE IV MASTER CHART - GROUP A

Sl No.	Group	IP/OP No.	Age (years)	Sex	Residence	Occupation	Eye	Risk Factors		Duration of symptoms	Ocular Examination					Laboratory Investigations			Follow up at Day 3	Total healing duration	Side Effects Observed	Final visual acuity	Outcome
												Ulcer											
								Injury	Others		Visual Acuity	Location	Severity	Vascularization	Hypopyon	Gram Stain	Culture isolates	ABRD					
1	A	335275	60	F	R	HW	LE	Y	N	2d	6--24	LM	NSv	N	N	NOS	STE	N	IMP	2w	NO	6--18	CS
2	A	338530	36	F	R	FR	LE	Y	N	5d	6--60	PR	NSv	N	N	NOS	STV	N	IMP	1w 3d	NO	6--24	CS
3	A	338898	60	F	R	LB	LE	Y	DC	6d	6--36	PR	NSv	N	N	GPC	STA	N	IMP	1w 4d	NO	6--24	CS
4	A	343303	45	F	U	SV	LE	Y	ST	4d	6--18	PR	NSv	N	N	NOS	STP	N	IMP	2w	NO	6--9	CS
5	A	344804	20	M	U	IW	LE	N	N	3d	CF 1mts	CN	Sv	N	2mm	GPC	NOG	N	IMP	2w	NO	CF 2mts	CS
6	A	347885	85	F	U	HW	RE	Y	N	6d	6--9	LM	NSv	Y	N	NOS	STA	N	IMP	1w 5d	NO	6--9	CS
7	A	351535	75	M	R	LB	LE	Y	LD	4w	CF 3mts	CN	Sv	Y	1mm	NOS	STA	N	IMP	2w	NO	CF 3mts	CS
8	A	351932	70	M	R	FR	LE	Y	DM	5d	CF 1mts	CN	Sv	Y	2mm	NOS	STV	N	IMP	2w 3d	NO	CF 2mts	CS
9	A	352271	61	F	U	FR	RE	Y	N	1w 5d	6--60	PR	NSv	Y	N	NOS	BCL	N	IMP	2w 5d	NO	6--24	CS
10	A	353964	34	M	R	IW	LE	N	N	6d	CF 3mts	CN	Sv	N	1mm	NOS	NOG	N	IMP	2w	NO	CF 2mts	CS
11	A	359664	75	F	U	HW	LE	N	DM	1d	6--9	LM	NSv	Y	N	GPC	STE	N	IMP	2w	NO	6--9	CS
12	A	366530	55	M	R	FR	RE	Y	N	1d	6--36	PR	NSv	N	N	NOS	NOG	N	IMP	2w 3d	NO	6--24	CS
13	A	369656	55	M	R	FR	RE	N	N	3d	CF 3mts	CN	NSv	N	1mm	NOS	PSM	N	IMP	2w 4d	NO	CF 5mts	CS
14	A	370890	51	M	R	LB	LE	Y	N	4d	6--60	PR	NSv	N	N	NOS	NOG	N	IMP	2w 3d	NO	6--60	CS
15	A	371401	50	M	U	LB	RE	N	N	3d	CF 3mts	CN	Sv	N	2mm	NOS	NOG	N	IMP	1w 5d	NO	CF 4mts	CS
16	A	374559	65	F	U	HW	LE	Y	N	2w 2d	CF 3mts	CN	Sv	Y	2mm	GPC	STA	N	NI	NH	NO	6--60	TF
17	A	374614	60	M	R	SV	LE	Y	DC	2d	CF 3mts	CN	Sv	Y	1mm	NOS	STP	N	IMP	2w	NO	CF 3mts	CS
18	A	377071	72	M	R	LB	LE	N	N	1d	CF 2mts	CN	NSv	N	1mm	GNB	NOG	N	IMP	2w 3d	NO	6--60	CS
19	A	387335	60	M	R	FR	RE	Y	N	2w 2d	CF 3mts	CN	Sv	Y	1mm	NOS	STE	N	IMP	2w 5d	NO	CF 3mts	CS
20	A	387863	45	M	U	SV	RE	N	N	1d	CF 2mts	CN	Sv	N	2mm	GPC	NOG	N	IMP	2w	NO	CF 4mts	CS
21	A	391992	50	M	R	LB	RE	Y	HR	2d	6--36	PR	NSv	Y	N	NOS	STE	N	IMP	2w 3d	NO	6--24	CS

ANNEXURE IV MASTER CHART - GROUP A

Sl No.	Group	IP/OP No.	Age (years)	Sex	Residence	Occupation	Eye	Risk Factors		Duration of symptoms	Ocular Examination					Laboratory Investigations			Follow up at Day 3	Total healing duration	Side Effects Observed	Final visual acuity	Outcome
												Ulcer											
								Injury	Others		Visual Acuity	Location	Severity	Vascularization	Hypopyon	Gram Stain	Culture isolates	ABRD					
22	A	394373	39	F	U	IW	LE	Y	N	4d	6--24	PR	NSv	Y	N	GPC	STA	N	IMP	2w 3d	NO	6--9	CS
23	A	395607	30	M	R	FR	RE	N	N	5d	CF 2mts	CN	Sv	N	1mm	NOS	NOG	N	IMP	2w 4d	NO	CF 2mts	CS
24	A	398346	35	F	U	IW	LE	Y	N	1w 1d	6--24	PR	NSv	N	N	NOS	STE	N	IMP	1w 2d	NO	6--9	CS
25	A	399536	53	F	U	HW	RE	Y	N	3d	CF 4mts	CN	Sv	N	1mm	GPC	STE	N	IMP	2w 1d	NO	6--24	CS
26	A	416781	80	M	R	HW	RE	Y	DC	1w 3d	6--9	LM	NSv	Y	N	NOS	STP	N	IMP	2w 3d	NO	6--6	CS
27	A	416851	65	M	R	LB	RE	N	N	6d	CF 4mts	CN	Sv	N	1mm	NOS	STV	N	IMP	1w 5d	NO	CF 3mts	CS
28	A	424282	54	M	R	LB	LE	N	N	3w 3d	CF 3mts	CN	Sv	N	1mm	GNB	PSM	N	IMP	2w 2d	NO	CF 3mts	CS
29	A	424590	55	M	R	LB	RE	N	N	1d	CF 1mts	CN	Sv	N	3mm	GNB	NOG	N	IMP	1w 4d	NO	CF 3mts	CS
30	A	429802	36	F	R	LB	LE	Y	HR	1d	6--18	PR	NSv	Y	N	NOS	STE	N	IMP	2w	NO	6--9	CS

ANNEXURE IV - KEY TO MASTER CHART

ABRD	-	Antibiotic resistance to the treatment drug
BCL	-	Bacillus
CC	-	Congestion / Chemosis
CF	-	Counting fingers
CFZ	-	Cefazolin
CN	-	Central
Cn	-	Conjunctival necrosis
CS	-	Corneal scar
d	-	Days
DC	-	Dacryocystitis
DM	-	Diabetes Mellitus
ECO	-	E coli
F	-	Female
FR	-	Farmer
GNB	-	Gram negative bacilli
GPC	-	Gram positive cocci
HMCF	-	Hand movements close to face
HR	-	Home remedy
HW	-	Housewife
IMP	-	Improved
IW	-	Other Indoor worker
LB	-	Labourer

LD	-	Lid disorder
LE	-	Left eye
LM	-	Limbal
M	-	Male
mm	-	Millimetres
mts	-	Metres
N	-	No
NH	-	Not healed with the treatment drug
NI	-	Not improved
NO	-	None
NOG	-	No growth
NOS	-	No organisms seen
NSv	-	Non severe
PL	-	Perception of light
PR	-	Peripheral
PSM	-	Pseudomonas
R	-	Rural
RE	-	Right Eye
ST	-	Topical steroid
STA	-	Staphylococcus aureus
STE	-	Staphylococcus epidermidis
STP	-	Streptococcus pneumoniae
STV	-	Streptococcus viridans
SV	-	Serviceman

Sv	-	Severe
TF	-	Treatment failure
TOB	-	Tobramycin
U	-	Urban
w	-	Weeks
Y	-	Yes