

A Comparative Study of Role of Newer Antibiotics on Bacterial Corneal Ulcer

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ABSTRACT

Introduction: Cornea is a transparent, avascular structure, constituting 1/6th of the anterior fibrous coat eyeball and providing about two thirds of the eye's refractive power. Inflammation or infective condition of the cornea results in disruption of its epithelial layer with involvement of the corneal stroma resulting in a painful condition called as corneal ulcer. Despite the best available treatment options course of the disease is unpredicted and prognosis is uncertain. With the advent of newer antibiotics there is a paradigm shift in the treatment of bacterial corneal ulcer. This study was carried out to study the role of newer antibiotics in the treatment of bacterial keratitis so that the complications and aftermath of corneal ulcer can be overcome.

Material and Methods: A prospective, observational, cross-sectional study was conducted among patients attending ophthalmology OPD and IPD in a tertiary care teaching hospital of Jharkhand.

Results: Total 50 patients with corneal ulcer were studied after meeting the inclusion criteria. Corneal ulcer was more commonly seen in males (59.97%). Most common age group affected was 51-60 years. Gram positive cocci were found in 70% cases followed by gram negative bacilli (16%). Staph aureus was found in 59.58% of isolates and Pseudomonas aeruginosa in 17.02%. History of trauma was noted in 76.59% of cases. Vegetative matters constituted over 65% of cases of trauma. Moxifloxacin and Besifloxacin and to a lesser extent Cefazolin was the most effective antibiotics in most of the cases of bacterial corneal ulcer. Gatifloxacin and Ofloxacin were almost equally effective in gram positive bacteria but are mildly sensitive to Pseudomonas infection. A few cases of Pseudomonas ulcer are resistant to Gatifloxacin, Ofloxacin, Cefazolin and Cephaloridine. Ofloxacin and Tobramycin had better effect of Pseudomonas but had mild effect on gram positive pure and mixed infections.

Conclusion: Study suggests most effective therapy to be 0.5% Moxifloxacin for aerobic gram negative organism. Besifloxacin 0.6% was effective in most of Gram positive and Gram negative infections.

Keywords: Bacterial Corneal Ulcer, Gram Positive Bacteria, Gram Negative Bacteria, Moxifloxacin, Besifloxacin

primary physiological function of cornea are 1) to act as a major refracting medium; and 2) to protect the intraocular contents. It fulfills this duty by maintaining its transparency and replacement of its tissues. The transparency is the result of peculiar arrangement of corneal lamellae, avascularity and relative state of dehydration, which is maintained by barrier effects of epithelium and endothelium and the active bicarbonate pump of the endothelium. It gains nutrition via simple diffusion or active transport through aqueous humour and by diffusion from the perilimbal capillaries. Oxygen is derived directly from air through the tear film. This is an active process undertaken by the epithelium.¹

A corneal ulcer is a break in the epithelium with underlying stromal necrosis which results in permanent corneal opacity, which if not taken care of may lead to gross visual disturbance and if complicated may cause loss of the eye.¹ In India there are over 12 million blind people of which 15.4% are corneal blind, out of these 9.34% are solely because of corneal ulceration.² Corneal ulcer is a common entity encountered in general practice and the affected communities are farm workers, miners, industrial workers etc.³ Despite the best available treatment options, it poses a challenging problem to the ophthalmologists as etiology is varied, course is unpredicted and prognosis is uncertain. Early diagnosis and prompt treatment may prevent sight threatening sequelae. If the disease advances, it has the potential to lead to irreversible damage. Usually corneal ulcer heals, leaving behind various grades of opacification incapacitating an individual, who remain a liability to the family and community for the rest of their life.

Virulence of the organism and integrity of host defense mechanism are the important determinant in causing corneal ulceration. With breach in corneal epithelium due to minor or major trauma, there is breach in physical and chemical barriers. This leads to secondary infection caused by the organism either present in conjunctival sac or exogenously.⁴ Intact corneal epithelium can be evaded by Neisseria gonorrhoea, Neisseria meningitidis and Corynebacteria diphtheriae only. Pneumococcus can when the corneal

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INTRODUCTION

Cornea forms anterior one sixth of the outer fibrous coat of the eyeball. It is composed of an outer stratified squamous non keratinized epithelium, an inner dense connective tissue stroma with its resident fibroblast like keratocytes and a mono layered cuboidal epithelium bordering the anterior chamber. Thickness of cornea in the centre is about 0.52mm while at the periphery it is 0.7 mm. The two

epithelium is damaged. Other than this various pyogenic organism, viruses, fungi can cause corneal ulcer.^{5,6} Some disease conditions like ocular pemphigoid, keratoconjunctivitis sicca, Stevens Jhonson syndrome also cause secondary bacterial keratitis.

Various antibiotics have been used for treatment of bacterial keratitis. Previously used antibiotics like Methicillin, Cephalosporins, Aminoglycosides, Erythromycin, Tetracyclin and Chloramphenicol have become resistant.^{7,8} Thus in recent years, there is a paradigm shift in the treatment of bacterial corneal ulcer with the use of newer antibiotics like Ofloxacin, Gatifloxacin, Tobramycin, Besifloxacin and Moxifloxacin.⁹ However with the use of these antibiotics also the incidence of corneal ulcer has kept on increasing, mainly because of injudicious use of steroids and increase in resistance of the organism.¹⁰⁻¹³ Therefore the selection of antibiotics is important to reduce the complications and to prevent the dreaded sequel of corneal ulcer.

This study was carried out to study the pathogens associated with the bacterial corneal ulcer and to study the role of newer antibiotics in the treatment of bacterial keratitis so that the complications and aftermath of corneal ulcer can be overcome.

MATERIAL AND METHODS

A study was carried out in RIO, RIMS, Ranchi on patients attending Ophthalmology OPD and IPD during May 2011 to October 2012 and clinically suggestive of corneal ulceration. A detailed clinical history of patient was taken. Clinical examinations involving both general and local examinations of the affected eye with slit lamp was conducted. Ulcer details were noted and necrotic exudates and debris was removed with sterile normal saline. Scrapings from the corneal ulcer bed and margin were collected after instillation of anesthetic eyedrops, using a sterile Bard Parker blade no.15 and it was sent to the microbiology department for further evaluation. Meanwhile the treatment was initiated as per the study protocol certified and accepted by institutional ethics committee of RIMS, Ranchi. Study was conducted under the aegis of declaration of Helsinki and proper consent from the patients was taken before starting the study. All the findings were documented in a standard performa prepared with the help of faculty members of Department of Ophthalmology. This was a prospective study to identify the common etiological agents, predisposing factors, age, gender, and occupational distribution of the patients and to study the clinical features and management of corneal ulcer.

STATISTICAL ANALYSIS

Statistical analysis was done with the help of descriptive statistics and result was expressed in percentage.

RESULTS

The study included 50 cases for study after meeting the inclusion criteria. Figure 1 represents the result of bacteriological examination where 70% cases were gram positive cocci, followed by gram negative bacilli (16%). Staph aureus was found in 59.58% of isolates and

Type of occupation	No. of cases	Percentage
Farm workers	18	38.29
Labourers	5	10.63
Vendors	2	4.25
Businessmen	1	2.12
Electrician	1	2.12
Florist	4	8.51
Student	2	4.25
Housewife	4	8.51
Children	10	21.27

Table-1: Incidence of corneal ulcer in different occupation

Socio economic status	No. of cases	Percentage
Higher	3	6.38
Middle	12	25.53
Lower middle	22	40.43
Poor	13	27.66

Table-2: Corneal ulcer in different socio economic strata of society

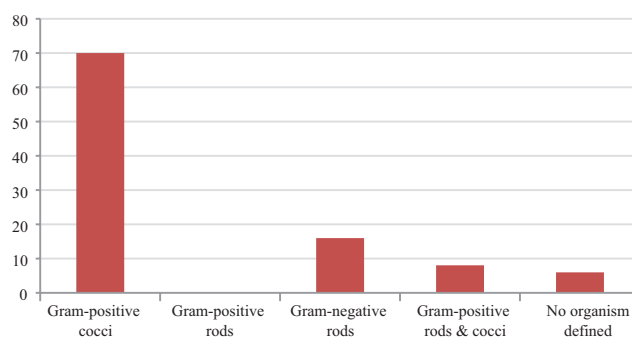


Figure-1: Bacteriological profile of corneal ulcer (%)

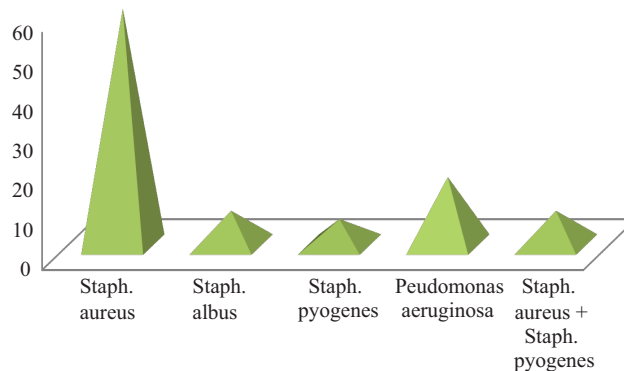


Figure-2: Incidence of different pathogens (%)

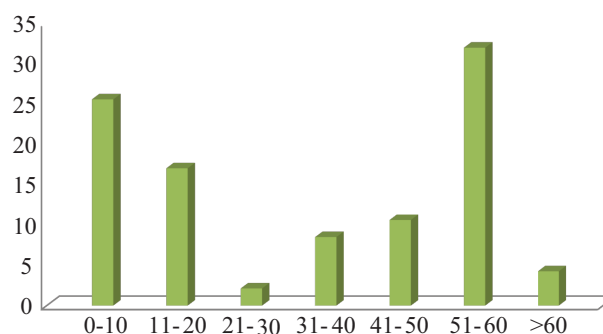


Figure-3: Break up of various organism in various age groups(%)

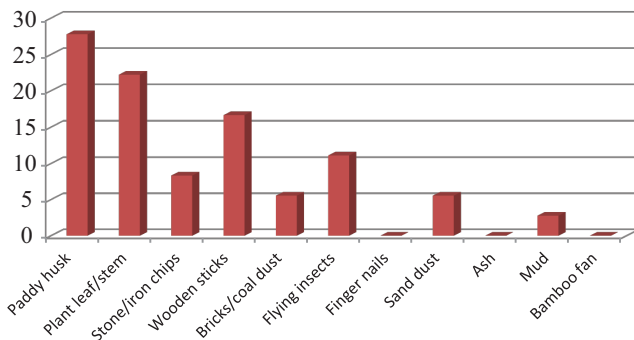


Figure-4: Traumatic agents(%)

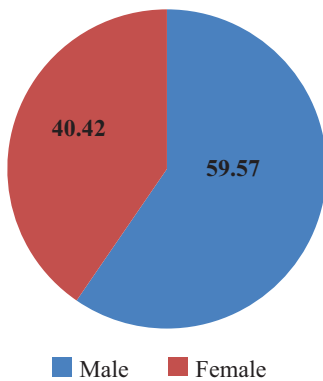


Figure-5: Sex Incidence (%)

Pseudomonas aeruginosa in 17.02%. 8.51% was mixed culture (Staph aureus and Staph albas) Figure 2. Staph aureus was predominantly found in extreme of ages i.e. 0-10 and 51-60 year age group (Figure 3). Definite history of trauma was noted in 76.59% of cases. Vegetative matters such as paddy husk, plant leaf/stem and wooden stick together constituted over 65% of cases of trauma. Flying insects were causative agents in 11.11%, and stone/iron chips in 8.33% of cases (Figure

4). It was also found that younger patients and persons older than 50 year were more prone to injury and subsequent development of corneal ulcer. In this study, corneal ulcer is more common in males (59.97%) (Figure 5). Farm workers were most exposed occupation group (38.29%) of cases followed by laborers. 21.27% children from rural and urban background were affected (Table 1). In this study it was also found that lower middle class and poor accounted for almost two third cases of corneal ulcer (Table 2). Total 9 patients (17%) had associated conditions of eye and adenexa.

In this study, 12.76% cases had central corneal ulcer i.e. ulcer situated in the central 5 mm diameter and 87.23% cases had peripheral corneal ulcers i.e. within 3 mm from the limbus. Hypopyon was seen in 23.40% of cases. It was observed that Moxifloxacin and Besifloxacin and to a lesser extent Cefazolin was the most effective antibiotics in most of the cases of bacterial corneal ulcer. Tobramycin had better effects on *Pseudomonas aeruginosa* but moderate effect on Staphylococcal infection. Gatifloxacin and Ofloxacin were almost equally effective in gram positive bacteria but are mildly sensitive to *Pseudomonas* infection. A few cases of *Pseudomonas* ulcer are resistant to Gatifloxacin, Ofloxacin, Cefazolin and Cephaloridine. Ofloxacin and Tobramycin had

better effect of *Pseudomonas* but had mild effect on gram positive pure and mixed infections.

The cases were followed up for a period of 6 weeks. The period of healing was about 2-3 weeks in maximum number of cases (70.20%). In two cases there was total loss of the eye and evisceration had to be done. It was also found that normally the corneal ulcer took 2 to 3 weeks to heal after proper antibiotics were started. Few cases which took longer time were either mixed infection or due to poor compliance on the part of the patients or due to secondary bacterial infection acquired during hospital stay. In majority of the cases, the end result was leucoma 36.17%, followed by nebula 34.04%. It was also seen that patients who turned up earlier had lesser grades of opacification than those who turned up later for treatment.

DISCUSSION

Present study showed the high incidence of *Staphylococcus aureus* causing corneal ulcer. Similar results were seen in study by Asbell P et al.⁶ in 33%, Mahajan VM et al¹⁴ in 31% and Rao et al¹⁵ in 35% of cases. Incidence of *Staphylococcus albus* in this study was found to be 20% in pure culture and 4.4% in mixed culture with *Staphylococcus aureus*. Nema et al¹⁶ found *Staphylococcus albus* in 33.6% of cases, Rohtagi et al¹⁷ in 50% of cases and Asbell P et al⁶ in 16% of cases. Thus *Staphylococcus aureus* and *Staphylococcus albus* are the main pathogens causing bacterial keratitis.

Streptococcus is relatively uncommon pathogen in corneal ulcers. In the present study, *Streptococcus pyogenes* was found only in 3 cases (6.67%) as pure culture and in 1 case as mixed culture with *Staphylococcus aureus*. Nema et al found *Streptococcus virridans* in 3% and Asbell P et al in only 1% of cases in their study.

Pseudomonas aeruginosa is the most commonly found gram negative bacteria in this study. They are motile with the help of polar flagella, highly virulent and capable of causing disastrous effect on corneal stroma by producing calcium activated collagenases. In the present study, this organism was isolated in 17% of cases and all were pure culture. Nema et al reported this in 5.5% of cases, Rohtagi et al in 3.5% of cases. The present finding suggests that there is rise in the incidence of *Pseudomonas* infection causing bacterial keratitis.

Mixed culture (*Staphylococcus aureus* and *Streptococcus pyogenes*) were obtained only in 4 cases (8.51%) in this study. Most of these are normally present in conjunctival sac. All the cases showing mixed culture had a definite history of trauma.

Sensitivity tests were carried out in this study by disc method, placing the antibiotics (Moxifloxacin, Besifloxacin, Ofloxacin, Gatifloxacin, Tobramycin, Cefazolin, Cephaloridine) discs.

Staph aureus was most sensitive to Moxifloxacin, Besifloxacin, and Cefazolin and moderately sensitive to Ofloxacin and Tobramycin.

Of the 28 isolates of *Staphylococcus aureus*, 22 cases were most sensitive to Moxifloxacin, Besifloxacin, and Cefazolin,

moderately sensitive to Gatifloxacin, Tobramycin and Ofloxacin and mild sensitive to Cephalexin. Remaining 6 cases were highly sensitive to Moxifloxacin moderately sensitive to Besifloxacin, and least sensitive to Cephalexin. Staphylococcus albus was found in 4 cases. Out of 4 cases, 2 cases were most sensitive to Moxifloxacin, Besifloxacin, moderately sensitive to cefazolin and mild sensitive to gatifloxacin, Ofloxacin and Tobramycin. It was least sensitive to Cephalexin. Leibowitz HM¹⁸ compared the effect of Ciprofloxacin and Tobramycin. He found that Ciprofloxacin was effective in 94.5% of bacterial keratitis and Tobramycin in 91.9% cases of Gram positive keratitis. Hyndiuk RA, Eiferman RA et al¹⁹ in a comparative study of Ciprofloxacin vs. Fortified Tobramycin-Cefazolin concluded that Ciprofloxacin ophthalmic solution (0.3%) monotherapy is equivalent clinically and statistically to standard therapy of Fortified Tobramycin – Cefazolin for the treatment of bacterial corneal ulcer and also produced significantly less discomfort.

Gokhale NS et al⁷ has shown that Ciprofloxacin is superior to other antibiotics in terms of Post antibiotic effect, penetration to ocular tissue, high activity in pus and high intraocular efficacy.

3 cases of streptococcus pyogenes were most sensitive to Moxifloxacin, Besifloxacin, Ofloxacin, moderately sensitive to Gatifloxacin and Tobramycin. It was resistant to Cephalexin. Moxifloxacin, Cefazolin and Besifloxacin has excellent effect on Streptococcus and Ofloxacin is almost equally effective. These studies have shown that there is emergence of new strains of Staphylococcus and Streptococcus also.

Of the gram negative rods, Pseudomonas aeruginosa is the most important organism. In the present sensitivity work, 8 cases were most sensitive to Moxifloxacin, Cefazolin, Besifloxacin and Tobramycin. Out of 8 cases, 3 cases were resistant to Gatifloxacin, Ofloxacin, Cephalexin and cephazolin but moderately sensitive to Tobramycin. Moxifloxacin, Besifloxacin and Tobramycin have almost equal effect on Pseudomonas aeruginosa.

Of the 4 cases of mixed culture, comprising Staph aureus and Strept pyogenes (4 cases), these were most sensitive to Moxifloxacin, Besifloxacin and Cefazolin. Four cases of mixed culture comprising Staph aureus and Strept pyogenes was highly sensitive to Moxifloxacin, Besifloxacin, moderately sensitive to Gatifloxacin and Ofloxacin and mild sensitive to Tobramycin and Cephalexin. It shows that even for mixed Gram positive cultures, Moxifloxacin and Besifloxacin is the most effective drug than any other antibiotics.

After healing of cornea, the amount of scarring depends upon the virulence of bacterial infection and it causes impaired vision. The grade of corneal ulcer depends on the depth of corneal ulcer involved. Visual loss is often preventable or kept to its minimum if the cause is determined early and appropriate treatment is begun. Antibiotics must be administered in timely manner and in sufficient quantity to inhibit bacterial replication and to limit invasion and

destruction of corneal stroma by the causative organism. Both Gram positive and Gram negative bacteria can cause serious infection of cornea. Therefore if one is to treat such infection with a single antibacterial agent, it should be a broad spectrum antibiotic eye drop.

The organisms commonly associated with bacterial corneal ulcers are increasingly become resistant to standard therapy. Borrmann and Leopold²⁰ reported 8-10% of the ulcerative keratitis is caused by aminoglycosides resistant strains of Pseudomonas aeruginosa and subsequently it appears that resistance in Gram positive organism is also increasing. Data indicates that Moxifloxacin, Besifloxacin and Cefazolin is highly effective against common ocular pathogens causing corneal ulcer and these are more efficacious and with wider spectrum of action than aminoglycosides. Thus these observations suggest that Moxifloxacin can be effectively used as a single agent to treat bacterial keratitis. No systemic side effects and alteration of laboratory parameters have been reported with use of topical Moxifloxacin eye drops.

CONCLUSION

In this study, 50 cases of bacterial corneal ulcer were studied in details with a view to explore and assess the role of various etiological factors responsible for the causation of bacterial corneal ulcer as well as the sensitivity of newer antibiotics in treatment of bacterial corneal ulcer. Trauma was responsible for maximum number of cases with wooden stick trauma, stone, paddy husk and plant leaf were the common causative agents. Incidence of bacterial corneal ulcer was highest in the age group 0-10 years and above 50 years. This may be due to lowered tissue resistance in these extremes of life. Male were affected more commonly, this may be due to outdoor nature of work performed by male. Bacterial corneal ulcer was found to be common in lower middle class and poor, accounting to almost two third of the cases under the study. Staphylococcus aureus, Pseudomonas aeruginosa, Staphylococcus albus and Streptococcus pyogenes in decreasing order respectively were the causative agent. Most effective therapy suggested was 0.5% Moxifloxacin for aerobic gram negative and aerobic micro-organism. Besifloxacin 0.6% was effective in most of Gram positive and Gram negative infections.

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