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Original Research Article

Comparative Evaluation of Fourth Generation Fluoroquinolones with Fortified Cephazolin in the Treatment of Bacterial Corneal Ulcers

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ABSTRACT

Purpose: To study efficacy of fourth generation fluoroquinolones versus conventional fortified cephazolin eye drops for the treatment of bacterial corneal ulcers.
Method: 40 diagnosed cases of bacterial corneal ulcers were randomly allotted into two groups: Group 1 patients were treated using fortified cephazolin (50 mg/ml) and, group 2 with commercially available fourth generation fluoroquinolone-Moxifloxacin 0.5% eye drops.
The responses to treatments were analyzed according to the size of corneal ulcer and anterior chamber cell reaction at second and third weeks. Also size of the residual corneal opacity was analyzed after complete healing of corneal ulcer was compared.
Data were statistically analyzed using appropriate test of significance using SPSS software (version16.0)
Results: Data was statistically analyzed using t- test. In this study, both the groups were equally matched in terms of size of the ulcer and anterior chamber cell reactions, at the time of presentation with p- values 0.85 and 0.06.
At 2 weeks after initializing the treatment, the difference in response to treatment in group 2 was statistically significantly better as compared to group 1 with p values of 0.008 and 0.0004 for corneal ulcer size and anterior chamber cell reactions, respectively. Similarly, with $p< 10^{-6}$ for both at week 3 of treatment.
Comparing the size of residual corneal opacity after complete healing of the corneal ulcers in group 2 was statistically significantly smaller as compared with group 1 with p=0.0004.
Conclusion: The current study shows that treatment response of bacterial corneal ulcers with fourth generation fluoroquinolones is significantly better than conventional treatment with fortified cephazolin eye drops.

Keywords: Bacterial corneal ulcer, fortified cephazolin, fluoroquinolones, moxifloxacin.

INTRODUCTION

A corneal ulcer or ulcerative keratitis is an infective condition of the cornea involving disruption of its epithelial layer with the involvement of the corneal stroma. [1] It is a common condition in humans particularly in the tropics, in developing countries they are caused by trauma, particularly with vegetative matter as well as chemical injury, contact lenses and infections. Other eye conditions can cause corneal ulcers such as entropion, distichiasis, corneal dystrophies and keratoconjunctivitis sicca (dry eye). Bacterial keratitis is caused by Staphylococcus aureus, Streptococcus

viridans, Escherichia coli, Pseudomonas, Nicardia and other bacteria. [1]

Bacterial keratitis can occur in any part of the cornea, but infections involving the central or paracentral cornea are of paramount importance. Scarring in this location has the potential to cause substantial visual loss, [2] even if the infecting organism is successfully eradicated. Although some bacteria (e.g., *Neisseria gonorrhoeae*) can invade an intact corneal epithelium, most cases of bacterial keratitis develop at the site of an abnormality or defect in the corneal surface.

Risk factors include contact lens use, anterior segment surgery, ocular trauma, chronic epithelial defects, other ocular surface disease, and local and systemic immunosuppression. Likely pathogens vary by geography and etiology as well as the previous use of antibiotics. Patients present with pain, redness, photophobia, foreign body sensation, and varying degrees of decreased vision. The hallmark finding is a single suppurative corneal infiltrate, usually central or paracentral, with an overlying epithelial defect. [3] Atypical presentations, such as intraepithelial keratitis or infectious crystalline keratopathy, are rare.

Bacterial corneal ulcer require intensive antibiotic therapy to treat the infection Fortified drugs were the conventional line of treatment, which mainly included cephalosporins, aminoglycosides, penicillins, beta lactamases, fluoroquinolones, macrolides, sulphonamides, tetracyclines and chloramphenicol. [4]

Cephalosporins are semi-synthetic, penicillin-like bactericidal agents which interfere with bacterial cell wall synthesis. They act against staphylococci and penicillinase-producing Streptococci as well as some gram negative bacteria especially Escherichia coli, Proteus and Klebsiella. Third and fourth generation cephalosporins are also effective against Pseudomonas species. [5]

Cefazolin[6] (also known as cefazoline or cephazolin) is a semi-synthetic first generation cephalosporin for parenteral administration. Cefazolin has broad-spectrum antibiotic action due to inhibition of bacterial cell wall synthesis. It attains high serum levels and is excreted quickly via the urine. The bactericidal action of cephalosporins results from inhibition of cell wall synthesis. By binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, it inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins.

Fourth generation fluoroquinolone monotherapy (e.g.: Gatifloxacin or moxifloxacin) is a good alternative to the conventional therapy and has demonstrated encouraging results, documented by meta-analysis and randomized controlled trials where both forms of treatment have shown comparable results in terms of efficacy and safety. [7]

Fluoroquinolones demonstrate added advantages over fortified antibiotics in terms of better stability, longer shelf life and reduced epitheliotoxicity, with the added advantage of not requiring refrigeration. [7]

Among the fluoroquinolones, the fourth generation (gatifloxacin and moxifloxacin) demonstrate the superiority over older generations (ciprofloxacin, ofloxacin) in terms of better coverage against both Gram-positive and Gram-negative microbes with no resistance documented until date. [7] Moxifloxacin has got the highest aqueous humour penetration, followed by gatifloxacin, with ciprofloxacin having the least penetration into the aqueous humour.

Bacterial keratitis accounts for a significant proportion of infectious keratitis worldwide and may have diverse clinical presentation depending on the geographical location and climatic conditions. Gram-positive bacteria such as coagulase-negative Staphylococcus, Staphylococcus aureus, and Streptococcus species account for most the organisms isolated. [1] The protocol for the management of bacterial keratitis ideally

involves collection of corneal scraping material for smear and culture and starting empirical intensive antimicrobial therapy until culture and antibiotic sensitivity reports are available. The regimens of empirical therapy practiced across the world are either monotherapy with a broad-spectrum antibiotic [8] or a combination of two antibacterial drugs to cover both gram-negative and gram-positive organisms.

This prospective, randomized study was conducted to evaluate and compare the efficacy and safety of therapy with fortified cephazolin 50mg/ml eye drops versus monotherapy with moxifloxacin hydrochloride 0.5% eye drops in patients with bacterial corneal ulcers.

MATERIALS AND METHODS

STUDY AREA: Study was carried out in department of ophthalmology at a tertiary care hospital in Central India.

STUDY SUBJECTS: All patients diagnosed with bacterial corneal ulcer with diameter 2-8 mm. Patients with unilateral corneal ulcer that was clinically and microbiologically bacterial in etiology and 2–8 mm in diameter were included in the study if they were willing to participate and complete at least 3 weeks of follow-up. Antibiotic susceptibility testing for both the drugs cephazolin (50 mg/ml) and moxifloxacin 0.5% of the bacterial isolates was done according to standard method. After taking the corneal scraping, the patient was prescribed the study treatment.

Group 1 received treatment with fortified cephazolin (50 mg/ml) eye drops.

Group 2 received treatment with commercially available fourth generation fluoroquinolone- Moxifloxacin 0.5% eye drops.

TYPE OF STUDY: Hospital based Randomized control trial

SAMPLE SIZE: All patients attending ophthalmology OPD fulfilling inclusion criteria

Patients were selected according to following criteria:

a) Inclusion criteria:

1) All patients diagnosed with bacterial corneal ulcer with diameter 2-8 mm.
2) The patients were screened for microbiology culture and antibiotic sensitivity testing, and those with bacterial etiology with sensitivity positive for both the drugs were included
3) Those who have not taken any prior treatment or instilled any antibiotic eye drops.

b) Exclusion criteria:

1) Patients of recurrent corneal ulcers.
2) Patients with preexisting corneal dystrophy
3) Patients with uncontrolled diabetes mellitus
4) Immunocompromised patients.

Duration of study: 18 months.

Procedure: This was a prospective unmasked clinical trial. Ethical clearance was obtained from the Ethics Committee. Written informed consent was obtained from all patients before initiation of any study medication or study-related procedure. Patients were enrolled from the outpatient department. Patients with unilateral corneal ulcer that was clinically and microbiologically bacterial in etiology and 2–8 mm in diameter were included in the study if they were willing to participate and complete at least 3 weeks of follow-up.

At presentation the largest diameter of the corneal ulcer was measured with the help of slit-lamp biomicroscope after fluorescein staining.

Corneal ulcers were scraped for Gram stain analysis and potassium hydroxide wet mount. A sterile Kimura spatula was used to directly inoculate the scraped material onto blood agar and Sabouraud dextrose agar medium.

After taking the corneal scraping, every alternate patient was allotted either group 1 or 2 treatment, without any further delay.

Group 1 received treatment with fortified cephazolin (50 mg/ml) eye drops.

Group 2 received treatment with commercially available fourth generation fluoroquinolone- Moxifloxacin 0.5% eye drops.

Preparation of fortified cephazolin (50 mg/ml) eye drops [9]

A 'positive' culture required at least 10 colonies of the same species on 2 or more culture media or confluent growth on multiple inoculation sites on one solid medium. [10] Antibiotic susceptibility testing for both the drugs cephazolin (50 mg/ml) and moxifloxacin 0.5% of the bacterial isolates was done according to standard method. After taking the corneal scraping, the patient was prescribed the study treatment.

Patients were divided into 2 groups by randomization by systematic random sampling. Group 1 received combination therapy with fortified antibiotics, that is, cephazolin (50mg/ml) and Group 2 received monotherapy with moxifloxacin 0.5%.

The patients were advised to put one drop from the study medications each hour round the clock for the initial 48–72 hours. Ancillary therapeutic measures such as lid hygiene, and oral analgesics were permitted. No alternative concomitant antibiotics were allowed. Adjunct medications were prescribed such as cycloplegics (homatropine bromide 2%), antiglaucoma medications, and preservative-free lubricants as required. All other concomitant medications were noted. Follow-up examination was done initially every 48– 72 hours. At each follow-up, slit-lamp biomicroscopic examination was conducted.

The size of the ulcer and infiltrate were noted at three instances for statistical analysis: first, initially at the time of presentation and later at 2 and 3 weeks after starting treatment as described above.

The ulcer status was defined according to criteria laid down in following table.

Ulcer Status and Titration of Treatment		
Ulcer Status	Definition	Treatment Modification
Healing ulcer	Ulcer/infiltrate decreasing in size but not completely re-epithelialized	Medications were tapered as follows: days 3–6: 1 drop at 2 hourly intervals round the clock; days 7–9: 2 hourly intervals in waking hours; days 9: 6 hourly intervals- continued till the ulcer was healed completely
No change in ulcer. Worsening ulcer	Ulcer/infiltrate of same size at the end of 72 hrs. Ulcer/infiltrate increasing in size or evidence of complications like spread of infection, endophthalmitis, ulcer perforation, and adverse drug reaction.	In this case, the medication was discontinued and the case was taken as treatment failure. The cause, if any, was noted, and the patient was put on a drug regimen as seemed appropriate. The patient was followed up in the study on an intention-to-treat basis.
Healed ulcer	Complete re-epithelialization with no fluorescein staining of cornea	Antibiotics were stopped if the ulcer healed

The study medications were then tapered as per the clinical condition of the ulcer as shown in the above table. Ulcers that worsened or showed no change on treatment after a minimum duration of 3 days were considered as treatment failures. They were given alternative antibiotic therapy as considered appropriate by the treating ophthalmologist. All patients were followed up regularly till they reached either of the outcomes, that is, healed ulcer or treatment failure.

The response of the treatment was analyzed according to the anterior chamber

cell reaction (SUN classification system 2005) [11] and size of corneal ulcer on the second and third weeks. Also size of the residual corneal opacity was analyzed after complete healing of the corneal ulcer as evidenced by slit lamp microscopy examination with negative fluorescein staining under cobalt blue filter.

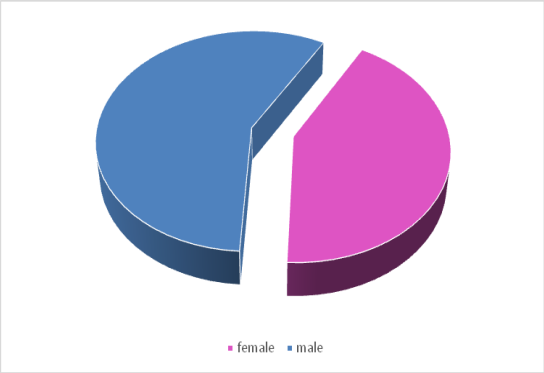
The SUN working group grading system for anterior chamber cells

Grade	Cells in field
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

All patients were also evaluated for safety of study medications. Any adverse reaction to the study medication such as stinging sensation, burning, allergic blepharitis, corneal precipitates, or headache were noted.

RESULTS

Gender distribution: 40 patients consisting of 17 females and 23 males were included in this study.



The response to treatment in groups 1 and 2 was analyzed comparing 3 parameters:

1. Size of the ulcer at weeks 2 and 3
2. Sun classification of anterior chamber cells reaction at weeks 2 and 3
3. Size of residual corneal opacity after complete treatment of corneal ulcer

1. ANALYSIS BASED ON SIZE OF CORNEAL ULCER:

Size of corneal ulcer (in mm) at the time of presentation in

- Group 1 was mean of 4.75, mode of 5, Median 5, SD 1.04
- Group 2 mean 5.2, mode 4, Median 5, SD 1.56 mm
- By application of t test p value is 0.85, >0.05 hence the difference is statistically insignificant.

Size of corneal ulcer (in mm) after starting treatment:

Week 2:

- Group 1: Mean 2.5, Mode 2, Median 2, SD 0.92
- Group 2: Mean 1.65, Mode 2, Median 2, SD 1.01
- By t-test P value 0.008,<0.05 hence statistically significant.

Week 3:

Similarly comparing response to the treatment in the two groups at the end of 3rd week, the p value is $<10^{-6}$

2. ANTERIOR CHAMBER CELL REACTION (SUN WORKING GROUP OF CLASSIFICATION) [11]

❖ At the time of presentation

AC reaction in patients of Group 1 and 2 is statistically equally matched with a p value of 0.06

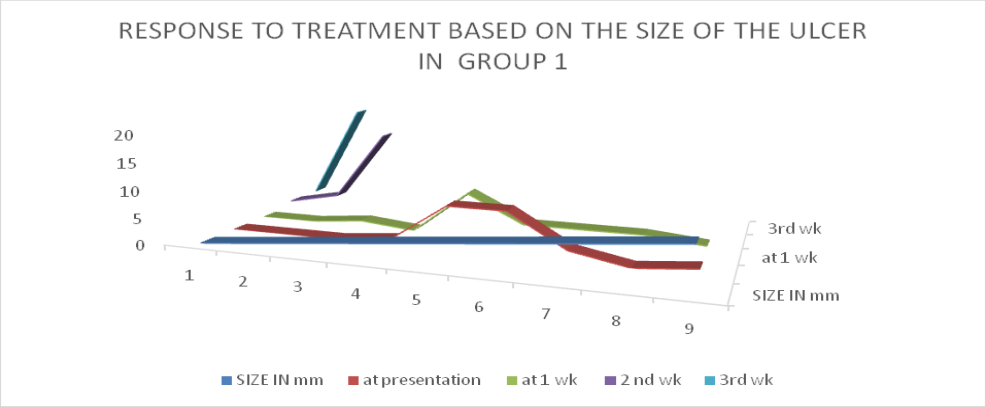
❖ Two weeks after treatment anterior chamber cell reaction

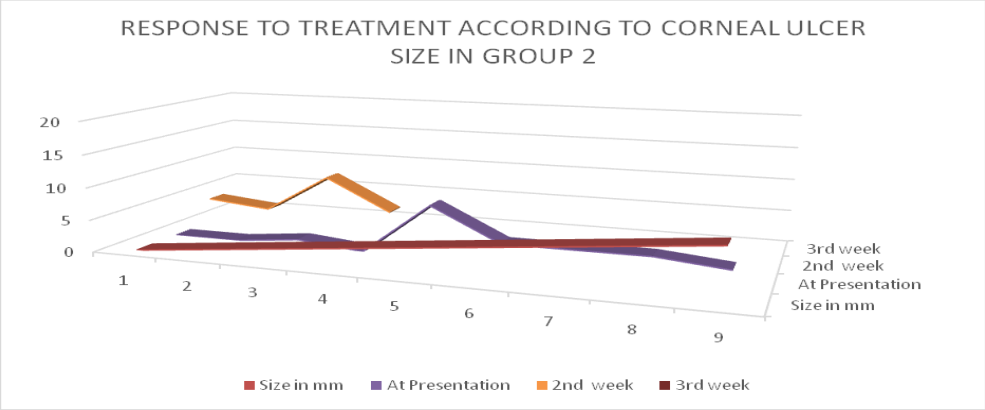
- Group 1 mean 1.75, Median 2, Mode 2, SD 0.53
- Group 2 Mean 0.8, Median 1, Mode1, SD O.74
- t-test p value 0.00004 difference statistically highly significant

❖ 3rd week

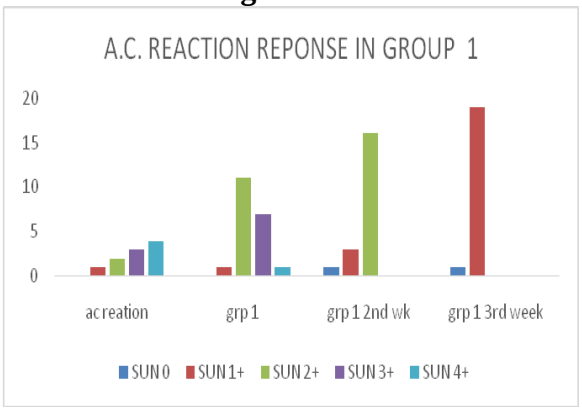
p- value less than 10^{-6} highly significant

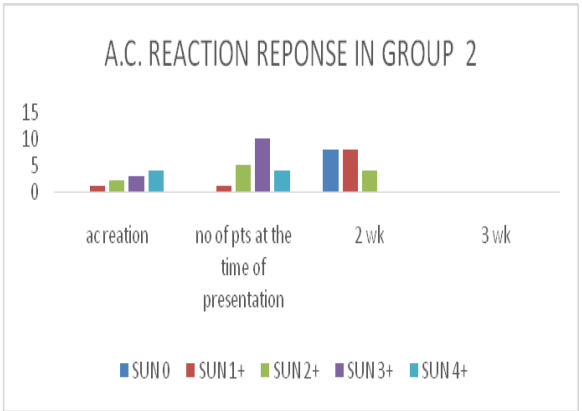
Graphical representation:





Graphical representation of AC cell reaction according to SUN classification:

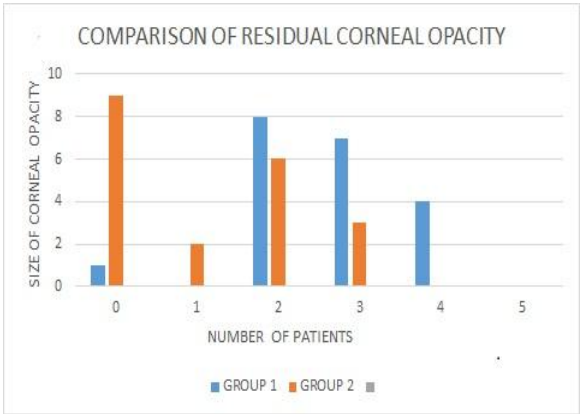




3. RESIDUAL CORNEAL OPACITY (in mm)

The outcomes of treatments in groups 1 and 2 were analyzed by comparing size of the residual corneal opacity as evidenced by slit lamp microscopy examination with fluorescein staining under cobalt blue filter.

- Group 1 Mean 2.55, Median 2.5, Mode 2, SD 0.92
- Group 2 Mean 1.15, Median 1, Mode 0, SD 1.15
- p = 0.00004 applying t-test, difference statistically highly significant.



DISCUSSION

The successful management of bacterial corneal ulcers is based on prompt identification and effective treatment with an appropriate antibiotic. Unfortunately gram stain and culture results are not always positive, hence various authors suggest initializing blanket therapy with broad spectrum topical antibiotics. [12]

The current study was designed to compare and evaluate the efficacy and safety of fourth-generation fluoroquinolones and fortified cephazolin in the treatment of bacterial corneal ulcers. Only 40 patients were enrolled because this was a time-bound study. The 2 treatment groups were comparable with regard to baseline demographic characteristics of age, sex or laterality, and mean duration of symptoms before presentation. There were 23 males (58%) and 17 females (42%). The corneal ulcer was seen more commonly in males in a ratio of 0.74.

The response to treatment in groups 1 and 2 was analyzed comparing 3 parameters that is size of the ulcer, anterior chamber cells reaction at end of second and third week of treatment and residual corneal opacity at the end of the treatment after complete healing and re-epithelialization of the corneal ulcer.

Various studies were undertaken on similar parameters like the Gangopadhyaya et al. [13] in which they compared the clinical efficacy of commercially available fluoroquinolone drops with the use of combined fortified antibiotics (tobramycin 1.3%-cefazolin 5%) in treatment of bacterial corneal ulcer of 140 patients and concluded that fluoroquinolones have a shorter duration of intensive therapy and quicker clinical response of healing (p=0.02) as compared to combination of fortified antibiotics.

In a meta-analysis by M S Hanet et al. [14] they concluded that it is reasonable to consider fluoroquinolone as the first choice for empirical treatment in most cases of suspected bacterial keratitis. Similar findings were suggested by A. Austin et al. [15] in a study conducted on 140 eyes.

In our study we concluded that patients in group 2, that is, those treated with moxifloxacin 0.5% eye drops responded to the treatment earlier, had clearer corneas at the end of the treatment, with significantly greater reduction in the size of corneal ulcer at the end of 2^{nd} week ($p=0.008$) and $p<10^{-6}$ at the end of 3^{rd} week, as compared to group 1 (fortified cephazolin 50mg/ml)

The anterior chamber cell reaction, as measured according to SUN working group classification, showed a better response in group 2 patients with $p=0.0004$ at 2^{nd} week of treatment and $p,10^{-6}$ at 3^{rd} week, which is significantly better as compared to response of patients in group 1.

The residual corneal opacity, after complete healing of the bacterial corneal ulcer, was significantly lesser in size in patients of group 2 ($p=0.0004$) as compared to group 1.

Thus, our findings were concurrent with Gangopadhyaya et al., [13] M S Hanet et al. [14] and A. Austin et al. [15]

Additional benefit of monotherapy with fourth generation fluoroquinolone was longer shelf life, no need of refrigeration, and availability of commercially prepared eye drops as compared to need of reconstitution required for preparing fortified cephazolin eye drops.

The additional cost for reconstituting fortified cephazolin eye drops consist of price of injectable antibiotic plus a preservative free commercially available lubricating eye drops. Also, need of refrigeration [16] adds to the cost to the treatment. The shelf life [17] of reconstituted fortified cephazolin eye drop is limited to 1 week when stored at 4 degrees Celsius, thus making repeated preparations inevitable, adding to the cost of treatment and requiring skilled personnel.

CONCLUSION

The current study shows that response to the treatment of bacterial

corneal ulcers with fourth generation fluoroquinolones is significantly better than conventional treatment with fortified cephazolin eye drops, with earlier healing and re-epithelialization of the ulcer.

Treatment with fourth generation fluoroquinolones is more economical for the patient as owing to its longer shelf- life without need of refrigeration, as compared with fortified cephalosporin eye drops.

The morbidity due to residual corneal opacity is significantly lesser with fourth fluoroquinolones as compared with fortified cephalosporins.

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