CLINICAL STUDY

Comparison of topical 0.3% ofloxacin with fortified tobramycin plus cefazolin in the treatment of bacterial keratitis

ANITA PANDA, RAKESH AHUJA, S. SRINIVAS SASTRY

Abstract

Purpose **Ofloxacin is a broad spectrum fluoroquinolone antibiotic with good ocular penetration. We compared ofloxacin 3% solution with a combination of fortified tobramycin sulphate and cefazolin sodium solutions in the treatment of culture-proven bacterial keratitis.**

Methods **Thirty eyes with culture-proven bacterial corneal ulcers were enrolled in a prospective randomised, controlled, double-masked study for comparison. The ofloxacin drop and saline were decanted into two identical-looking bottles to the tobramycin and cefazolin. The cases were randomly allocated into treatment with 0.3% ofloxacin solution or a combination of fortified antibiotics (1.5% tobramycin and 10% cefazolin solutions; control group) along with supportive cycloplegic, vitamins and anti-glaucoma therapy. Student's *t*-test was used to compare the results.**

Results ***Staphylococcus aureus*** **and coagulase-negative staphylococci were the two most common organisms isolated. Resolution of the ulcer was achieved in 93% and 87% of cases in the ofloxacin and control groups respectively. The mean time required for symptomatic relief was 7.8 ± 1.54 days and for epithelial healing 15.0 ± 3.86 days in ofloxacin group, compared with 8.33 ± 1.54 days for symptomatic relief and 15.46 ± 3.86 days for epithelial healing in the control group. Post-resolution best corrected visual acuity of 20/200 or better was achieved in all but one eye in both groups.**

Conclusions **Ofloxacin and combined fortified tobramycin and cefazolin topical drops were comparable for treating cases of bacterial corneal ulcer. However, considering its easy availability and cost-effectiveness, monotherapy with ofloxacin is preferred over the combined fortified tobramycin and cefazolin therapy.**

Key words Fluoroquinolone, Keratitis, Ofloxacin, *Staphylococcus*

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Bacterial infection of the cornea produces a wide spectrum of clinical signs and symptoms ranging from small peripheral superficial keratitis to deep corneal stromal ulcerations. Early diagnosis and prompt and adequate therapy is essential to eradicate the infectious agents, to prevent tissue damage and to minimise scarring or melting.[1] This further helps in preservation of the vision with maintenance of near-normal tissue integrity – the ultimate goal for therapy of infectious keratitis. Many antibiotics have been used in the past for treatment of bacterial keratitis. Several *in vitro* studies suggest that many bacteria are becoming resistant to commonly used antibiotics. Therefore there is a need to study the efficacy of newer antibiotics as and when demanded.

Ofloxacin, a new fluoroquinolone, is an anti-infective agent with potency against a wide range of gram-positive and gram-negative bacteria and obligate anaerobes.[2] Though a number of studies have been reported from western countries, no such trial has been conducted in India, perhaps due to non-availability of the drugs on the Indian market. Recently, though the drug has not come to market, it has been prepared and tested by an Indian company, Ranbaxy. To the best of our knowledge there are no published reports from India about its efficacy. We undertook a clinical trial to assess the clinical efficacy of topical ofloxacin 0.3% for the treatment of bacterial keratitis in a prospective double-masked, randomised, comparative manner versus a combination of fortified ophthalmic solutions of cefazolin sodium 50 mg/ml and tobramycin sulphate 1.5%.

Patients and methods

Patients who were suffering from bacterial keratitis and attended the Corneal service of Dr Rajendra Prasad Centre for Ophthalmic Sciences for treatment were included in the study. All the

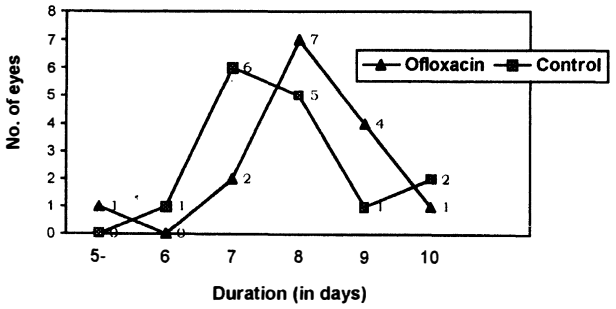

Fig. 1. *Time required for symptomatic relief* (n = *30).*

patients had a complete initial ocular examination including visual acuity, anterior segment biomicroscopy with assessment of size, location, depth and number of stromal infiltrates, and measurement of intraocular pressure. The size of the defects were measured after fluorescein staining and the ulcers were graded based on the classification routinely followed at our centre[3]. Anterior chamber inflammation (wherever possible) and the presence of hypopyon were also recorded. Corneal scrapings obtained from each patient were cultured in accordance with the standard protocol on blood agar and Sabouraud's agar, in addition to smear examination by gram staining and KOH wet mount preparation. A culture was considered positive when there was confluent growth of bacterial organisms on multiple 'c' streaks on one solid medium.[4] Patients who, though diagnosed clinically as having bacterial keratitis, showed either smear or culture positivity for fungi were excluded from the study. Thus, 30 patients who had both smear and culture positivity for bacteria were enrolled in the study.

Topical ofloxacin, saline, tobramycin and cefazolin were packaged in identical plastic bottles and labelled as 1 to 4. Details of the actual formulations were kept in a sealed flap until the end of the study. All 30 patients were randomised to receive either one bottle of ofloxacin and one bottle of normal saline solution (1 + 2) or one bottle of 1.5% tobramycin solution and 5% cefazolin solution (3 + 4).

The drug instillation protocol was one drop of each of the two solutions every 30 min for 6 h, 1 hourly on days 1–3, 2 hourly on days 4–5 and then 4 hourly until 1 week after complete resolution of the ulcer. A 5 min interval was allowed between the two drops and the drugs were instilled during the patients' waking time. Additional supportive treatment included vitamins, cycloplegic and anti-glaucoma therapy.

Clinical response to the therapy was monitored daily at the slit lamp until complete resolution. At each examination the degree of change in the epithelial defect relative to the baseline was assessed by fluorescein staining, infiltrate, aqueous flare and cells, and ciliary congestion. Subjective improvement in visual acuity and symptomatic relief were also noted. Resolution of the corneal ulcer was defined by improvement in visual acuity, complete re-epithelisation with non-progression of the stromal infiltrates, disappearance of corneal oedema and increased visualisation of iris details.

Table 1. *Composite summary* (n = *30)*

Features	Ofloxacin group (*n* = 15)	Control group (*n* = 15)
Age range (years)	15–70	14–72
Male:female ratio	3:2	3:2
Aetiology		
Trauma	6	7
Topical steroid use	2	2
Contact lens use	1	1
Mean epithelial defect (mm)	36.306 ± 3.57 (median 36; range 30–42)	35.756 ± 4.805 (median 36; range 30–43)
Hypopyon	11	9
Symptomatic relief (days)	7.8 ± 1.54 (median 8, range 6–10)	8.33 ± 1.54 (median 8, range 5–10)
Duration of healing (days)	15.0 ± 3.86 (median 13.5, range 10–26)	15.46 ± 3.86 (median 14, range 11–26)
Visual acuity		
Pre-treatment	PL,PR to CF	PL,PR to CF
Post-treatment	CF to 20/60	CF to 20/80
Residual opacity		
Full thickness	2	3
⅔ thickness	3	4
½ thickness	4	3
⅓ thickness	5	3

Statistical analysis

Comparisons between the study group and controls were made by Student's *t*-test.

Results

The age range of the ofloxacin group was 15–70 years while that of the control group was 14–72 years (Table 1). In both groups the M:F ratio was 3:2 (Table 1). The most frequent organism isolated in both the groups was coagulase-negative staphylococcus and *Staphylococcus aureus* (Table 2). All the ulcers were of grade III with average epithelial defect size of 36.306 ± 3.57 mm^2 and 35.756 ± 4.80 mm^2 in the ofloxacin and control groups respectively (Table 1). Six eyes from the ofloxacin group and 7 from the control group had a history of prior trauma and in 2 eyes from each group topical steroid use caused the ulcer; one eye from each group had contact-lens-induced ulcer. The average time required for symptomatic relief was 7.8 ± 1.54 days (range 6–10 days) in the ofloxacin group compared with 8.33 ± 1.54 days (range 5–10 days) in the control group (Fig. 1). The difference between the two was statistically significant

Table 2. *Organisms isolated* (n = *30)*

Organisms	Ofloxacin (*n* = 15)	Control (*n* = 15)
Staphylococcus aureus	5	5
Coagulase-negative staphylococci	5	6
Proteus sp.	1	0
Pseudomonas sp.	2	2
Moraxella sp.	1	0
Haemophilus sp.	1	1
Pneumococcus sp.	0	1

($p = 0.05$). Similarly, the duration of healing in the ofloxacin group was 15.0 ± 3.86 days (range 10–26 days) as against 15.46 ± 3.86 days (range 11–26 days) in the control group (Table 1, Fig. 2). The difference between the two groups was again statistically not significant ($p = 0.46$). One eye from the ofloxacin group and 2 eyes from the control group remained refractory at the end of 4 weeks despite early symptomatic relief; for these eyes therapeutic penetrating keratoplasty was carried out. Almost all the eyes in both groups had a pre-treatment visual acuity of PL,PR to counting fingers, which improved to counting fingers to 20/60 in the ofloxacin group and counting fingers to 20/80 in the control group (Table 3) 3 months after resolution. Residual full-thickness corneal opacity 3 months after resolution was observed in only 2 eyes of the ofloxacin group as against 3 eyes of the control group (Table 1). No ocular or systemic side-effects were encountered in any of the patients from either group.

Discussion

One of the most important principles in the management of infective keratitis is the initiation of an early and effective antimicrobial drug with the least toxicity. Fluoroquinolones, developed in the late 1980s, are antibiotics which inhibit bacterial DNA gyrase, a topoisomerase enzyme that inserts negative supercoils into DNA.[5] Ofloxacin is a synthetic fluorinated 4-quinolone antibiotic with rapid bactericidal activity against a wide range of organisms. Though its effectiveness and safety have been discussed at length since the late 1980s, its clinical use began in the early 1990s for the treatment of external ocular infection[6] and later for bacterial corneal ulcer.[7,8] Considering its efficacy against gram-positive and gram-negative organisms, O'Brien *et al.*[7] in 1995 recommended it as a suitable single drug for the initial treatment of bacterial keratitis. Based on the results from a comparative study with that of tobramycin and cefazolin, they further reported the safety of 0.3% ofloxacin.[7] However, to date no published report is available in the Indian literature.

In the present comparative, randomised prospective study we selected only grade III ulcers of moderate severity. We did not include either mild or severe-grade cases: a mild degree of ulcer may not provide good information because of its quick response to treatment

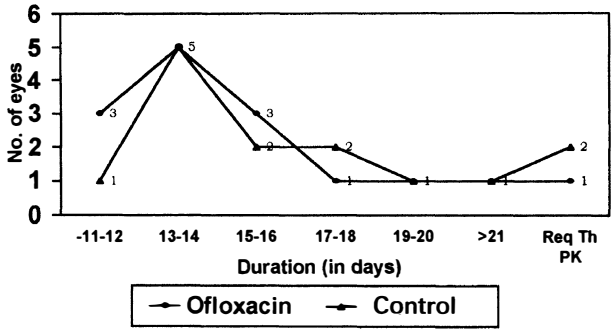

Fig. 2. *Time required for complete healing* (n = 30).

Table 3. *Visual acuity* (n = 30)

Visual acuity	Pre-therapy		Post-therapy	
	Ofloxacin ($n = 15$)	Control ($n = 15$)	Ofloxacin[a] ($n = 15$)	Control[a] ($n = 15$)
PL,PR	2	2	–	–
HM	5	6	–	–
CF	8	7	1	1
20/200	–	–	3	4
20/120	–	–	5	5
20/80	–	–	4	3
20/60	–	–	1	–

[a]Therapeutic penetrating keratoplasty done for refractory corneal ulcer in 1 eye in the ofloxacin group and 2 eyes in the control group.

and a severe grade may require additional medical/surgical therapy. Combined therapy of topical fortified tobramycin 1.5% and cefazolin 5% was used as control as these two drugs are used worldwide for the management of bacterial keratitis.

The data analysis of our study revealed that trauma was the most frequent factor responsible for bacterial keratitis, which was in agreement with the previous studies.[9,10] Further, it was noted that while the use of prolonged topical corticosteroid is known to cause proliferation of fungi, 13% of our cases had a history of corticosteroid use. It was also observed that though the range of time required for symptomatic relief was the same both in the monotherapy and combined therapy groups the mean time to relief was significantly different between the two groups ($p < 0.05$). This indicates that monotherapy with 0.3% ofloxacin is a better alternative for the treatment of bacterial keratitis than fortified therapy as regards symptomatic relief. Moreover, monotherapy with a drug which is already commercially available in a prepared form is preferable to having the drugs prepared.

O'Brien *et al.*[7] found that over 35% of eyes healed within 7 days in both the ofloxacin and combined tobramycin and cefazolin groups. However, none of our cases showed resolution prior to 10 days. This could be attributed to the fact that their study included less severe cases while our cases were moderately severe. But on the 14th day complete resolution was observed in 53% and 40% of our ofloxacin group and control group respectively. This does not concur with the findings of the Ofloxacin Study Group[8] who observed resolution in 62% and 68% of cases on the 14th day. As regards overall healing, our results were similar to those of O'Brien *et al.*[7] at 4 weeks: 93% resolution in the ofloxacin group and 87% in the control group compared with 89% and 86% respectively in O'Brien *et al.*'s series. Given the aetiological variation and severity of the ulcer in our study, our findings cannot be compared with American studies. But they suggest that the more severe the ulcer, the longer the duration of healing despite maximum effective therapy. Finally, neither visual acuity improvement nor sequelae such as corneal opacity showed a statistically significant difference between the two groups.

In earlier studies, the percentage of culture negativity has been reported[7,9,10] and found to be of varying frequency. But to make the study more meaningful we included the culture-positive cases only. Further, previous authors have commented on the non-efficacy of ofloxacin against streptococci, which is a major concern.[8,11] However, no comment can be given at this time as no cases of streptococcal ulcer were identified in the present study.

Conclusions

In summary, monotherapy with 0.3% ofloxacin drops for treating bacterial keratitis should be encouraged and can be tried as a first-line drug for all cases of bacterial keratitis. Further, it offers several advantages over combined fortified therapy, such as being a single agent convenient for the patient to apply, commercially available, stable at room temperature[7] and does not require additional formulations thus eliminating potential contamination of the drop. However, as with all antibiotics, the factor of development of resistance over time should be kept in mind.

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