Section: Miscellaneous

Original Research Article

EVALUATION OF EFFICACY AND SAFETY OF BESIFLOXACIN OPHTHALMIC SUSPENSION AND CIPROFLOXACIN OPHTHALMIC SOLUTION FOR THE TREATMENT OF BACTERIAL CONJUNCTIVITIS IN A RANDOMIZED COMPARATIVE TRIAL

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Abstract

Background: Acute bacterial conjunctivitis is a common ocular condition that affects all age groups. Bacterial conjunctivitis is treated with broad-spectrum topical ophthalmic antibiotic eye drops with certain limitations. Fluoroquinolones are still considered by many to be the antibiotics of choice on account of their broad-spectrum potency and low toxicity. Besifloxacin is the only fluoroquinolone specifically designed for ocular topical use. The purpose of this study was to assess the clinical and antimicrobial efficacy of Besifloxacin ophthalmic suspension and to assess the safety of besifloxacin ophthalmic suspension compared with ciprofloxacin ophthalmic solution. **Materials and Methods:** A single blind randomized study was conducted in ophthalmology department where patients with bacterial conjunctivitis were randomly divided into two groups in 1:1 ratio by block randomization method, i.e Group A (30 patients) received Besifloxacin ophthalmic suspension three times daily and Group B (30 patients) received Ciprofloxacin ophthalmic solution three times daily for a period of 5 days. Ocular examinations and Culture examinations of conjunctival swab were done at screening visit and follow up and the outcome was evaluated by using four point rating scale. **Result:** A total of 60 patients with culture confirmed bacterial conjunctivitis were randomized, based on 95% confidence interval (CI) of the difference, Besifloxacin was not second-rate to Ciprofloxacin for clinical resolution on day 6 (90% vs. 86.7%, respectively) and for microbial eradication on day 6 (86.7% vs. 80% respectively). There was no statistically significant difference between the two treatment groups for either efficacy end points on day 6 (P>0.05). Besifloxacin and Ciprofloxacin were well tolerated. The incidence of ocular adverse events like eye pain and eye irritation was similar between treatment groups, however eye pain occurred more often in Ciprofloxacin treated eyes (3.33% for Besifloxacin vs. 6.67% for Ciprofloxacin; P = 0.6667). **Conclusion:** The fluoroquinolone antibiotic, Besifloxacin ophthalmic suspension was not second-rate to Ciprofloxacin ophthalmic solution and provided better safety and efficacy (clinical and microbiological) outcomes when used for the treatment of bacterial conjunctivitis.

INTRODUCTION

Acute conjunctivitis is a common ocular condition that affects all age groups. While viral conjunctivitis, also known as pink eye, is thought to be most common, it is estimated that up to 78% of all cases of acute conjunctivitis in children and 50% of cases in adults are of bacterial origin1. In fact, bacterial conjunctivitis is the most common eye condition seen by primary care physicians, and may account for up to 1% of all primary care visits.[1]

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Bacterial conjunctivitis can often be distinguished from viral conjunctivitis by signs such as mucopurulent discharge, chemosis, conjunctival injection and crusting with mucopurulence. The most common causative microbes in adults include gram positive organisms like Staphylococcus aureus, Staphylococcus epidermidis and Stretococcus pneumoniae and the gram-negative pathogen Haemophilus influenzae. S.aureus is the most common in adults, while children are most prone to H. influenzae.

Like viral conjunctivitis, bacterial conjunctivitis is generally a self-limited condition usually lasting for 7 days.[2] Nonetheless, evidence also suggests that topical antibiotics can shorten the disease time, reduce contagious spread and reduce the risk of progression to potentially irreversible ocular damage. Thus, the current recommended strategy for managing acute infectious conjunctivitis is to promote supportive care for the first couple days of symptoms and then, if no improvement, start topical antibiotic drops.[3] Supportive care includes frequent eye cleansing with sterile water and gauze, warm water compresses, proper hand and eyelid hygiene, and temporary use of artificial tears for comfort. However, if the conjunctivitis presents with marked mucopurulence, it would not be unreasonable to immediately begin topical broad-spectrum antibiotic treatment along with the supportive care.

Once antibiotics are clinically indicated, the standard of care for bacterial conjunctivitis is broad-spectrum topical ophthalmic antibiotic eye drops. Various classes of antibiotics have been used including aminoglycosides, polymyxin B combinations, macrolides, sulfonamides and fluoroquinolones. Aminoglycosides (Tobramycin and gentamycin) require frequent dosing (1–2 drops every four to six hours for ten days), which can lead to poor patient compliance. In addition, despite their frequent use, aminoglycosides demonstrate poor anti-microbial activity against Streptococci, which limits their use as a broad-spectrum treatment for conjunctivitis.[4] Azithromycin is not preferred due to its unequal gram-negative and positive coverage. Erythromycin is no longer recommended because its activity against S. aureus has diminished. Fluoroquinolones are still considered by many to be the antibiotics of choice for ocular infections on account of their broad-spectrum potency and low toxicity.[5,6]

One major consideration in the selection of an antibiotic is bacterial resistance. In the absence of routine swabbing, microbial culture and sensitivity determination, clinicians rely upon low levels of resistance to increase the likelihood of the efficacious choice of treatment. Development of resistance may be caused by a number of factors including antibiotic overuse in systemic infections, prophylactic use, sub-therapeutic use and misuse in non-bacterial infections.[7] Resistance has been noted in the third generation fluoroquinolones (ciprofloxacin, levofloxacin and ofloxacin) and rates of resistance are increasing, especially for gram-positive bacteria.[8] Although the newer fourth generation fluoroquinolones, gatifloxacin and moxifloxacin have lower published rates of resistance, these numbers are increasing likely due, in part, to their use in systemic infections and in part to their ubiquitous use in the treatment of conjunctivitis and prophylaxis of the ocular surface at the time of surgery. Thus, there is an increasing demand for an effective antibiotic for bacterial conjunctivitis with low rates of bacterial resistance that is effective in treating the most prevalent ocular infections and which can be Besifloxacin in conjunctivitis used reliably as an empiric therapy due to its broad spectrum coverage.

Besifloxacin ophthalmic suspension 0.6% is fourth generation topical fluoroquinolone for treatment of bacterial conjunctivitis in adults and children older than 1 year. Besifloxacin is the only fluoroquinolone specifically designed for ocular use. Unlike older antibiotics of this class, Besifloxacin is not used for systemic infections. Restriction to topical use only, renders Besifloxacin unique in its class and theoretically reduces the risk for the development of resistance due to decreased systemic exposure.[2] Consistent with other fluoroquinolones, besifloxacin binds to DNA gyrase and topoisomerase IV, two enzymes that are critical for DNA replication in bacteria. Unlike previous generations in this class, Besifloxacin has a relatively equal affinity for inhibiting the above enzymes. The preferential targeting of one enzyme over the other is one factor that contributed to the resistance rates in the previous fluoroquinolone generations8. Resistance to besifloxacin would require spontaneous mutation in two enzymes, which is a less probable event. The primary objective of this study was to assess the clinical and anti-microbial efficacy of Besifloxacin ophthalmic suspension in patients with bacterial conjunctivitis. Secondly, to assess the safety of Besifloxacin ophthalmic suspension compared with Moxifloxacin Ophthalmic solution in patients with bacterial conjunctivitis.

MATERIALS AND METHODS

Study design: Single blind randomized study.

Study period: The study was conducted over period of three months from June 2023 to August 2023.

Study site: Department of Ophthalmology, Government Thiruvarur Medical College, Thiruvarur

Inclusion Criteria

- Age – More than 1 yr
- Patients of bacterial conjunctivitis in one or both eyes
- Patients of either gender
- Patients with patent nasolacrimal duct

Exclusion criteria

- Patients using other topical ophthalmic medications
- Patients who had ocular surgery within 6 weeks
- Patients having other ocular diseases like iritis, keratitis

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- Pregnant patients
- Female patients of child bearing age not taking adequate birth control measures
- Patients with obstructed nasolacrimal duct

Study protocol: The study was initiated after getting proper ethical clearance from Institutional Ethical Committee. (IEC no. 019/IEC/GTMC/2023). Informed consent was obtained after a detailed explanation of the study purpose and methods. For this study, about 60 patients with symptoms of bacterial conjunctivitis were randomly divided into two groups in 1:1 ratio by block randomization method, i.e., Group A (30 patients) received Besifloxacin ophthalmic suspension 0.6% three times daily and Group B (30 patients) received Ciprofloxacin ophthalmic solution 0.5% three times daily.

Study evaluation: This is a single blind study; therefore patients were unaware of treatment given to them. The patients were treated with either besifloxacin or moxifloxacin for a period of 5 days and they were asked to come for follow up on 6th day. Patient's demographic data and medical history was recorded at screening visit. Ocular examination & Culture examinations of conjunctival swabs were done at screening visit & follow up.

Ocular examination:

Ocular symptoms:

- Burning sensation
- Stinging sensation
- Foreign body sensation
- Tearing
- Itching
- Photophobia
- Ocular discomfort

Signs: Conjunctival discharge, Bulbar conjunctival injection, Palpebral conjunctival injection.

Cardinal signs	Grade			
	0	1	2	3
Conjunctival discharge	No discharge	Small amount of mucopurulent or purulent discharge without matting of eyelids	Moderate amount of mucopurulent or purulent discharge with obvious matting of eyelids	Profuse amount of mucopurulent or purulent discharge with tight matting of eyelids
Bulbar conjunctival injection	Normal vascular pattern	Mild degree of vascular injection without subconjunctival haemorrhages	Moderate degree of vascular injection with scattered petechiae associated subconjunctival haemorrhages	Severe degree of vascular injection giving a "Beef" red eye appearance
Palpebral conjunctival injection	Normal papillary response	Small follicles or fine papillary reaction	Large follicles or confluent papillary reaction with	Marked inflammatory reaction with
		with mild hyperemia	pronounced hyperemia	epithelial necrosis

Conjunctival swab – culture:

Table 2 Drug efficacy assessment[a]

Colony-forming units per swab	*Bacterial species*
More than 0 (Class A)	Group A streptococci *Streptococcus pneumoniae* All Gram negative rods *Neisseria* sp.
More than 10 (Class B)	Alpha-haemolytic streptococci *Staphylococcus aureus* Other micrococcaceae *Branhamella catarrhalis*
More than 100 (Class C)	*Staphylococcus epidermidis* *Bacillus* sp.
More than 10 000 (Class D)	*Corynebacterium* sp. and diphtheroids

[a] According to the criteria of Cagle *et al*[3]

Efficacy parameters:

The study was evaluated by using four point rating scales

1. Ophthalmologist's clinical impression of change from baseline in cardinal signs
2. Change from baseline in ocular symptoms
3. Microbial eradication

Efficacy parameters outcomes:

Outcomes	GRADE			
	0 resolved	1 improved	2 no change	3 worse
Cardinal signs	Absence of cardinal signs	At least one unit improvement	No overall response	At least one unit worsening
Ocular symptoms	Absence of symptoms	At least one unit improvement	No overall response	At least one unit worsening
Microbial eradication	Absence of baseline organisms, no growth	Decrease below pathogenic criteria	No overall response or improvement	Increase in baseline organisms

Safety Parameters: Ocular safety was determined by evaluating the incidence and severity of adverse events and significant changes from baseline in biomicroscopy, ocular symptoms, visual acuity.

Statistical Analysis: Basic statistical evaluation including Mean, Median, SD, etc. was calculated for the raw data. Efficacy variables such as ocular symptoms, Cardinal signs and Microbial eradication were calculated using Chi square test & Fisher's exact test.

RESULTS

During the study period, a total of 80 patients were screened, in which 60 patients were randomized as per inclusion and exclusion criteria. Of the 60 patients, Group A (n=30 patients) who received besifloxacin ophthalmic suspension 0.6%, 66.7% were men (20/30) and 33.3% were women (10/30). Group B (n=30 patients) who received ciprofloxacin

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ophthalmic solution 0.5%, 73.3% were men (22/30) and 26.7% were women (8/30). The details of study population as shown in [Figure 1].

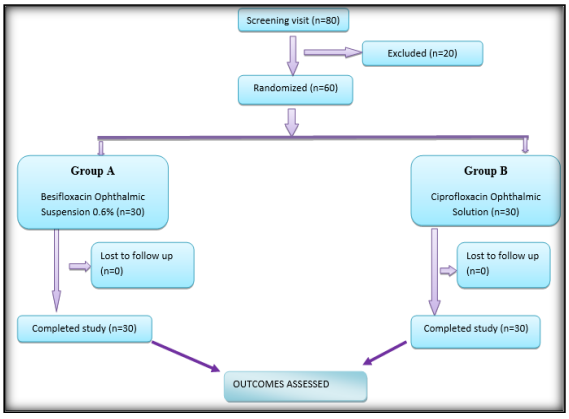

Figure 1. Flow chart showing the disposition of patients

Patient demographic characteristics like age and gender are shown in [Table 1]. The numbers of patients reporting allergies and/ or relevant medical histories were similar between treatment groups. Baseline ophthalmic examination findings, including visual acuity, biomicroscopy and ophthalmology, also were similar between treatment groups.

[Table 2] presents the primary efficacy end point data for clinical resolution on day 6 for the culture confirmed patient population. On day 6 (Visit 2), 83.3 %, (25/30) and 86.7 % (26/30) of patients treated with Besifloxacin ophthalmic suspension and Ciprofloxacin ophthalmic solution, respectively, had clinical resolution. Besifloxacin was not second-rate to Ciprofloxacin, and there was no significant difference in clinical resolution between treatment groups (P=0.2463). Besifloxacin ophthalmic suspension also was shown to be second-rate to Ciprofloxacin solution in regard to microbial eradication in culture confirmed population (Table 2). On day 6 (Visit 2) microbial eradication occurred in 86.7% (26/30) of patients receiving Besifloxacin and 80% (24/30) of patients receiving Ciprofloxacin. No second-rate effect was demonstrated and there was no significant difference between treatments (P=0.2437).

Clinical resolution and microbial eradication by baseline infection with either gram-positive and gram negative organisms did not differ significantly from the overall study results [Table 3]. The rates of clinical resolution and microbial eradication with Besifloxacin did not differ significantly from those obtained with Ciprofloxacin, with the exception of microbial eradication for infections caused by gram-negative organisms on day 6, for which the rate was significantly better with Besifloxacin. However, besifloxacin was significantly more effective than ciprofloxacin on day 6 for clinical resolution with 88.8% (16/18) achieving resolution with besifloxacin versus 85% (17/20) with ciprofloxacin (P=0.7486).

All randomized patients were included in the safety analysis (30 besifloxacin, 30 ciprofloxacin). Treatment with both study drugs was well tolerated, with most occurred adverse events (AEs) was mild to moderate. The most ubiquitous ocular AE are summarized in [Table 4]. Only eye pain and eye irritation were reported as AEs, there was no statistically significant difference between besifloxacin and ciprofloxacin groups, eye pain was occurred in 3.33% of patients treated with besifloxacin, 6.67% of patients treated with ciprofloxacin. Eye irritation was occurred in 3.33% of patients treated with besifloxacin, 3.33% of patients treated with ciprofloxacin.

Table 1: Demographics characteristics of study population

Characteristic	Besifloxacin ophthalmic suspension 0.6% (n=30)	Ciprofloxacin ophthalmic solution 0.5% (n=30)
Age (Yrs)		
Mean (SD)	48.7 (20.6)	43.4 (23.9)
Range	1-72	1-72
Gender, n (%)		
Men	20 (66.7%)	22 (73.3%)
Women	10 (33.3%)	8 (26.7%)

Table 2: Clinical resolution and microbial eradication in baseline designated study eyes on day 6 (visit 2)

Efficacy Variable	No. of patients (%)		P value *
	Group A	Group B	
Day 6 (Visit 2)			
Clinical resolution	27 (90)	26 (86.7)	0.2463
Microbial Eradication	26 (86.7)	24 (80)	0.2437

Table 3: Clinical resolution & microbial eradication on day 6 (visit 2)

Efficacy Variable	No. of patients (%)		P value ❖
	Besifloxacin ophthalmic suspension 0.6%	Ciprofloxacin ophthalmic solution 0.5%	
Gram positive organisms			
Day 6 (Visit 2)			
Clinical resolution	16/18 (88.8)	17/20 (85)	0.7486
Microbial Eradication	16/18 (88.8)	16/20 (85)	0.7419
Gram negative organisms			
Day 6 (Visit 2)			

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Clinical resolution	11/12 (91.6)	9/10 (90)	0.7046
Microbial Eradication	10/12 (83.3)	8/10 (80)	0.7409

❖ Fisher exact test

Table 4: Incidence of ocular adverse events in besifloxacin ophthalmic suspension 0.6% and ciprofloxacin ophthalmic solution 0.5% treated patients

Adverse Event	Incidence, n (%)		P Value❖
	Besifloxacin ophthalmic suspension (n=30)	Ciprofloxacin ophthalmic solution (n=30)	
Eye pain	1 (3.33%)	2 (6.67%)	0.6667
Eye Irritation	1 (3.33%)	1 (3.33%)	0.7000

❖ Fisher exact test

DISCUSSION

The results of this study show that Besifloxacin ophthalmic suspension 0.6% was similar in efficacy and safety outcomes to Ciprofloxacin ophthalmic solution when used three times daily for five days for the treatment of bacterial conjunctivitis. Clinical resolution rates was 90% for Besifloxacin and 86.7% for Ciprofloxacin by day 6 (P=0.2463). Microbial eradication occurred in 86.7% and 80% of patients treated with Besifloxacin and Ciprofloxacin respectively, on day 6 (P=0.2437).

Secondary analysis of the investigators global assessment of response at base line visit and follow-up visits also was not significantly different between treatment groups, and Besifloxacin provided similar bacterial eradication rates as ciprofloxacin at day 6 against the pathogens (H. influenzae, S. pneumoniae, S.aureus and S. epidermidis) most commonly identified in this study. Finally, treatment emergent ocular AEs were similarly low in each treatment group. Eye pain and eye irritation were the most commonly occurred AE for which there was no statistically different between besifloxacin and ciprofloxacin groups, eye pain was occurred in 3.33% vs 6.67% of patients treated with besifloxacin and ciprofloxacin (P= 0.6667). Eye irritation was occurred in 3.33% vs 3.33% of patients treated with besifloxacin and ciprofloxacin (P= 0.7000).

The results obtained with Besifloxacin ophthalmic suspension in this study are similar to the results obtained in two recent vehicle controlled studies with Besifloxacin. The author reported rates of clinical resolution and microbial eradication with Besifloxacin of 73.3% and 88.3% respectively, on day 8 after 5 days of treatment in 118 patients with acute bacterial conjunctivitis,[9] whereas Tepedino et al,[10] showed rates of clinical resolution and microbial eradication with Besifloxacin 84.4% and 88.4%, respectively, on day 8 after 5 days of treatment in 390 patients with acute bacterial conjunctivitis. In these studies, the rates of clinical resolution and microbial eradication obtained with vehicle were lower by approximately 10 % to 30 %, depending on the time of assessment and out come studied; indicating that Besifloxacin ophthalmic suspension provides activity above and beyond that contributed by the normal immune processes is an important consideration because bacterial conjunctivitis often is self limiting. Likewise, the results with Ciprofloxacin in this study were similar to those observed in a placebo controlled study evaluating Ciprofloxacin administered thrice daily for four days for the treatment of bacterial conjunctivitis. In addition, the clinical and microbial efficacy rates with Besifloxacin observed in this study are similar to those observed with other fluoroquinolones (e.g., Norfloxacin, Ofloxacin and levofloxacin) in the treatment of bacterial conjunctivitis, albeit the other agents were administered more frequently and for prolonged dosing schedules.[11-15]

Moreover, in both treatment groups, the rate of clinical resolution increased considerably, whereas the rate of bacterial eradication decreased slightly over that time. This is due to recolonization of some eyes might have resulted in non-eradication.

CONCLUSION

At the outset, this randomized single blind study concluded that treatment of bacterial conjunctivitis with besifloxacin ophthalmic suspension 0.6% produces safety and efficacy outcomes that are similar to those seen with ciprofloxacin ophthalmic solution 0.5% and comparably Besifloxacin produces better therapeutic response with respect to clinical resolution and microbial eradication. The present study strongly suggests that thrice daily dosing regimen, Besifloxacin is an effective and safe treatment for patients with bacterial conjunctivitis.

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