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Original Article

A Randomized Controlled Trial to Assess the Efficacy of Topical Besifloxacin 0.6% versus Moxifloxacin 0.5% in Bacterial Conjunctivitis

J. Komathi[1], C. K. Devipriya[2], G. Amudha[3], B. Bhuvaneswari[4]

[1]Associate professor of pharmacology, Omandurar Government medical college, Chennai, [2]Tutor in Pharmacology, Government mohan kumaramangalam medical College, Salem, [3]Assistant professor, Department of radiodiagnosis, Government arignar anna memorial research institute,Kanchipuram, [4]Associate Professor, Department of Pharmacology, Government Medical College, Ariyalur

Abstract

Background: Bacterial conjunctivitis is an inflammation of the conjunctiva is defined as conjunctival hyperaemia associated with a mucopurulent or purulent discharge. Besifloxacin is a topical fluoroquinolone and developed specifically for ophthalmic use. The broad-spectrum activity of besifloxacin includes potent activity against the drug-resistant strain of various bacteria.

Aim: To compare the efficacy and tolerability of two drugs, Topical Besifloxacin 0.6% and Topical Moxifloxacin 0.5%, in patients diagnosed with bacterial conjunctivitis in a tertiary care hospital.

Methodology: 163 patients were recruited and randomized into either group A to receive Topical Besifloxacin 0.6% ophthalmic suspension three times for 5 days or group B to receive Topical Moxifloxacin 0.5% solution three times for 5 days. Clinical examination, screening with Cumulative sum scale score(CSS) and laboratory investigations were done at baseline,4th day, and 7th day. Efficacy was measured by improvement of symptoms assessed by CSS scoring. Tolerability was ensured by assessing the patient outcome on the 10th day using a four-step scale.

Results: The mean CSS score reduction from 9.85 at baseline to 0.88 in Group A (Besifloxacin) and from 10.49 at baseline to 1.08 in Group B (Moxifloxacin) on the 4th day of treatment and the 7th day of treatment, the scores were reduced to 0.00. The reduction in CSS score was statistically significant within groups (p-value <0.001). The mean CSS score reduction between Group A and Group B did not show a statistically significant difference (P-value = 0.40). The score for tolerability on the 10th day showed no significant difference between the group statistically. (p-value = 0.193)

Conclusion: This study confirms that both Besifloxacin and Moxifloxacin are equally effective in treating bacterial conjunctivitis. Tolerability profile is better for Besifloxacin suspension than Moxifloxacin solution in the treatment for bacterial conjunctivitis.

Key words: Conjunctivitis, Besifloxacin, Moxifloxacin, Cumulative sum score

INTRODUCTION

Conjunctivitis is an inflammation or infection of the transparent membrane(conjunctiva) that lines the eyelid and covers the white part of the eyeball. It is a common condition of the eye that occurs worldwide and affects all ages and social strata[(1)]. It can be caused by several different bacterial or viral pathogens but may also be caused by allergies, irritants or medications. Most types of conjunctivitis are self-limiting, but some may progress and cause serious ocular and extra-ocular complications. [(2)]

Most causes of conjunctivitis are benign, but depending on the immune status of the patient and the aetiology, conjunctivitis can progress to increasingly severe and sight-threatening infections. The incidence of bacterial conjunctivitis was estimated to be 135 in 10,000 in study Smith and Waycaster. [(3)] The prevalence of conjunctivitis varies according to the underlying cause, which may be influenced by the patient's age, as well as the season of the year. However, bacterial conjunctivitis is one of the most common ocular surface infections.

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Corresponding Author: Dr. C. K. Devipriya, Tutor in Pharmacology, Government mohan kumaramangalam medical College, Salem

Acute bacterial conjunctivitis is common and caused by direct eye contact with infected secretions. The most common isolates are H.influenza, S.pneumonia, S.aureus. and Moraxella catarrhalis. The most common pathogens for bacterial conjunctivitis in adults are Staphylococcal species, Streptococcus pneumoniae and Haemophilus influenza. In children, the disease is often caused by H influenzae, S pneumoniae, and Moraxella catarrhalis. [4] The course of the disease usually lasts for 7 to 10 days.

Common symptoms in acute bacterial conjunctivitis are redness, grittiness, stickiness, lacrimation and photophobia. Other possible symptoms are burning sensation and dryness of the eyes. Signs of acute bacterial conjunctivitis are hyperaemia or redness of the conjunctiva, conjunctival discharge, foreign body sensation. Marginal corneal ulcer, superficial keratitis, blepharitis or dacryocystitis are the complications of conjunctivitis. [5] For making appropriate treatment and management of conjunctivitis, focused ocular examination and history is necessary. The type of eye discharge and ocular symptoms are used for finding the cause of conjunctivitis. A purulent or mucopurulent discharge is mostly due to bacterial conjunctivitis, but a watery discharge is mostly due to viral conjunctivitis. [6] Itching is associated with allergic conjunctivitis. [7]

Topical antibiotic therapy is the mainstay of treatment. Ideally, the antibiotic should be specific for the causative organism. For example, chloramphenicol, aminoglycosides (gentamicin, neomycin, tobramycin), quinolones (ciprofloxacin, ofloxacin, levofloxacin, lomefloxacin, gatifloxacin, moxifloxacin,besifloxacin), macrolides (erythromycin, azithromycin), polymyxin B, fusidic acid and bacitracin are the available antibiotics.

Topical antibacterial drops are the standard treatment for bacterial conjunctivitis since they achieve higher antibiotic concentrations at the infection site to prevent contagious spread, disease course and recurrence are also reduced. It also decreases vision-threatening complications. However, inappropriate use of antibiotics leads to increased drug resistance, necessitating the continued development of new antibiotics.

In many clinical trials, besifloxacin demonstrated efficacy and safety in treating patients with bacterial conjunctivitis and was safe and well-tolerated with no observed contraindications. [8] Though multiple classes of drugs are available for pharmacological management of conjunctivitis, Fluoroquinolones are the mainstay of treatment for acute bacterial conjunctivitis.

The only fluoroquinolone specifically designed for ocular use is Besifloxacin. Therefore, it is not used for systemic infections like other older antibiotics. In bacterial conjunctivitis, a common source for treatment failure is bacterial resistance. Therefore, restriction to topical use only renders besifloxacin unique in its class and theoretically reduces the risk of developing resistance due to decreased systemic exposure.

Besifloxacin has improved pharmacodynamic properties compared with other commonly used fluoroquinolones and has shown to be safe and efficacious in clinical studies. For S. aureus, S. epidermidis and S. pneumonia, besifloxacin demonstrates a lower minimum bactericidal concentration than moxifloxacin, gatifloxacin, ciprofloxacin, azithromycin and tobramycin. For the pathogens mentioned above, besifloxacin is the most potent antibiotic. It has broad-spectrum activity against anaerobic bacteria, gram-positive and gram-negative bacteria. The purpose of this study is to compare two of the drugs from this class of fluoroquinolones, namely Besifloxacin 0.6% ophthalmic suspension versus Moxifloxacin 0.5% ophthalmic solution in terms of efficacy and tolerability among acute bacterial conjunctivitis patients attending the ophthalmology outpatient department in Chengalpattu Medical College and Hospital.

Aim

To assess the efficacy of Besifloxacin 0.6% ophthalmic suspension in Patients with Bacterial conjunctivitis.

Objective

To compare the clinical and antibacterial efficacy of Besifloxacin and Moxifloxacin in patients with bacterial conjunctivitis.

MATERIALS AND METHODS

A randomized, open-label, comparative active-controlled study was conducted in the Department of ophthalmology and microbiology at Chengalpattu medical college from January 2018 to December 2018. 150 male and female patients attending ophthalmology OPD who are clinically diagnosed with bacterial conjunctivitis were included.

Inclusion Criteria

1. Age: Above 18 years, both male and female
2. Patients who are clinically diagnosed with bacterial conjunctivitis.
3. Patients with visual acuity >6/60in both eyes.
4. Patients willing to give written informed consent.

Exclusion Criteria

1. Patients with other forms of conjunctivitis like viral or allergic conjunctivitis.
2. Patients already using any topical eye drops.

3. Patients with any history of ocular surgery within 6 weeks of study entry.
4. Patients with iritis, active ulcerative keratitis, recurrent corneal erosion syndrome.

The study was conducted after Institutional Ethical Committee approval. Patients who fulfilled the selection criteria were recruited for the study. The study was conducted according to good clinical practice guidelines. Written informed consent was obtained from all patients in regional language in the prescribed format and explained the study purpose and procedures before their enrollment in the study. In illiterate patients, the study procedure and their right to withdraw or contact the principal investigator were explained in case of any side effects, and a left thumb impression was obtained.

Randomization was done by the lots method. Among the 182 patients recruited and screened, 163 were enrolled in the study. Patients were assigned either to group A to receive study drug TopicalBesifloxacin 0.6% three times a day or to group B to receive Topical Moxifloxacin 0.5% three times a day for five days.

Demographic details and complete history were recorded during enrolment. In addition, clinical examination, screening with cumulative sum score and lab investigations were done at baseline.

Group A received TopicalBesifloxacin 0.6% ophthalmic suspension three times a day for five days. Group B received Topical Moxifloxacin 0.5% ophthalmic solution three times a day for five days.

Efficacy is measured by the response in terms of improvement of symptoms assessed by scoring with Cumulative sum score at baseline, at 4th day, and 7th day. **Tolerability** is assessed at the end of the 10th day using the 4-step scale, treatment outcome, and local tolerance of study medication.

The difference in cumulative sum scoring between two groups A and B was assessed by the student t-test. The culture was taken at 0 (baseline), 4th day and 7th day. The difference in cumulative sum score within the groups before and after treatment was analyzed using student paired t-test. The variations in the culture report between group A and group B were analyzed by chi-square test. In addition, the percentage of incidence of adverse effects among the study groups were analyzed.

RESULTS

In this study, 163 patients diagnosed with acute bacterial conjunctivitis were screened, randomized and included to participate in the study. Thus, 150 patients, i.e.,91.46 % of group A and 92.59% of group B, completed the study. In group A, 7 members lost to follow up. In Group B, 6 members lost to follow up. The highest number of patients were observed in the range of 41- 50 years [Figure 1].

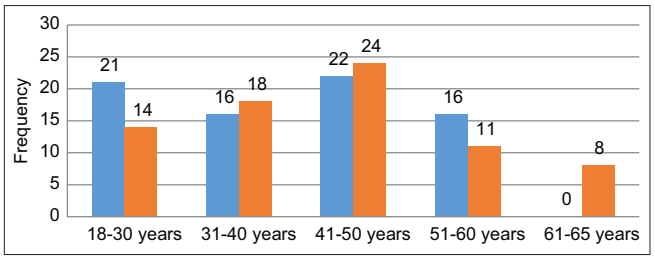

Figure 1: Age Distribution

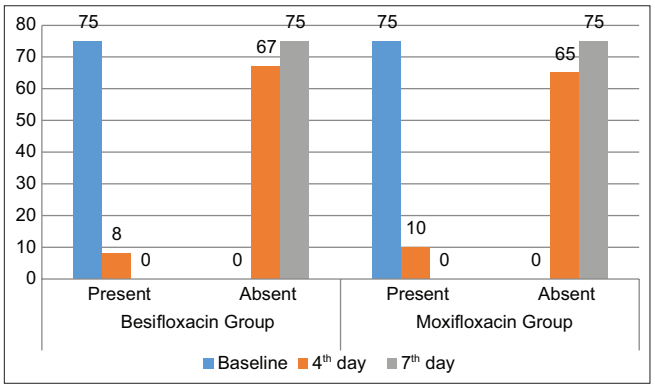

Figure 2: Comparison of bacterial culture between the Groups

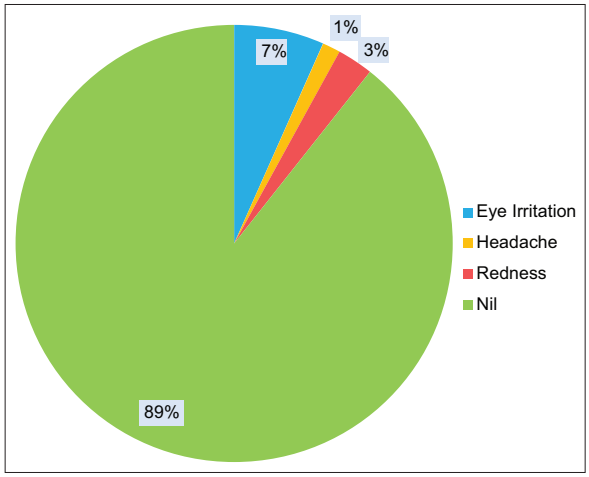

Figure 3: Adverse events in Group A

Common bacterial pathogens found in culture was Staph aureus, Streptococcus pneumonia, Staph. epidermidis, Klebsiella, E.coli, and mixed isolates found were Moraxella catarrhalis, proteus [Table 1].

By the 4th day, no bacterial colonies were observed in 89.3% of Group A and 86.7% of Group B. There was

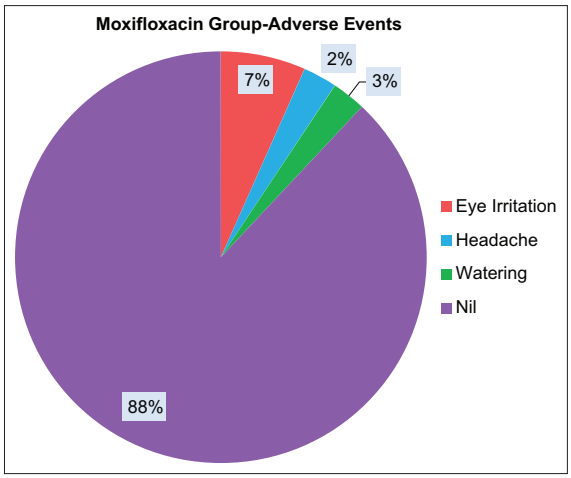

Figure 4: Adverse events in Group B

Table 1: Common Bacterial pathogens

Bacterial Pathogens	Besifloxacin Group		Moxifloxacin Group	
	Frequency	Percentage	Frequency	Percentage
Staph aureus	51	68	48	64
Streptococcus Pneumonia	9	12	12	16
Staph epidermidis	3	4	6	8
Klebsiella	3	4	5	7
E. Coli	6	8	1	1
Mixed Isolates	3	4	3	4
Total	75	100.0	75	100.0

Common bacterial pathogens found in culture was Staph aureus, Streptococcus pneumonia, Staph. epidermidis, Klebsiella, E. coli, and mixed isolates found were Moraxella catarrhalis, proteus

no significant difference between the treatment groups in terms of reduction in the bacterial growth in culture during the study [Figure 2].

There is no statistically significant difference in CSS from baseline to 4th day and 7th day [Table 2].

There are no serious adverse effects reported. Among adverse events reported, eye irritation was the most common ADR, followed by redness, Headache in Besifloxacin group [Figure 3].

Moxifloxacin group - common adverse effects reported were Eye irritation, followed by headache and watering [Figure 4].

There was a significant difference in 4-step scale tolerability scores on 10th day between groups. Besifloxacin is better tolerated than Moxifloxacin eye drops (p=0.319) [Table 3].

There was no significant difference in tolerability scores on 10th day between groups. Besifloxacin is better tolerated than Moxifloxacin eye drops (p=0.193) [Table 4].

Table 2: Comparison on cumulative sum score between groups

Cumulative sum score	Besifloxacin		Moxifloxacin		P value
Ocular Discharge					
Baseline	2.39	0.695	2.47	0.664	0.47
4th Day	0.24	0.43	0.31	0.464	0.36
7th day	0	0	0	0	-
Conjunctival Hyperaemia					
Baseline	2.4	0.678	2.4	0.658	1
4th Day	0.33	0.644	0.49	0.795	0.78
7th day	0	0	0	0	-
Ocular Itching					
Baseline	0.13	0.342	0.15	0.356	0.81
4th Day	0.08	0.273	0.04	0.197	0.3
7th day	0	0	0	0	-
Ocular Pain					
Baseline	1.71	1.063	1.97	1.013	0.11
4th Day	0.08	0.273	0.07	0.251	0.75
7th day	0	0	0	0	-
Ocular Watering					
Baseline	1.6	0.805	1.65	0.762	0.67
4th Day	0.08	0.395	0.13	0.502	0.47
7th day	0	0	0	0	-
CSS					
Baseline	9.85	3.84	10.49	3.51	0.28
4th Day	0.88	1.7	1.12	1.81	0.4
7th day	0	0	0	0	-

Statistically no significant difference in mean score reduction from baseline to 4th day and 7th day

Table 3: Tolerability score on the Tenth day

4-STEP SCALE 10TH DAY	Besifloxacin Group		Moxifloxacin Group	
	Frequency N=75	Percentage	Frequency N=75	Percentage
0 (Poor)	0	0	0	0
1 (Fair)	3	4.0	3	4.0
2 (Good)	60	80.0	66	88.0
3 (Excellent)	12	16.0	6	8.0

Table 4: Score for tolerability on 10th day

Tolerability score assesses on the 10th day	Mean	Std. Deviation	P-value
Besifloxacin Group	2.12	0.401	0.193
Moxifloxacin Group	2.04	0.346	

DISCUSSION

Our study findings show the highest prevalence of bacterial conjunctivitis was observed in 41-50 years with 29.3% and 32.0% in groups A and B, respectively. The mean age for group A is 40.29±12.41 years, and group B is 42.49 ±13.64 years. There was no significant statistical difference in mean ages between the two groups (P-value = 0.303). This was similar to a previous study by Agius-Fernandez *et al.*[9] The least prevalence was seen in 61-65 years.

Culture confirmed bacterial conjunctivitis study population were evaluated for bacteriological improvement during treatment with the study medications. At baseline, the bacterial species involved in Besifloxacin (Group A) and Moxifloxacin (Group B) treatment groups. Staphylococcus aureus (Group A 72%, Group B 64%) was the most prevalent organism, followed by Streptococcus pneumonia (Group A 12%, Group B 16%), Staphylococcus epidermidis (Group A 4%, Group B 8%) and Klebsiella (Group A 4%, Group B 7%). The predominance of staphylococcus aureus seen in our study is similar to the okesolo study, where it was 74.9%.[10] It was also similar in other studies, which demonstrated the same trend. [11] It was also similar to cavuota *et al.*[12]

Both the study medications resulted in a significant reduction in the mean score of the bacterial colony count during the trial period. By the 4th day, no bacterial colonies were observed in 89.3% of Group A and 86.7% of Group B. There was no significant difference between the treatment groups in terms of reduction in the bacterial growth in culture during the study.

The clinical efficacy was measured as the Cumulative Sum Score CSS[9]of 5 key signs and symptoms of acute bacterial conjunctivitis; these comprise ocular discharge, conjunctival hyperaemia, ocular itching, ocular pain and watering, which were recorded on a 4-step scale of 0 to 3: 0 = absent, 1 = mild, 2 = moderate and 3 = severe. Thus, the maximal CSS possible in any patient was 20, and the minimum score possible was 0. Therefore, the CSS was designated as the primary clinical efficacy variable. In addition, the success of treatment was assessed from the patients' statement and local tolerance of the study medications using a four-step scale.

In this study, the mean ocular discharge scores in group A and group B during baseline visits were 2.39 and 2.47. The scores in both groups are comparable during the baseline visit. There was a significant difference in reduction of ocular discharge within the groups on the 4th day and 7th day ($p<0.001$). But there was no significant difference in p-value($P =0.36$)between the groups statistically.

The mean conjunctival hyperemia score during baseline is 2.40 in group A. However, the conjunctival hyperemia score reduced from 2.40 to 0.33 on the 4th day and from 0.33 to 0.00 on the 7th day in group A. There was a significant difference in the reduction of conjunctival hyperemia within group A on the 4th day and 7th day ($p<0.001$).

In group B the conjunctival hyperemia score was reduced from 2.40 to 0.49 on the 4th day and 0.49 to 0.00 on the 7th day [p value<0.001]. Thus, both Besifloxacin (Group A) and Moxifloxacin (Group B) effectively reduced conjunctival hyperaemia on the 4th day and 7th day. This was similar to the study done by Garg *et al.*[13], But there was no statistically significant difference in reducing conjunctival hyperemia (p-value =0.78) between the two groups.

In this study, the mean ocular itching scores in group A and group B during baseline visits were 2.6 and 2.45, respectively. Thus, the itching scores in both groups are comparable during the baseline visit. Furthermore, there was a significant difference in reducing itching within groups A and B on the 4th and 7th days ($p<0.001$). But there was no significant difference (pvalue=0.30) between the groups statistically. Thus both treatments were effective in treating itching.

The mean ocular pain score in group A on baseline visit was 1.71, and group B was1.97. In group, A 1.71 was reduced to 0.08 on the 4th day, and group B 1.97 was reduced to 0.07 on the 4th day ($p<0.001$). There was a significant difference in the reduction of score in group A and Group B from baseline to 4th day. But the difference in reduction of ocular pain scores between group A and group B was not statistically significant (p-value = 0.75)

The mean ocular watering score in group A on the baseline was 1.60 and in group B is1.65. In group A, the score was reduced from 1.60 to 0.08 on the 4th day, and in group B, the score of 1.65 was reduced to 0.13 on the 4th day. Thus, in group A and Group B, treatments effectively reduced ocular watering scores from baseline score [P value <0.001]. But the difference in reduction of ocular watering scores between group A and group B was not statistically significant [P value= 0.47].

The mean CSS score in group A on baseline visit was 9.85, and group B was 10.49. In groups A and B, treatments effectively reduced the mean score from the baseline score [P value <0.001]. On the 4th day, the mean CSS score was reduced to 0.88 in Group A and on the 7th day, the mean CSS was reduced to 0.00 in Group A. On the 4th day mean CSS score of 10.49 was reduced to 1.08 in Group B

And on the 7th day mean CSS was reduced to 0.00. Both the study medications resulted in a significant ($p < 0.001$) reduction in the mean CSS of the signs and symptoms during the trial period in bacteriologically confirmed bacterial conjunctivitis within groups A and B. There was no statistically significant difference ($p=0.40$) between the Besifloxacin and Moxifloxacin treatment groups regarding reduction in the mean CSS. Our study findings correlate with the previous multicentre study, which demonstrated that besifloxacin was not

inferior to moxifloxacin in the treatment of bacterial conjunctivitis [12]

The adverse events occurred in 17 out of 150 participants, 8 in group A and 9 in Group B. The adverse events noted were eye irritation, headache and redness in GroupA. The adverse events noted in Group B were eye irritation, headache and watering. There were no serious adverse events observed during the study. During follow up visits on the 4th and 7th-day visual acuity changes, Anterior chamber examination, fundoscopic changes were examined. No changes in these safety parameters were noted in both groups. The Adverse events were similar to the study done by Comstock *et al*.[8]

The score for tolerability in group A was good, excellent and fair in 80%,16% and 4%, respectively. In Group B, the score was good, excellent and fair in 88%, 8% and 4%, respectively. Eventhough there was no statistically significant difference in tolerability among the two groups (p value=0.193), 16% of the patients in the Besifloxacin group came under the excellent category. In contrast, only 8% of the patients came under the excellent category under the Moxifloxacin group.

CONCLUSION

This study confirms that both Besifloxacin and Moxifloxacin are equally effective in the treatment of bacterial conjunctivitis. However, the tolerability profile is better for Besifloxacin suspension than Moxifloxacin solution. Hence Topical Besifloxacin suspension is an alternative to Topical Moxifloxacin solution in the treatment for bacterial conjunctivitis.

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