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Original Article

Efficacy and Safety of Moxifloxacin 0.5% Eye Drops versus Tobramycin 0.3% Eye Drops in Pediatric Population with Purulent Bacterial Conjunctivitis

Prateek Koul[1], Vijayta Gupta[2]

[1]Senior Resident, Department of Ophthalmology, Veer Chandra Singh Garhwali Government Medical College, Pauri Garhwal, Uttarakhand, India, [2]Senior Resident, Department of Ophthalmology, Government Medical College Jammu, Jammu and Kashmir, India

Abstract

Aims: The study aims to determine the efficacy and safety of moxifloxacin 0.5% eye drops versus tobramycin 0.3% eye drops in pediatric population with purulent bacterial conjunctivitis.

Study design: Prospective, randomized, investigator-masked, clinical study was conducted on patients.

Place and Duration of Study: This study was conducted by the Department of Ophthalmology Veer Chandra Singh Garhwali Government Medical College, Srinagar, Uttarakhand, between March 2018 and February 2019.

Methodology: This study included 100 children with purulent discharge and bulbar conjunctival injection. Children either received moxifloxacin 0.5% 4 times a day for 5 days or received tobramycin 0.3% eye drops (every 2 h for 2 days and then 4 times for 5 days). Clinical signs were evaluated on days (D) 0, 3, and 7 and cultures on D0 and D7. The primary variable was the clinical cure (absence of bulbar injection and discharge) on D3 in the worst eye for patients with positive culture on D0.

Results: 100 culture-positive cases were included on D0. Moxifloxacin was superior to tobramycin in clinical cure rate on D3 (47.1% vs. 28.7%) $P = 0.013$) and was non-inferior to tobramycin on D7 (89.8% vs. 78.2%, respectively). Moxifloxacin treatment eradicated causative pathogens, including resistant species with a similar resolution rate to tobramycin (89.8% vs. 87.2%).

Conclusion: Moxifloxacin 0.5% eye drops provided a more rapid and effective clinical cure than tobramycin 0.3% eye drops in the treatment of purulent bacterial conjunctivitis in children, with 4 times dosing.

Key words: Bacterial, Conjunctivitis, Moxifloxacin, Tobramycin

INTRODUCTION

Conjunctivitis is one of the most common eye infections in childhood and a common cause of pediatric primary care visits and ocular complaints in pediatric emergency departments.[1] Bacterial infection accounts for up to 50% of all conjunctivitis cases in adults and as many as 70–80% of cases in children.[2]

Bacterial conjunctivitis is characterized by mucopurulent discharge and conjunctival hyperemia.[3] It is an extremely contagious disease caused by one or more bacterial species and affects both sexes, all ages and countries. It can also cause epidemics among people close quarters, including nursery, school, and student populations.[4] Mild cases are generally considered to be self-limiting resolving in 5–10 days. However, current consensus supports the use of topical antibiotics as they provide significantly better rates of early clinical cure and microbiological resolution compared with artificial tears.[5] Topical antibiotics are also known to reduce the rate of reinfection and prevent the spread of infection.[6]

There are only a few available options for the treatment of purulent bacterial conjunctivitis with topical antibiotics in children as most available. Topical antibiotics have been approved based on clinical studies performed on adults. Although regulatory health authorities worldwide

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Corresponding Author: Dr. Vijayta Gupta, Room No 13, SR Hostel, HNB Base Hospital, Srikot Pauri, Srinagar – 246 174, Uttarakhand.

encourage pediatric clinical studies, the efficacy and safety in its population are still undertested.

The objective of this study was to determine the efficacy and safety of moxifloxacin 0.5% eye drops compared to tobramycin eye drops and also its rapidity of action to support its indication in children, notably in those younger than 2 years of age. Secondary objective included determination of infection bacteriological profiles and microbiological resolution rates.

MATERIALS AND METHODS

This prospective, randomized, investigator-masked, clinical study was conducted on patients attending the eye OPD of Veer Chandra Singh Garhwali Government Medical College, Srinagar, Uttarakhand, India, during March 2018–February 2019.

Eligible patients were children from (1 day–18 years old) 100 in number with purulent bacterial conjunctivitis defined by mild-to-severe bulbar conjunctival injection and purulent discharge in at least one eye. Patients were excluded if they were premature newborns or had associated ocular pathologies [Table 1].

Systemic or ocular antibiotic, anti-inflammatory treatments were not authorized for use during the study.

Treatment Administration

On D0, eligible patients were randomly allocated (1:1 ratio) to one of the two investigator-masked study treatments. The randomization was stratified by age group (<4, 4–12, and 12–18 years). Patients received either moxifloxacin 0.5% on drop 4 times a day from D0 to D2 or tobramycin 0.3% eye drops one drops every 2 h on D0 to 1, then 4 times a day on D2 to 6.

Study Assessments and Outcomes

All patients were to attend three visits (D0, D3, and D7). An investigator who was masked to the treatment performed ophthalmologic examination, while other investigator was responsible for dispensing medications and assessing tolerance and safety.

Clinical Efficacy and Assessments

Cardinal clinical signs of bacterial conjunctivitis were assessed for each eye under slit lamp and grading were done. The primary efficacy variable was clinical cure as defined by the absence of bulbar conjunctival injection and purulent discharge in worst eye on D3 in the microbiologically positive full analysis set, i.e., patients with positive culture on D0. Secondary efficacy variable included clinical cure on D7 and other ocular signs (folliculopapillary reaction of palpebral conjunctiva, eyelid erythema, and lid swelling) and symptoms were scored on a four-point scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe. Pre-verbal patients were not assessed for symptom scores.

Table 1: Patients characteristics at baseline

Gender	Moxifloxacin (*n*=50)	Tobramycin (*n*=50)
Male	25	24
Mean age in years	2.7±3.0	3.2±3.9
Bulbar conjunctival injection in worst eye		
Absent	2 (4%)	2 (4%)
Mild	16 (32%)	18 (36%)
Moderate	25 (50%)	23 (46%)
Severe	7 (14%)	7 (14%)
Conjunctival purulent discharge in worst eye		
Absent	0	0
Mild	3 (6%)	2 (4%)
Moderate	26 (52%)	28 (56%)
Severe	21 (42%)	20 (40%)

Microbiological Assessments

A conjunctival swabbing was taken from each infected eye on D0 and D7. Bacterial specimens were analyzed by a local laboratory. A bacteriological sample was considered positive if bacteria isolated after culture were above the threshold following Cagle's microbiological criteria. Microbiological resolution (i.e., absence of bacteria or their reduction below the pathogenic threshold) was assessed on D7.

Safety Assessments

The safety analysis was based on the evaluation of adverse events, symptoms related to study medication instillation (i.e., burning/stinging/itching, stickiness, foreign body sensation, and blurred vision), ocular signs at slit-lamp examinations, visual acuity, and treatment tolerability by the investigator and patient or guardian. For preverbal children, unusual discomfort upon instillation was assessed by parent. If an exacerbated reaction was noted by the parents upon instillation of study medication to the child, the symptoms of itching/burning/stinging, stickiness, foreign body sensation, and blurred vision were recorded.

RESULTS

Clinical Efficacy

On D3, the clinical cure rate for the worse eye was significantly higher in moxifloxacin group compared with tobramycin group for patients in the Microbiologically positive full analysis set (47.1% vs. 28.7%; $P = 0.013$). On D7, there was no statistically significant difference in clinical cure rates between treatment groups (89.2% vs. 78.2%; $P = 0.077$), and non-inferiority of moxifloxacin to tobramycin was demonstrated [Table 2].

Table 2: Clinical cure rates in worse eye

	Moxifloxacin (*n*=50)	Tobramycin (*n*=50)	Between group difference	Superiority testing *P* value	Non-inferiority testing
Day 3	23 (47.1)	15 (28.7)	18.3	0.013	-
Day 7	45 (89.2)	39 (78.2)	11.0	0.077	−2.9 to 24.3

Table 3: Bacterial resolution (day 7) in worst eye

		Moxifloxacin (*n*=50)		Tobramycin (*n*=50)	
Organism	**Cagle's category**	**Day 0**	**Day 7**	**Day 0**	**Day 7**
Staphylococcus aureus	2	10	8/8	9	7/8
Staphylococcus epidermis	3	5	2/3	6	3/4
Coagulase-negative Staph	3	8	5/6	7	6/6
Streptococcus pneumoniae	1	15	12/13	16	13/14
Neisseria	1	1	1/1	1	1/1
Branhamella catarrhalis	2	1	1/1	1	1/1
Haemophilus	1	9	7/8	8	6/7
Pseudomonas	1	1	1/1	2	2/2
Overall resolution rate			89.8%		87.2%

Improvements of other ocular signs (eyelid erythema and lid swelling) were also noted on D3 and D7 but were not significantly different between groups (D3: $P = 0.067$, 0.662, and 0.498, respectively; D7: $P = 0.172$, 0.421, and 0.165, respectively).

Bacterial Resolution

The most frequent causative microbes isolated from patients at inclusion were haemophilus (31.5%), *Staphylococcus aureus* (17.7%), *Streptococcus pneumoniae* (14.8%), and coagulase-negative staphylococcus (12.8%). Overall, the bacteriological resolution rate in worst eye on D7 was similar in both groups with no notable difference between treatments ($P = 0.679$). A higher resolution rate was noted for *S. aureus* in patients treated with moxifloxacin (93.8%) versus 75% with tobramycin ($P = 0.252$) [Table 3].

Safety

Both treatments were well tolerated in all age categories, with no serious ocular AEs reported. Ocular AEs considered by the investigator as related to study drug were reported in 4 patients treated with moxifloxacin and 1 patient treated with tobramycin. These included erythema of eyelids, lid edema, and ocular hyperemia. All treatment-related ocular AEs were mild, except one case of severe ocular hyperemia in moxifloxacin group.

Itching/burning/stinging was the most common instillation-related ocular symptom reported on D3 in both treatment groups and was rated as "disturbing" or very disturbing for 7.6% of patients on moxifloxacin and 0.8% on tobramycin ($P = 0.003$). Neither corneal inflammation nor active inflammation of anterior chamber was noted for any patient on slit-lamp examination.

Clinically significant superficial punctuate keratitis was found in one moxifloxacin patient on D3 but it resolved by D7.

DISCUSSION

Randomized controlled studies with stratification by age group (i.e., neonates, infants, children, and adolescent) are designed to establish the efficacy and safety of medicinal products in the pediatric population which are strongly encouraged by the regulatory health authorities.[7] This study established the efficacy and safety of moxifloxacin 0.5% eye drops in children with average age of 3 years. Large proportion of patients younger than 24 months was seen in the study.

In this study, a short-term regimen (3 days) with moxifloxacin 0.5% drops 4 times daily provided a more rapid clinical cure in children with purulent bacterial conjunctivitis than did the tobramycin 0.3% eye drop regimen (every 2 h for 2 days and then 4 times for 5 days). When compared to tobramycin, efficacy of moxifloxacin was found to be significantly superior on D3 and non-inferior on D7. The clinical cure rates obtained for both antibiotics are very similar to those of previous studies that are 48% on D3 and 80% on D9 in moxifloxacin-treated children compared with 27% and 82% in tobramycin-treated children.[8]

The selection of patients with moderate-to-severe cardinal signs of acute conjunctivitis in this study may explain the relative high rate (71%) of positive bacterial culture noted at baseline. However, the bacteriological profile for patients in this study is similar to the one determined in the pediatric subgroup of an earlier randomized controlled study.[9]

Moreover, consistent with the causative microorganisms usually found in literature for acute conjunctivitis in young children.[10]

Haemophilus influenzae was the most frequently isolated pathogen, probably owing to the high incidence of associated otitis media in children with bacterial conjunctivitis as it is the most responsible pathogen.[11]

Streptococcus pneumoniae was also commonly detected in patients in this study.

Other pathogens, such as Gram-negative bacteria other than haemophilus, were found in new patients. Thus, a broad-spectrum antibiotic like moxifloxacin is justified for use as a first-line drug against purulent conjunctivitis in children. Most common causative agents differ from children than in adults, in which Staphylococcus species predominate. As most topical antibiotics are prescribed empirically without diagnostic bacteriological profile, these findings emphasize the importance of an etiological approach to determine best possible initial treatment.

The high rate of bacterial resolution noted in this study is consistent with the targeted efficacy of moxifloxacin 0.5% against bacterial spectrum found in children. Following moxifloxacin treatment, the bacteriological cure rate was about 90% (D7) ranging from 76.5% to 100% depending on the microbe. Moxifloxacin effectively eradicated all causative pathogens, including classically resistant species such as Acinetobacteria, Cornybacteria, and Enterobacteria.

Following moxifloxacin eye drop application, sustained antibiotic concentration in tears and conjunctival cells are usually higher than the plasma concentrations reached after oral moxifloxacin. This could explain why even bacteria resistant to plasma concentration of moxifloxacin are susceptible to eye drop treatment.[12] The pharmacokinetic properties of moxifloxacin justify the short-term treatment duration for 5 days for a rapid antibacterial action.[13]

In summary, moxifloxacin 0.5% eye drops are an effective and safe therapeutic option for purulent bacterial conjunctivitis in pediatric population notably in 0–2 years of age range. Moxifloxacin provided a superior clinical cure rate on D3 compared to tobramycin, combined with a more convenient dosage regimen.

CONCLUSION

The present study concludes that moxifloxacin 0.5% drops provided a more rapid clinical cure (47.1 vs. 28.7% $P = 0.013$) and resolution rate (89.8% vs. 87.2%) than tobramycin 0.3% eye drops in the treatment of purulent bacterial conjunctivitis in children with 4 times dosing regimen.

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