

# A Clinical Comparison of the Efficacy & Penetration of 0.6 % Besifloxacin in Cataract Surgery Cases

**Balasubramaniyan Nivetha**, M.Pharm.,

Assistant Professor, Department of Pharmacy Practice  
Excel College of Pharmacy, Komarapalayam

**Dr. ISMAIL A M**, M.Pharm., Ph.D.,

Department of Pharmacy Practice,  
Periyar College of Pharmaceutical Sciences for Girls, Tiruchirappalli, Academics & Research Dept., Dr. Agarwal  
Vasan's Eye Hospital, Tiruchirappalli.

**Dr. R.Senthamarai**, M.Pharm., Ph.D.,

Principal,  
Periyar College of Pharmaceutical Sciences for Girls, Tiruchirappalli,  
Academics & Research Dept., Dr. Agarwal Vasan's Eye Hospital, Tiruchirappalli

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## Abstract:

**Aims:** Determine the efficacy and aqueous penetration of 0.6% Besifloxacin in patients with cataract surgery after routine preoperative topical dosing.

**Settings and Design::**

Prospective, randomized, parallel, double-masked, clinical trial.

**Methods and Material:**

Patients (n -25) under Regimen A were given preoperative topical 0.6% Besifloxacin as One drop four times a day for two days before surgery. Patients (n -25) under Regimen B was given every 10 minutes for a total of 6 doses starting 1 hour before routine cataract Surgery. Aqueous humour was tested via paracentesis and concentrations of antibiotics were calculated using validated high performance liquid chromatography (HPLC) procedures. Microbiological Study was performed on conjunctival smear in patients before and after antibiotic administration

**Results:**

The study included 26 women and 24 men. The mean concentration of besifloxacin in aqueous humour was significantly same in both types of regimens, namely regime A and B, based on the penetration analysis.

**Conclusions:**

This research provides evidence-based conclusion that cataract surgery can be done as a out patient procedure without any risk to the patients and that in the aqueous humor besifloxacin has a greater penetrating capacity.

**Key-words:** Besifloxacin, antibiotic resistance, microbial eradication, Penetration

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## INTRODUCTION:

Cataract is one of the world's most severe causes of vision loss. According to the World Health Organization (WHO), cataract is the world's leading cause of blindness, responsible for 47.8 percent blindness and affecting 17.7 million blind people.<sup>1,2</sup> In India, 80% of blindness is caused by cataracts.<sup>3,4</sup> Various modifiable risk factors associated with cataracts include UV exposure, diabetes, obesity, body mass index (BMI), alcohol use, smoking, and socioeconomic factors; nevertheless, advancing age is the single most significant risk factor for cataracts.

Common symptoms include blurring of vision, glare, change of vision colour, double images, need for regular glass changes. Different types of Cataract forms include Senile Cataract, Nuclear Cataract, Cortical Cataract, Posterior Cataract Subcapsular, Congenital Cataract, Secondary Cataract, Traumatic Cataract.

Besifloxacin is a new fluoroquinolone with a wide spectrum of action against aerobic bacteria, possibly due to its N-1 cyclopropyl group and a substituent chloride at C-8. It is thought that C-8 chloride enhances activity against DNA gyrase and topoisomerase IV enzymes.<sup>5</sup> Besifloxacin is active in vitro against a wide variety of bacteria including the following gram-positive organisms:

*S aureus*, *S epidermidis*, *S pneumoniae*, *Streptococcus pyogenes*, *Corynebacterium* and *Propionibacterium acnes*. Besifloxacin has also shown activity against several gram-negative organisms in vitro, including *H influenzae*, *Moraxella bacteria*, *Klebsiella pneumoniae*, *Escherichia coli*, *Neisseria gonorrhoeae*, and *Pseudomonas aeruginosa*.<sup>6</sup> Besifloxacin was confirmed to have activity against several resistant microorganisms including ciprofloxacin and/or *S aureus* resistant to methicillin, *S epidermidis* resistant to methicillin, *S pneumoniae* resistant to penicillin, and *H influenzae* resistant to ampicillin.<sup>7</sup> Besifloxacin was also found to be bactericidal in time-kill tests against *S pneumoniae*, *S aureus*, coagulase-negative staphylococci and *H.influenza*.<sup>6,7</sup> .Because of the advent of resistance to the fourth generation of fluoroquinolones used to treat ophthalmic infections, besifloxacin's wide range of action and its efficacy against resistant microorganisms could be beneficial.<sup>8-9</sup>

The current study was performed to study the Clinical Efficacy and Corneal penetration of 0.6 % Besifloxacin after routine preoperative topical dosing in patients.

**Subjects and Methods:**

**Study site:** Vasana Eye Care Hospital, Tiruchirappalli.

**Study period:** The study was conducted during a Nine month period.

**Inclusion/exclusion criteria:**

Included were participants of either sex (otherwise healthy) who were eligible to undergo standard cataract surgery, 21 years of age or older, being able to understand and give signed informed consent.

Participants with intraocular inflammation, vulnerable to quinolone compounds, with higher intraocular pressure, corneal ulcer and keratitis and breastfeeding or pregnant women were excluded.

**Method of Study**

In this prospective randomized parallel double-masked clinical trial, patients having cataract extraction were given perioperative topical 0.6% besifloxacin suspension. Institutional review board/ethics committee approval was obtained. The 50 patients undergoing cataract extraction were divided randomly into two groups with 0.6% besifloxacin under Regimen A -25 patients and Regimen B -25 patients.

The patient's conjunctival smear was taken as baseline three days before surgery. Then each patient was administered the assigned medication randomly for three days at a dosage of a drop four times a day.

A second smear was taken after three days of administration at the time of surgery to measure the bacterial load and determine the drug's efficacy.

Conjunctival swab content was inoculated in a sterile vial with 0.3 ml of sterile saline. The swab was twirled in the saline over and over again. In the experiment, 0.1ml of the saline was inoculated on a 5% sheep blood plate, while 0.05ml each was inoculated on a cystine-tryptone-agar plate and a MacConkey agar plate.

After inoculation the plates were incubated at 37°C in a bacteriological incubator and tested for the plates after overnight incubation and after 48 hours. If bacterial growth was observed on the plates, the number of colonies in the streaked region of the plate was first calculated by counting the number of colonies and multiplying the same by 10.

A smear was prepared on a microscope slide of an individual colony and this was stained by the gram staining, dried and presented under the objective of oil immersion or a light microscope. If positive, the growth was considered to be staphylococcus aureus with the presence of beta haemolysis on blood agar and growth on MacConkey agar. If coagulase test was negative, with no beta-haemolysis on blood agar and no growth on MacConkey agar, the growth was known to be a coagulase-negative staphylococcus.<sup>11</sup>

**Penetration (Aqueous)**

Patients were instructed to use their antibiotic drops according to their specified regimens A or B.

**Regimen A:** 1 drop four times a day for two days ( 8 drops) by Conventional Mode of administration-25 patients and

**Regimen B:** 1 drop – 6 doses delivered every 10 min in the hour immediately preceding surgery (6 drops) by Pulse mode of administration-25 patients.

Through the aid of a tuberculin syringe, 0.2 ml of aqueous fluid was aspirated during surgery. The anterior chamber fluid was immediately placed in a sterilized cryogenic tube and deposited in a Ultra Low Freezer (Remi ®, Remi Instruments, Mumbai) at -40 ° C and remained frozen until analysis was completed. Every tube was labelled with a patient identification number (which meant that the subject was randomly assigned to the antibiotic), initials of the subject, date of the surgery and eye. The concentrations of topically applied fluoroquinolones were calculated using a reverse-phase, high-pressure liquid chromatography assay technique with an ultraviolet-visible detector of 275 nm wavelength.<sup>11</sup>

**Chromatographic Conditions**

Stationary Phase: Phenomenex 250x 4.60 mm 5 micron

Mobile Phase: Acetonitrile:water

Mobile phase ratio: 90: 10 % v/v

Flow rate: 1. 0 ml/min

Sample volume: 10µl

Detection: 275nm using UV Visible detector.

Data station: LC Real Time analysis

**RESULTS:**

The average age of the 50 patients under study was 40-80 years. Male patients numbered 24 (48%) and female patients numbered 26 (52%). Among this the patients having associated disease of diabetes alone 7 (44%), hypertension alone 7 (36%) both hypertension and diabetes were 6 (18%), and patients with anemia 15 (50%). Microorganisms isolated were *Staphylococcus albus* in 15(60%) patients, *Staphylococcus aureus* in 12 (48%) patients and *Proteus vulagris* in 10 (40%) patients.

During extra capsular cataract surgery, preoperative smears of the conjunctiva and anterior chamber fluid were taken in 50 patients by posterior chamber intraocular lens implantation. It was found that under Regimen A out of 25 patients, 15 patients (60%) had *staphylococcus albus*, 12 patients (48%) with *Staphylococcus aureus*, 10 patients (40%) with *Proteus vulgaris*, 5 patients (20%) with *klebsiella aerogenes* and 2 patients (8%) with *Micrococci*. In Regimen B, among 25 patients, 6 patients (24%) with *staphylococcus albus*, 16 patients (64%) with *Staphylococcus aureus*, 16 patients (64%) with *Proteus vulgaris*, 4 patients (16%) with *klebsiella aerogenes*, 6 patients (24%) with *Bacillus cereus* and 2 patients (8%) with *Brucella Species*. Preoperative Conjunctival smear has been found not to be effective for predicting AC fluid contamination or cataract surgery outcomes.

**DISCUSSION:**

Endophthalmitis remains a persistent complication of cataract surgery. Given the lack of this research on topical preoperative antibiotic agents, virtually all ophthalmologists preoperatively use some type of topical antibiotic agent.<sup>12, 13, 14</sup>

Fourth generation Fluoroquinolones have been generally recognized by cataract surgeons in the United States as the medications of choice for perioperative use. As resistance to older antibiotics, including fluoroquinolones, has increased, drugs of the fourth generation have been praised for their enhanced coverage of gram-positive pathogens and their decreased probability of causing more resistance[10]. This reduced resistance tendency is because it is unlikely that an organism would produce 2 simultaneous mutations, because this class of antibiotic agents will need resistance.<sup>15,16,17</sup>

Attaining a higher concentration of drugs at the target site often tends to minimize the production of drug resistance, since the concentration of mutant protection is normally 10 times higher than the minimum inhibitory concentration (MIC) for a given organism. Besifloxacin is in suspension which can reduce its anterior chamber penetration. Nevertheless, the longer duration of residence can result in increased penetration of the conjunctiva. In Previous Study it was found that besifloxacin concentration in the anterior chamber of the rabbits and monkeys was equivalent to that of moxifloxacin.<sup>18</sup>

Besifloxacin is less lipophilic due to monocyclic amine structure at the same position. In addition, commercial besifloxacin is formulated with the suspension, which has mucoadhesive properties to improve the drug's residence time on the eye surface.

Considering the above factors, Besifloxacin was studied for its penetration ability in aqueous humour in cataract patients. Patients are classified based on diagnosis, three types of cataracts, namely the posterior subcapsular cataract (PSC), the nuclear sclerosis grade cataract (NSGC) and the immature senile cataract (IMSC), were found to be prevalent in both regimens A and B. Two cases of Mature Senile Cataract (MSC) was observed in regimen B and no case of hyper mature Senile Cataract (HMSC) was observed in both regimen.

Based on penetration study, the mean concentration of Besifloxacin in the aqueous humour under Regimen A, it was observed that Penetration of Besifloxacin was maximum in Posterior Sub Capsular Cataract patients compared to Nuclear Sclerosis Cataract and Immature Cataract Patients. Similarly in Regimen B, it was found that Maximum Penetration was observed in Nuclear Sclerosis Cataract Patients compared to Posterior Sub Capsular Cataract patients, Immature Cataract and Mature Contract Patients. Based on the above study, the Overall Percentage of drug Penetration in aqueous humour observed in Regimen A (70.30 %) and Regimen B (74.97%) accordingly.

#### CONCLUSION:

Prophylactic eye drops are routinely used to prevent the Post Operative Complications. Fluoroquinone are widely used for eradicating the Ocular Pathogen including both Gram Positive and Gram Negative Organism.<sup>6,19,20</sup> Present Study was conducted on Besifloxacin, Fourth Generation Fluoroquinone antibiotic, to determine the antimicrobial potency and penetration Capability in Aqueous Chamber. Based on Correlation Coefficient analysis, it clearly shows

that no association was found between the grade of cataract and risk factors such as age, gender and Duration of Diabetes. The Most Prevalent Cataract among Patients was Nuclear Sclerosis Graded Cataract followed by Posterior Sub capsular Cataract. Besifloxacin shows maximum penetration in 74.97 percent in Pulse Mode Installation Compare to 70.30 percent in Conventional Mode of Administration. It's clearly shows that Pulse mode of administration of topical antibiotics before one hour shows maximum penetration compared to Conventional Style of 2 days before Surgery. Based on the above study, it was concluded that fluoroquinone antibiotic can be administered either as Preoperative topical Installation or Intra Caramel Injection at the end of Cataract surgery for endophthalmitis prophylaxis.

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