

Infections prophylaxis after cataract surgery: fluoroquinolones and anti-inflammatory drugs — alone or in combined medications?

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HIGHLIGHTS

The guidelines recommend different durations of use of fluoroquinolones and glucocorticoids after cataract surgery. Therefore, it seems reasonable to administer these drugs in separate preparations.

ABSTRACT

Cataract surgery is one of the most commonly performed medical procedures. Currently, the most commonly used antibacterials after ophthalmic surgery are moxifloxacin and levofloxacin. Of the steroidal anti-inflammatory drugs, loteprednol etabonate or dexamethasone phosphate are commonly used. Due to the fact that the current guidelines recommend different durations of use of fluoroquinolones (1–2 weeks) and glucocorticosteroids (3–4 weeks) in patients after cataract surgery, it seems justified to administer these drugs in separate preparations currently available on the market. There is a concern that the use of combination preparations may cause the patient to take fluoroquinolone for too long to maintain the anti-inflammatory effect of corticosteroids in the surgical site, and this may lead to the selection of resistant strains and increase the risk of adverse effects.

Key words: cataract surgeries, postoperative treatment, combined preparations

INTRODUCTION

Cataract surgery is one of the most commonly performed medical procedures. Although cataract surgery complications are not common, proper care after procedure is crucial to ensure the desired treatment outcome. Therefore, scientific associations have developed guidelines for pharmacological management after cataract surgery. They recommend the use of antibacterial and anti-inflammatory drugs. Currently, moxifloxacin and levofloxacin are the most commonly used antibiotics associated with ophthalmic surgery. The latter is a third-generation, broad-spectrum fluoroquinolone with high, sustained efficacy and low toxicity. The role of levofloxacin in the treatment and prevention of ocular infections is well-recognized. The results of a multicenter study conducted by the European Society of Cataract and Refractive Surgeons, showed that levofloxacin is used in many centers to prevent intraocular inflammation in post-cataract surgery patients [1]. Moxifloxacin is a novel fourth-generation fluoroquinolone that achieves the highest concentrations in ocular tissues among other fluoroquinolones. Importantly, it is the only antibacterial drug available in preservative-free eye drops. Moxifloxacin eye drops has been approved for pediatric use (including newborns), but due to limited clinical data on moxifloxacin safety in this age group, it is recommended to press children's tear ducts with a finger for about 2–3 min after eye drops administration to prevent absorption of the drug through the nasal mucosa.

Commonly used corticosteroids include loteprednol etabonate, dexamethasone alcohol suspensions, or dexamethasone phosphate. The degree of drug distribution within an eyeball depends on its chemical form. Intraocular penetration of acetates is the most effective, followed by alcoholic suspensions, and phosphates. The 1% lipophilic prednisolone acetate shows the highest extent of the intraocular penetration. Loteprednol etabonate, its direct derivative, has 10 times greater lipophilicity than dexamethasone [2]. On the other hand, the efficacy of glucocorticosteroids is determined by their ability to penetrate the ocular tissues and bind with the glucocorticoid receptor (GCR). Loteprednol etabonate exhibits greater potency than dexamethasone phosphate and a 4.3-fold higher GCR-binding affinity [3]. The anti-inflammatory efficacy and safety of loteprednol was confirmed in 2021 by Chen et al. [4] who compared the effect of 0.5% loteprednol suspension eye drops with the effect of 1% prednisolone eye drops in patients after corneal transplantation. Authors reported no differences between the groups in terms of the number of graft rejections, but at 6 months postoperatively, intraocular pressure was significantly higher in the group receiving prednisolone acetate than in the group receiving loteprednol.

The same parameter was studied by Sheppard et al. [5], who reviewed publications on the impact of loteprednol etabonate on intraocular pressure. The results confirmed the insignificant impact of loteprednol etabonate on intraocular pressure elevation, regardless of its form, dose, dosage regimen or treatment duration. Clinical studies have shown that loteprednol etabonate eye drops have a significantly weaker effect on raising intraocular pressure than prednisolone acetate or dexamethasone eye drops. Thus, loteprednol etabonate provides good control of post-operative inflammation, providing high efficacy and safety profile [5, 6].

The type of recommended drugs is similar, but it has not been precisely defined whether they should be used as a single or combined preparations. According to the 2018 Polish Society of Ophthalmology guidelines, patients following cataract surgery should receive fluoroquinolone eye drops for 7–14 days and steroid eye drops and a non-steroidal anti-inflammatory drug for 4 weeks. Since anti-infection and anti-inflammatory treatments differ in duration, we should prioritize the clinical value of drugs rather than their availability in combination formulations. Drugs should be based on novel substances with the highest efficacy and safety and allowing flexible treatment duration best achieved with single preparations.

In 2021, the Association of Polish Ophthalmic Surgeons proposed slightly different guidelines. They recommend intensive use of antibiotics for a limited time (at the maximum allowable dose level for 5–7 days), combination formulations of levofloxacin and dexamethasone sodium phosphate for 7 days, and then continue the treatment with a topical glucocorticosteroid for a total of 21 days. Due to the difference between the duration of antibiotic therapy (5–7 days) and the duration of steroid therapy (21 days), it seems optimal to use separate preparations, such as the latest generation fluoroquinolones and glucocorticosteroids with high potency and an exceptional safety profile.

Due to divergent views on how to use fluoroquinolones and anti-inflammatory drugs for perioperative prophylaxis, we asked experts in clinical pharmacology and medical microbiology for their opinion.

OPINION OF AN EXPERT IN CLINICAL PHARMACOLOGY

Due to their good intraocular penetration and action against Gram-positive and Gram-negative bacteria, third-generation fluoroquinolones (levofloxacin) and naphthyridine quinolones, i.e., fourth-generation fluoroquinolones (besifloxacin, gatifloxacin, and moxifloxacin) are recommended for the prevention and treatment of ophthalmic diseases. Sharma et al. [7] assessed the intraocular penetration of moxifloxacin hydrochloride into aqueous humor after oral and topical administration. Moxifloxacin 0.5% eye drops

were administered at 15-min intervals, starting 75 min before the surgery. Another group of patients received a single tablet of 400 mg of moxifloxacin, 12 h before surgery. The mean aqueous concentration of moxifloxacin was lower in the oral group ($0.504 \pm 0.30 \mu\text{g/ml}$) than in the eye drop group ($2.04 \pm 0.72 \mu\text{g/ml}$), indicating that it is justified to use moxifloxacin eye drops. The comparison of 3 fourth-generation fluoroquinolones (0.6% besifloxacin, 0.5% moxifloxacin, 0.5% gatifloxacin) showed that they reached a peak mean concentration (C_{max} , maximum concentration) in conjunctival tissue 15 min after dosing. However, moxifloxacin reached the highest C_{max} . Concentrations gradually decreased with each subsequent time point, and 12 h after dosing moxifloxacin still had the highest concentration. After another 12 h, the tissue concentration of gatifloxacin reached its lowest concentration and besifloxacin its highest (tab. 1). At the same time, it was shown that all three fluoroquinolones were well tolerated and reached conjunctival concentrations above the MIC_{90} for *Staphylococcus aureus* and *Staphylococcus epidermidis* for at least 2 h [8].

TABLE 1

Mean concentration (mg/g \pm SD) of selected fluoroquinolones in conjunctival tissue (according to [8]).

	15 min	2 h	6 h	12 h	24 h
0.6% besifloxacin	2.30 ± 1.42	0.418 ± 0.281	0.324 ± 0.355	0.122 ± 0.196	0.0338 ± 0.0262
0.5% moxifloxacin	10.7 ± 5.89	0.845 ± 0.440	0.228 ± 0.162	0.146 ± 0.123	0.0248 ± 0.0309
0.5% gatifloxacin	4.03 ± 3.84	0.448 ± 0.284	0.162 ± 0.205	0.0586 ± 0.0675	0.0186 ± 0.0133

Another study conducted in patients undergoing cataract surgery compared the aqueous concentration of eye drops containing 0.5% moxifloxacin or 0.3% gatifloxacin. Patients received 4 doses (at 10 min interval) of the drug (1 drop each) before cataract surgery. A sample of the aqueous fluid was taken immediately after the start of the surgery. Moxifloxacin achieved a 3.8 times higher aqueous concentration than gatifloxacin ($1.8 \pm 1.21 \mu\text{g/ml}$ vs. $0.48 \pm 0.34 \mu\text{g/ml}$) and exhibited higher efficacy against *Staphylococcus epidermidis* [9].

Bucci et al. [10] compared the pharmacokinetics of 1.5% levofloxacin and 0.5% moxifloxacin in aqueous humor prior to cataract surgery. The results showed a higher C_{max} ($1.43 \mu\text{g/ml}$) and area under curve (AUC) dose-response ($\text{AUC}_{0-6} - 6.1 \mu\text{g min/ml}$) in the aqueous humor for levofloxacin than moxifloxacin ($C_{\text{max}} - 0.87 \mu\text{g/ml}$; $\text{AUC}_{0-6} - 3.8 \mu\text{g min/ml}$). The authors suggested that levofloxacin may demonstrate a greater bactericidal potential.

There are some publications evaluating the pharmacokinetics of fluoroquinolones and glucocorticosteroids. Gomes et al. [11] compared aqueous humor concentrations of topically applied 0.5% moxifloxacin ophthalmic solution alone or in combination with 0.1% dexamethasone in patients undergoing routine phacoemulsification with intraocular lens implantation. Each drug was administered every 15 min 1 h preoperatively. In the group receiving moxifloxacin and dexamethasone eye drops, the mean concentration of moxifloxacin in the aqueous humor was 1644.3 ng/ml. In the group receiving moxifloxacin alone it reached 1280.8 ng/ml ($p = 0.01$). In both groups, moxifloxacin concentrations exceeded the MIC values for *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Enterococcus*. For fluoroquinolone-resistant *S. aureus*, moxifloxacin concentrations exceeded the MIC values in 44% of samples receiving moxifloxacin and dexamethasone eye drops, and only in 23% samples receiving moxifloxacin alone. Authors of the iPERME study assessed aqueous fluid concentrations after topical application of levofloxacin-dexamethasone eye drops and its single components in patients undergoing cataract surgery. No significant differences in concentration of levofloxacin were found between the group receiving single molecules and the group taking the combination eye drops, confirming no interaction on the corneal penetration of levofloxacin and dexamethasone [12].

Solomon et al. [13] showed that a combination therapy (eye drops containing 1% prednisolone acetate, 0.5% gatifloxacin and 0.075% bromfenac sodium) was as effective as administering the same medications in separate drops. The frequency of eyes experiencing adverse events was comparable in both study groups.

Emami et al. [14] compared the efficacy of steroids combined with antibiotics versus antibiotics alone in patients with clinically diagnosed endophthalmitis and in patients following intraocular surgery or intravitreal injections. The review included 4 clinical trials with a total of 264 participants. Patients received intravitreal dexamethasone for adjunctive steroid therapy and 2 intravenous antibiotics against Gram-positive and Gram-negative bacteria. The authors concluded that evidence showing better efficacy of steroids in conjunction with intravenous antibiotics administered alone for the treatment of acute endophthalmitis was insufficient. Therefore, authors recommended that future studies should be designed in a uniform and consistent manner.

Chen et al. [4] compared the efficacy and safety of 1% prednisolone acetate eye drops ($n = 96$) with 0.5% loteprednol suspension eye drops ($n = 138$) administered to corneal transplant patients. Thirty-five patients receiving prednisolone acetate eye drops and 27 treated with loteprednol developed corticosteroid-induced ocular hypertension.

Authors of the study observed no statistically significant differences in average intraocular pressure at 1 week, 1 month, 3 months and 12 months postoperatively. At month 6 postoperatively, intraocular pressure was significantly higher in the group receiving prednisolone than in the group receiving loteprednol. Moreover, there were no significant differences between the postoperative graft rejection in the two study groups [4].

OPINION OF AN EXPERT IN MEDICAL MICROBIOLOGY

The resistance to antimicrobial drugs is now a growing public health problem. It is predicted that by 2050 it will cause 10 million deaths per year – more than a cancer [15]. Therefore, we should prioritize rational use of antibiotics and antimicrobial drugs and follow infection control guidelines for health care settings (also in hospitals).

To reduce the risk of antibiotic resistance, antibiotics and other antimicrobial drugs should be used according to the following principles:

- only when justified
- in large enough doses
- with shorter treatment courses
- under strict observation of the intervals between doses.

Low doses or delaying dosing intervals contributes to the lower antibiotic concentration at the site of infection that can lead to the selection of resistant strains. As we have already mentioned, this can be prevented by limiting the use of antibiotics only to legitimate indications and for a short period of time. Experts in ophthalmology agree that topical povidone-iodine applied before cataract surgery and cefuroxime injection into the anterior chamber of the eye at the end of cataract surgery can prevent postoperative endophthalmitis. Authors of a recent comprehensive meta-analysis involving more than 6.8 million eyes in patients after cataract surgery found that cefazolin, vancomycin or moxifloxacin intraocular injections effectively prevent postoperative endophthalmitis [16]. Another method of POE prevention is a single intravitreal injection of a combination of 3 mg triamcinolone and 0.2 mg moxifloxacin, but this treatment method is currently not available in Poland [17].

There are still no uniform guidelines for the topical use of antibiotics (fluoroquinolones) after cataract surgery. Some ophthalmologists believe that topical antibiotics are unnecessary after routine cataract surgery and should be administered only in complicated cases [17, 18].

Quinolones and fluoroquinolones are synthetic chemotherapeutics with broad bactericidal spectrum. Since they do not exist in nature, they are not antibiotics but products of chemical synthesis. Their mechanism of action involves

the inhibition of DNA gyrase and topoisomerase IV, which are essential enzymes in bacterial DNA transcription and replication.

Fluoroquinolones are active against a wide range of aerobic Gram-positive and Gram-negative bacteria and for that reason they are often recommended by clinicians (including ophthalmologists). Unfortunately, this may increase the risk of selecting resistant strains.

The fourth-generation quinolones such as naphthyridine derivatives (e.g., moxifloxacin) have better penetration to ocular tissues than previous generations. Furthermore, they show greater activity against drug-resistant Gram-positive pathogens. Because endophthalmitis following cataract surgery is most frequently caused by Gram-positive bacteria, third- and fourth-generation fluoroquinolones can help prevent this complication. It should be noted, however, that methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* resistant to newer generation fluoroquinolones are being increasingly isolated [19].

Unfortunately, under-dosing or prolonged use of antimicrobial agents in the treatment or prevention of infections can promote the selection of resistant strains [20]. This is particularly true for the quinolones, as their use is characterized by relatively rapid selection of resistant strains compared to other antimicrobial agents. Iwasaki et al. demonstrated a significant increase in the MIC values of moxifloxacin and gatifloxacin against Gram-positive bacteria isolated from patients with keratitis in 2014–2016 [20]. Therefore, attention should be paid to the rational use of antimicrobial agents that involves appropriately large doses and keeping the treatment duration to a minimum. In this regard, a single-drug formulations are recommended over combination drugs, since according to the recent ophthalmology guidelines, anti-inflammatory drugs should be administered for a longer duration than antimicrobials. However, it should be noted that some clinical trials indicate the efficacy of compounded preparations.

Rizzo et al. analyzed the effects of 1-week course of levofloxacin + dexamethasone eye drops in managing patients after cataract surgery [21]. The authors showed that the concentrations of both drugs at the site of action was high enough to prevent infection and inhibit the inflammatory process despite relatively short treatment duration. Unlike corticosteroids, which should be used in decreasing doses, antibiotics and antimicrobial chemotherapeutics must be used in appropriately high doses throughout the treatment [22].

It should be emphasized that choosing antimicrobial agents in a particular health care facility is based on the local drug susceptibility patterns based on bacteria isolated from patients from a hospital or a department (epidemiological map).

CONCLUSIONS

Since current ophthalmology guidelines recommend different drug administration regimens following cataract surgery (1–2 weeks for fluoroquinolones and 3–4 weeks for glucocorticosteroids), it seems reasonable to use them in separate commercially available preparations. There is a risk that patients may take fluoroquinolone combination formulations for too long to maintain the anti-inflammatory effect of glucocorticosteroids at the site of the surgery, which may lead to the selection of resistant strains and increased risk of side effects.

Therefore, separate treatments based on the novel drugs and supervised by an experienced practitioner can ensure treatment success. Moreover, the clinical value of anti-infection and anti-inflammatory drugs should be prioritized rather than their availability in combination formulations. Separate formulations allow for choosing flexible treatment

duration that takes into account patient's individual needs. On an ongoing basis we should monitor results of clinical trials on reducing the duration of glucocorticosteroid use to 1 week or to inject a single-dose of antimicrobial drug in combination with a glucocorticosteroid during ophthalmic surgery. If the current ophthalmic guidelines are updated, then patients will be taking one combination formulation for 7 days. This will increase patient compliance and reduce the risk of not purchasing one of the single drugs due to their high cost.

In the case of combination formulations (antimicrobial agent + glucocorticosteroid) injected into the vitreous body during surgery, topical eye drops will not be recommended in the postoperative period. The final treatment regimen for a given patient is, of course, chosen by an ophthalmologist – alone or in consultation with a panel of specialists after considering local antimicrobial susceptibility patterns.

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