

Aus der Augenklinik und Poliklinik der Ludwig-Maximilians-Universität München

Direktor: Prof. Dr. A. Kampik

**Comparison of Conjunctival Application of Topical 0.5 %
Levofloxacin and 1% Povidone-Iodine Flushing versus Povidone-
Iodine alone in Patients undergoing Intraocular Surgery:
A Prospective Randomized Study**

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Vorgelegt von

Israel Aguirre-Romo

Mexiko Stadt

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**Mit Genehmigung der Medizinischen Fakultät
der Universität München**

Berichterstatter:

Prof. Dr. med. A. Kampik

Mitberichterstatter:

**Prof. Dr. H. Rüssmann
Prof. Dr. B.H. Belohradsky
Prof. Dr. Dr. J. Heesemann**

Mitbetreuung durch den

Promovierten Mitarbeiter:

Dr. rer. nat. Herminia Miño de Kaspar

Dekan:

Prof. Dr. med. D. Reinhart

Tag der mündlichen Prüfung:

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*Carminae et Emmanuel dicatum: si vos
absentes, hoc opus impossibile fuisset.*

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1. Introduction

1.1 Prevention of infections after intraocular surgery

Most postoperative ocular infections (i.e. endophthalmitis) are caused by the patient's own normal flora.^{10;11;90} These infections are rare, severe and arise from any kind of surgical procedure that disrupts the integrity of the ocular globe (i.e. cataract surgeries, radial keratotomy, retinal surgeries and glaucoma filtering surgeries).⁵⁴ The worst of these infections is a postoperative endophthalmitis (POE): a severe infectious inflammation involving the anterior and posterior segments of the eye, with severe visual loss in 30 %, and blindness in 18 % of the patients (Fig. 1).^{71;97;98}

The best preoperative prophylaxis has yet not been found. Several studies have been conducted to reduce preoperative bacterial load on the conjunctiva. Antiseptics like povidone-iodine (PVI) lower preoperative bacteria and decrease incidence of POE. Flushing of conjunctival fornices with PVI alone is considered as the best proven prophylaxis before intraocular surgery.^{7;14;89} Also, antibiotics appear to play an important role in decreasing bacterial load before surgery.⁴⁸ Different antibiotics have been studied in combination with PVI.⁹ Nevertheless, the antibiotic susceptibility of bacteria changes; as a consequence there are high levels of resistance to most of the antibiotics previously studied (i.e. Neosporin, norfloxacin, tobramycin, ciprofloxacin).^{46;83} Because of low corneal penetration, most antibiotics studied do not achieve satisfactory intraocular levels.^{24;30;37;69;79} Last-generation fluoroquinolones have much lower rates of bacterial resistance than ofloxacin and ciprofloxacin, and a delayed propensity to development of resistance.⁶¹ Levofloxacin (third generation fluoroquinolone) has a high corneal penetration rate when used topically and reaches excellent intraocular levels.⁹⁸ Though fluoroquinolones and PVI lower conjunctival bacterial load^{4;59;66}, no study has compared their effect to patients treated with PVI alone. In the Department of Ophthalmology at the University of Munich the only prophylaxis before intraocular surgery was soaking of the orbital skin with 10% Povidone-iodine and flushing of the conjunctiva with 10 ml 1% povidone-iodine.



Figure 1. POE after a pars plana vitrectomy; Clinical appearance: surgical wound, inflamed conjunctiva, hypopyon and corneal edema.

Incidence of POE:

The incidence of postoperative endophthalmitis is reported to be around 0.07 to 0.3 %, as reported in the last 20 years. There are some differences in the observed rates between different authors and countries (Table 1).⁸⁷

Table 1. Incidence of POE in the last 21 years.

Study	Place	Period	Incidence (%)
Aaberg, <i>et al.</i> ¹	USA	1984-1994	0.093
Kattan, <i>et al.</i> ⁵²	USA	1984-1989	0.072
Colleaux, <i>et al.</i> ²⁶	Canada	1994-1998	0.072
Versteegh, <i>et al.</i> ⁹⁴	Netherlands	1988-1998	0.10
Fisch, Salvant. ³⁵	France	1988-1989	0.31
Mayer, <i>et al.</i> ⁸¹	UK	1991-2001	0.16
Kamalarajah, <i>et al.</i> ⁵⁰	UK	1999-2000	0.14
Semmens, <i>et al.</i> ⁸²	Australia	1980-2000	0.18
Sandvig, <i>et al.</i> ⁸⁰	Norway	1996-1998	0.10
Schmitz, <i>et al.</i> ⁸¹	Germany	1996	0.148
Montan, <i>et al.</i> ⁷⁰	Sweden	1998	0.26
Nagaki, <i>et al.</i> ⁷²	Japan	1998-2001	0.13

1.2 Role of the conjunctival normal flora

Normal conjunctival flora:

The bacterial flora of untreated human conjunctiva has shown various growth patterns from conjunctival samples between different studies and authors^{16;33;91}. The results of bacterial growth from conjunctival swabs show a predominant presence of coagulase-negative *staphylococci* (CNS): i.e. *Staphylococcus epidermidis* (Table 2). Less frequent bacteria are *S. aureus*, microaerophilic bacteria (i.e. *Corynebacterium sp.*), *Streptococcus sp.* and Gram-negative rods (i.e. *E. coli*, *Pseudomonas aeruginosa*).

Table 2. Found bacteria in cultures from healthy conjunctivas.

Bacteria	<i>Fahmy, 1975</i>	<i>Boes, 1992</i>	<i>Starr, 1995</i>
Coag. neg. <i>staphylococci</i>	95.4 %	60 %	58 %
<i>Staphylococcus aureus</i>	14.8 %	8 %	7 %
<i>Streptococcus sp</i>	4.4 %	4 %	1 %
Gram-negative rods *	7.8 %	4 %	5 %
Anaerobics **	44 %	12 %	2 %
Others ***	3 %	0 %	3 %
Sterile	0 %	25 %	24 %
Patients (N)	N = 499	N = 100	N = 1000

* *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *E. coli*, *Proteus sp.*, *Klebsiella sp.*, *Enterobacter cloacae*;

** *Propionibacterium. acnes*, *Corynebacterium sp.*, *Clostridium sp.*, *Peptostreptococcus sp.*;

*** mixed of Gram- positive, Gram-negative, and anaerobic bacteria.

Bacteria in postoperative endophthalmitis:

Bacteria causing postoperative endophthalmitis most likely originate from the normal bacterial flora of the patient's own conjunctiva and eyelid^{10;90}. In 75 % to 95 % of reported cases, the causative organisms are gram-positive cocci. As described by the Endophthalmitis Vitrectomy Study¹¹, varieties of coagulase-negative *staphylococci* (CNS) are the main causes of acute endophthalmitis⁴³ (Table 3).

Table 3. Result of cultures from postoperative endophthalmitis⁴³.

Percentage	Etiology
70 %	<i>Staphylococcus epidermidis</i> and other coagulase negative <i>staphylococci</i> (CNS)
24 %	<i>Staphylococcus aureus</i>
6 %	Gram-negative rods
< 1 %	Other, i.e.: <i>Propionibacterium acnes</i> , <i>Pseudomona aeruginosa</i> , <i>Haemophilus influenzae</i> .

Less frequently, acute endophthalmitis is caused by *streptococci* and Gram-negative rods. Anaerobic or microaerophilic organisms such as *Propionibacterium acnes* are more commonly found in chronic and late intraocular inflammations^{14;45} (table 3). Because gram-positive cocci are the main cause of acute POE, methods intended to reduce conjunctival bacterial flora should be effective against these bacteria.

Large prospective studies evaluating the effectiveness of prophylactic methods to reduce POE are not feasible due to its low incidence. However as an alternative, surrogate markers such as the reduction of preoperative conjunctival bacterial flora are usually applied to demonstrate the efficacy of prophylactic measures.^{7;14;15;48;66;67;89}

1.3 Alternatives for the prevention of postoperative infections

Strategies preventing postoperative infections begin with the adoption of usual prophylactic measures like providing a sterile operative field, strict hospital policies regarding the prevention of nosocomial infections, and scrubbing of the periorbital skin with povidone-iodine.

Alternatives for the prevention of postoperative infections after intraocular surgery are summarized in Table 4. Many methods have failed to give convincing evidence of their utility and/or safety: mechanical techniques (i.e. saline irrigation, lash trimming), subconjunctival antibiotics and irrigating solutions with added drugs (i.e. heparin or antibiotics). Conjunctival

flushing with povidone-iodine (PVI) and topically applied antibiotics have proved to be safe and effective in reducing the bacterial load before intraocular surgery⁸⁷.

Table 4. Summary of prophylactic methods in postoperative endophthalmitis.

Prophylactic Method	Result	Practicality
Saline irrigation	No evidence supporting its use.	Easy to perform.
Lash Trimming	No evidence supporting its use.	Impractical and uncomfortable.
Subconjunctival antibiotics	Evidence supporting a positive reduction in POE, there remains however a lack of standardized reports supported by epidemiologic studies, and the concern about the toxic effects has not been cleared. Most proposed subconjunctival antibiotics are not the best option to reduce Gram-positive <i>cocci</i> (main cause of POE).	Invasive. Increases cost. Risk of traumatic complications.
Heparin in irrigating solution	Uncertain.	Increased cost and time. Invasive.
Irrigating solutions containing antibiotics	Aminoglycosides: Severely toxic to the retina. Vancomycin: Small and limited studies suggest utility; not supported by epidemiological studies. Since the active threshold of the intraocular concentration of antibiotics is rather short, microbiological experience discourages their use.	Increased cost and time. Invasive.
Topical preoperative antibiotics	Probed diminished infectivity of the conjunctiva. Fluoroquinolones have high ocular penetration and a wide bacterial spectrum, including Gram-positive <i>cocci</i> . There are no current standards that apply to the combination of fluoroquinolones with povidone-iodine flushing.	Easy and relatively low cost. Non-invasive.
Povidone-iodine flushing	Best proved prophylaxis, in both clinical and epidemiological studies.	Easy and low cost. Non-invasive.

Mechanical preoperative techniques:

The most frequently used mechanical preoperative techniques are for example irrigation with saline solutions and the trimming of eyelashes:

- **Saline irrigation:** Active flushing of the conjunctival sacs with an isotonic saline fluid (saline irrigation) is performed before intraocular surgery. A masked prospective study demonstrated that irrigation with a saline solution did not reduce the bacterial flora of the conjunctiva compared with unirrigated fellow control eyes.⁴⁸ A non-infected lacrimal system does not appear to play an important role in the contamination as shown in a large prospective study of 700 consecutive patients undergoing planned cataract extraction. Preoperative irrigation of the lacrimal system with balance salt solution did not significantly influence intraoperative aqueous humor contamination rates.⁶⁹ In a German survey, saline irrigation was not associated with a reduction in the incidence of endophthalmitis.⁸¹
- **Lash trimming:** Some surgeons cut the edges of the lashes before intraocular surgery. There are no studies demonstrating that lash trimming reduces the risk of endophthalmitis.⁸¹ One study of 50 patients undergoing cataract extraction confirmed that lash trimming before surgery did not alter the periocular bacterial flora present on the morning of surgery and at any time during the first four postoperative days.⁷⁴

Subconjunctival antibiotics:

The injection of subconjunctival antibiotics was one of the first prophylactic methods proposed when using antibiotics⁸⁷. Subconjunctival antibiotics have an apparent effect on human conjunctival flora as well as in animal models for the prevention of postoperative infections.^{2;30;32;84} Nevertheless, epidemiological data is scarce. Studied agents are from the cephalosporin group (i.e. cephaxolin and ceftazidime), chloramphenicol and gentamicin sulfate. One masked study compared subconjunctival cephazolin with preoperative topical antibiotics (1 % fusidic acid and chloramphenicol).³⁰ Quantitative bacterial counts from the conjunctiva and lash lines of each patient 24 hours before, on the morning of, and 48 hours after surgery showed significant reductions of the ocular microflora in the group that received subconjunctival cephalosporin, compared with those who received preoperative topical antibiotics. There are no similar studies comparing subconjunctival antibiotics with topical 3rd and 4th generation fluoroquinolones.

Aminoglycosides (gentamicin) were considered useful based on animal models.² Apparently, an antimicrobial prophylaxis of 20 mg subconjunctival gentamicin sulfate at the

time of surgery significantly reduced the incidence of postoperative bacterial endophthalmitis in aphakic rabbits exposed to *S. aureus*.² A similar result has been observed after using the same antibiotic regimen in a rabbit model.³² In another animal endophthalmitis model subconjunctival ceftazidime was used successfully.⁸⁴ Sub-Tenon's administration of gentamicin failed to prevent endophthalmitis as opposed to an intravitreal injection of 30 µg gentamicin.⁷⁵

In the German broad epidemiological survey from Schmitz *et al*, administration of subconjunctival antibiotics at the end of surgery was not associated with reduced incidence of endophthalmitis, while representing potential surgical and toxic risks.⁸¹

Irrigating solutions with added drugs:

During intraocular surgical procedures, isotonic irrigating solutions are used. Some surgeons add drugs to these irrigation fluids as another alternative to prevent postoperative infections.

- **Irrigating solutions with added heparin:** *In vitro* studies show that heparin lowers bacterial adhesion to the surface of artificial intraocular lenses used in cataract surgery. Studies evaluating aqueous contamination rates with heparin show mixed results. Apparently, heparin reduces adhesivity of *S. epidermidis*, *S. aureus*, and *P. aeruginosa*.⁷⁷ There is a discussion that heparin may reduce adherence by placing a highly hydrated layer between the bacteria and the IOL surface.⁷⁷ However, a randomized, double-masked, controlled study showed no significant difference in the rate of culture-positive anterior chamber aspirates between the heparinized group and the control group (31 % vs. 27 %, respectively).⁶²

Irrigating solutions with added antibiotics: This is the most controversial preventive method in ophthalmology. Some studies have supported its use⁸¹. Potential toxic effects to corneal endothelial cells should not be ignored.^{18;21;22;27-29;65} Other authors claim that the effect of antibiotics in the irrigation solution may be ultimately ephemeral because the half life of any antibiotic is achieved approximately two hours after surgery.^{42;57} Aminoglycosides and vancomycin are the ones most frequently used.

Aminoglycosides: An Indian study in 1976 demonstrated the effectiveness of intraocular gentamicin in irrigation solutions to prevent postoperative infections⁷⁶, compared to topical and systemic chloramphenicol.⁷⁶ This was also confirmed by another study in 1984.³⁸ Nowadays, preventive intraocular Aminoglycosides are not used due to the evidence of their toxicity.^{18;21;22;27-29;31;65}

Vancomycin: This antibiotic is used to treat infective endophthalmitis. It has a low retinal toxicity, and as a result, many authors used it in irrigating solutions with some rate of success (sterile intraocular fluids after surgery and low inflammation rate) in animal and *in vitro* models.^{3;12} Unfortunately, clinical protocols in patients under cataract surgery failed to support this hypothesis and thus discourage its use.^{58;59} The antibiotic is used only during the procedure. As a result, bacteria have a short exposure time to the drug. A microbiological model proved that, with the short exposure time to the antibiotic, there is little effect on the organisms commonly responsible for endophthalmitis.⁴² Other studies showed low maintenance of bactericidal levels.⁵⁷

1.4 Povidone-Iodine (PVI)

PVI is a strong antiseptic with minimal secondary effects (i.e. red eye, allergic reactions) in healthy conjunctivas.^{7;14;89} It is applied in concentrations of 1 – 5 % by directly flushing of the upper and lower fornices of the conjunctiva before an intraocular procedure (Fig. 2).

In 1984, Apt and Isenberg⁷ described a chemical preparation using povidone-iodine before cataract surgery. In this masked prospective study 30 consecutive patients undergoing eye surgery showed that povidone-iodine (Betadine) dilutions decreased numbers of colonies by 91 % and decreased the numbers of species by 50 % when treated with PVI. These findings were statistically significant compared to the untreated fellow control eyes.⁷

A large German survey indicated a significant reduction in the relative risk of postoperative endophthalmitis for the application of povidone-iodine on the conjunctiva.⁸¹ Another group of investigators conducted a large open-label nonrandomized parallel trial

during an 11-month period, in which topical 5 % povidone-iodine was used preoperatively in one set of five operating rooms, whereas silver protein solution was applied in another set of five rooms.⁸⁹ In all cases, surgeons continued to use their customary prophylactic antibiotic. The patients with povidone-iodine showed a significantly ($P < 0.03$) lower incidence of culture-positive endophthalmitis, compared with the silver protein group. There were no adverse reactions to povidone-iodine.

In a large prospective controlled trial Speaker and Menikoff found evidence for an association between prophylaxis with povidone-iodine and lower incidence of postoperative endophthalmitis.^{88;89} This is the biggest prospective study correlating a prophylactic measure with the ultimate outcome parameter: postoperative endophthalmitis.

The ability of povidone-iodine preparation to decrease the conjunctival flora has been confirmed in several other studies.^{14;15;45;55} Povidone-iodine preparation decreases the conjunctival load of *Propionibacterium acnes*, a common cause of chronic postoperative endophthalmitis.^{14;45} In one study of 488 patients undergoing cataract extraction, povidone-iodine solution decreased the incidence of *P. acnes* isolation from the conjunctiva from 36.7 % to 9 %.⁴⁵ In another study with 261 patients undergoing intraocular surgery, 60 of 261 conjunctival swabs (23 %) taken after application of antibiotic eye drops (polymyxin/B sulfate, neomycin sulfate, and gramicidin in combination) but before povidone-



Figure 2. Flushing of upper and lower fornices with PVI.

iodine application were positive for *P. acnes*. After povidone-iodine treatment, five (1.9 %) remained culture positive ($P < 0.001$).¹⁴ A similar study by the same group demonstrated a

similarly beneficial effect with respect to *staphylococci*, the most common causative bacteria of endophthalmitis.¹⁵

Povidone-iodine is a strong chemical antiseptic. It can be applied to the conjunctiva prior to any ocular incision. It cannot be used as a postoperative agent because of risks of intraocular leak. In animal models by Alp, Elibol *et al* corneal edema was observed in all eyes of groups who received even minor quantities of intraocular povidone-iodine.⁶ In the same study, minimal amounts of intraocular povidone-iodine did not significantly change the endothelial cell morphology and the mean endothelial cell count. There was no significant difference in corneal thickness between groups without povidone-iodine and those with only minimal amounts, however toxicity effects occurred at higher intraocular concentrations. Nevertheless, histopathological examination by transmission and scanning electron microscopy showed corneal changes even in those eyes with minimal amounts of intraocular povidone-iodine.⁶

When povidone-iodine is used in preparing the eye for intraocular surgery and as an alternative to postoperative antibiotics, inadvertent leakage of PVI into the anterior chamber must definitely be prevented.⁶ Despite the potential problems discussed, it is unlikely that preoperative treatment with povidone-iodine would leak into the anterior chamber. The reason is that all excess fluid is dried before making the first incision.

Given in a concentration of 1% in a study by Binder *et al*, PVI treatment significantly reduced conjunctival colonization.¹⁵ Ferguson, in a comparative study, found a concentration of 5 % more effective than a 1% concentration of PVI.³⁴ But the studies are not comparable, because the former applied 10 ml flushing and the latter 2 ml. A newer report on application of PVI proved a conjunctival irrigation with 10 ml of 5 % povidone-iodine to be more effective in reducing the bacterial load on the conjunctiva compared to the same concentration dosis given in two eye drops.⁶⁷

1.5 Topical preoperative antibiotics

When considering the option of adding an antibiotic to the PVI prophylaxis, many ophthalmologists give topical antibiotics before surgery^{81;85}. Topical preoperative antibiotics should decrease the ocular surface flora that may potentially enter the anterior chamber during surgery. In addition, some topical agents, especially fluoroquinolones, can penetrate the cornea to achieve effective concentrations in the anterior chamber.⁴⁴

In contrast to the experience with the PVI prophylaxis, there are no broad epidemiological studies showing that the adoption and use of antibiotics after a major surgery would reduce the incidence of endophthalmitis. The use of antibiotics to prevent intraocular infections has been promoted, but consistent antibiotic use is still not a routine practice in all centers. There is a paucity of literature evaluating the effect of topical antibiotics on the incidence of postoperative infections. Prospective, randomized clinical and bacteriological studies evaluating the effect of topical antibiotics on the bacterial conjunctiva flora have been also conducted.

Because of their broad spectrum and good corneal penetration, topical fluoroquinolones are interesting in the prevention of endophthalmitis. The next sections will focus on topical antibiotic prophylaxis with drugs other than fluoroquinolones, followed by fluoroquinolones themselves.

1.5.1 Topical antibiotics: Other than fluoroquinolones

Most of them have been shown effective in reducing conjunctival bacterial load before intraocular surgery, but it has not been consistently proven that they reduce the intraocular fluid contamination. Some have high rates of resistance amongst infective bacteria. Thus, several studies evaluating anterior chamber aspirates have not demonstrated any significant effect of these antibiotics on intraocular levels of bacteria after surgery.^{24;30;37;69;79} A study examined the vitreous fluid obtained during pars plana vitrectomy in 40 consecutive patients undergoing pars plana vitrectomy and who were randomly assigned to receive either 0.3 % gentamicin eye drops or placebo preoperatively.³⁷ There were less bacterial growth from the vitreous of patients who received gentamicin preoperatively. Additionally, in a large prospective study of 700 consecutive patients undergoing planned cataract extraction, anterior

chamber aspirates were shown to be culture-positive in 14.1% at the beginning and in 13.7 % at the end of surgery. Preoperative treatment with neomycin did not significantly influence intraoperative aqueous humor contamination rates.⁶⁹

One multicentered open-label study evaluated the effect of a one day course of topical tobramycin on the preoperative conjunctival smears of 313 asymptomatic patients before cataract surgery. Eleven coagulase-negative *staphylococci* (CNS) sensitive to tobramycin persisted in 41 of 110 patients (37.3 %) and *S. aureus* sensitive to tobramycin persisted in 4 of 30 patients (13.3 %). Newly acquired potentially pathogenic bacteria were demonstrated in 6 of 115 (5.2 %) previously negative and 22 of 198 (11 %) previously positive conjunctival cultures. Each of the gram-negative bacteria could be eliminated by a one day treatment of topical prophylaxis with tobramycin eye drops and ointment in this study. The authors note that the estimated statistically determined elimination rate also supported the potential role of topical tobramycin in prophylaxis.¹³ Nevertheless, tobramycin does not have the capability to penetrate the cornea and reach the therapeutic levels found in treatment with fluoroquinolones.⁴⁴

Topical antibiotics other than fluoroquinolones plus PVI in POE prophylaxis

Only few studies related to topical antibiotics stressed the potentially additive role of antibiotics in combination with povidone-iodine for the reducing of the bacterial conjunctival flora before intraocular surgery.^{9;48} In one study topical Neosporin ophthalmic solution given three times daily was compared with topical povidone-iodine in the fellow eye for 3 days preoperatively.⁴⁸ When used independently, the antibiotic and povidone-iodine solutions caused a similar decrease in the number of colonies and species of bacteria cultured from the ocular surface. Used together both regimens showed that the decrease was more pronounced, with 83 % of the conjunctival swabs showing no bacterial growth.⁴⁸ In a similar study, the authors compared the out-patient use of povidone-iodine for 3 days before surgery with a 3-day course of a combination neosporin ophthalmic solution placed on the other eye. Cultures taken just before the preparation of the operative field with povidone-iodine showed a similar reduction of bacteria by each regimen. Cultures taken after preparation with povidone-iodine showed a further reduction for both regimens, but this was even more pronounced in eyes previously treated with the antibiotic ($P < 0.02$).⁹ Another study suggested that preoperative topical gentamicin (1 drop each hour for 10 hours) and povidone-iodine showed a similar

decrease in ocular surface flora.⁶⁰ Another group described a placebo-controlled, randomized, double-blind clinical trial evaluating the efficacy of patient-administered 1 % fusidic acid viscous eye drops (4 times per day for 7 days) in clearing *S. epidermidis* and *S. aureus* from the lids and conjunctiva of 79 patients before cataract surgery.⁴⁰ There was a statistically significant reduction of bacteria isolated from the lid margins and the conjunctiva in the patients treated with antibiotics.⁴⁰

1.5.2 Topic antibiotics: Fluoroquinolones

The emerging resistance toward the main causative agents of postoperative endophthalmitis (coagulase negative *staphylococci*) to the previously used preoperative topical antibiotics prompted the use of other substances. It is thought that broad systemic use of these antibiotics caused the resistances to arise, and not the topical use.^{46;83} The main benefit of fluoroquinolones are that they inhibit bacterial replication. The two main bacterial enzymes targeted by the fluoroquinolones are the topoisomerase II (also known as DNA gyrase) and topoisomerase IV.⁴⁷ The activity of newer fluoroquinolones against both Gram-positive and Gram-negative bacteria and their good corneal penetration are convincing arguments for promoting their use.

Antecedents

In the 1990's, three topical fluoroquinolones were available for topical ophthalmic use in the United States: 0.3 % ciprofloxacin, 0.3 % ofloxacin, and 0.3 % norfloxacin. Norfloxacin (0.3%) never achieved widespread use due to its relatively poor antimicrobial activity. Both 0.3 % ciprofloxacin and 0.3 % ofloxacin were rapidly adopted for the treatment and prophylaxis of ocular infections. In fact, they are still used for the treatment of self-limited external eye infections such as bacterial conjunctivitis as well as more serious infections such as bacterial keratitis.^{56;73;85;95} However, to date no randomized clinical trials have been performed in an attempt to investigate the epidemiological role of these topical antibiotics prior to ophthalmic surgery.⁵⁹

In the last ten years, an increasing tendency to adopt the use of topical fluoroquinolones for prevention of postoperative infections has been noted. Because of the

newly registered resistance described, bacterial coverage became an issue worthy of consideration regarding antibiotic prophylaxis and agent selection. An emergence of resistance has been noted among gram-positive organisms because of excessive systemic use of fluoroquinolones, traditionally chosen for topical prophylaxis because of their broad spectrum of activity.^{4,39} In addition, there are also reports of resistance to fluoroquinolones among Gram-negative organisms.²³

Ocular penetration

As we know, fluoroquinolones are capable of penetrating the cornea enabling them to achieve significant intraocular concentrations sufficient enough to suppress the replication of infective pathogens that might contaminate the eye at the end of the surgery.⁴⁴ Because of resistance, the use of fluoroquinolones of third (levofloxacin) and fourth-generation (moxifloxacin and gatifloxacin) has been suggested. Fourth-generation fluoroquinolones have a high spectrum of activity with increased penetration into ocular tissues.⁶¹ Levofloxacin (a third-generation fluoroquinolone), with high-activity against gram-positive pathogens⁴⁷, offers the highest penetration of all fluoroquinolones.⁹⁸

Time of prophylaxis

To reach intraocular therapeutic levels fluoroquinolones require a specific time to penetrate the cornea and conjunctiva. There are two recent prospective randomized studies. One compared the administration of topical ofloxacin 1 hour before surgery with administration 4 times daily for 3 days before surgery. The results suggested that the longer the regimen was applied, the higher its efficacy in decreasing surface contamination and intraocular activity.⁹³ In this study, 42 % of eyes in the 1-hour group showed positive conjunctival culture immediately before surgery, compared with 19 % of eyes in the 3-day group. Immediately after surgery, 34 % and 14 % of eyes had positive cultures in the 1-hour and 3-day group respectively. Quantitatively, fewer bacteria were isolated from eyes in the 3-day group compared to those in the 1-hour group.³⁶ Another study by the same group evaluated the contamination rate of microsurgical knives during cataract surgery, comparing the 3-day with the 1-hour preoperative application of topical ofloxacin. The results showed that 26 % of knives in the 1-hour group were positive for bacterial growth compared with only 5 % in the 3-day group.⁶⁶

Resistance

Although fluoroquinolones have traditionally been chosen for topical prophylaxis because of their broad spectrum of activity against bacterial pathogens, resistance has been emerging to this class of antibacterials, particularly among Gram-positive organisms.³⁹ An increase of resistance to ciprofloxacin and ofloxacin was noted from 1993 to 1997 amongst *S. aureus*, coagulase-negative *staphylococci*, and *Streptococcus* species, approaching 50 % of isolates examined in some cases.³⁹ Another study in South Florida reported a three-fold increase in resistance to fluoroquinolones amongst *S. aureus* isolates⁴, and there are also reports of resistance to fluoroquinolones amongst Gram-negative organisms.²³

Resistances among older fluoroquinolones have been attributed to inappropriate sublethal dosing in systemic treatments.⁵⁹ Besides the third-generation fluoroquinolones (i.e. levofloxacin), the fourth-generation fluoroquinolones, such as gatifloxacin and moxifloxacin, offer a possible alternative in an area of emerging resistance. These agents confer a dual-binding mechanism of action in gram-positive organisms, inhibiting both DNA gyrase and topoisomerase IV, which is believed to expand their spectrum of activity to inhibit bacterial strains otherwise resistant to older fluoroquinolones.^{36;64} Recently they have been confirmed to show higher efficacy against preoperative multiresistant isolates.⁶⁸

1.5.3 Levofloxacin

The third and fourth generation fluoroquinolones available in the United States for topical ophthalmic use are: levofloxacin 0.5 % (third generation), gatifloxacin 0.3 %, and moxifloxacin 0.5 % (fourth generation). The main advantage of these compounds is their similar strong gram-positive activity compared to older fluoroquinolones, like ciprofloxacin and ofloxacin.⁶¹ Additionally, other discussed and potentially beneficial features shared by some of these antibiotics include enhanced drug delivery into the anterior segment, improved activity against certain strains of atypical mycobacterium, and lowered likelihood of selection for resistant bacterial strains.⁴⁴

Moxifloxacin and gatifloxacin offer improved spectrum of activity, increased penetration into ocular tissues and delayed propensity to the development of bacterial

antibiotic resistance.⁶¹ Nevertheless, levofloxacin has higher activity against gram-positive pathogens⁴⁷, and has shown high intraocular penetration after topical application.⁹⁸

1.6 Combination of povidone-iodine and levofloxacin

Certain measures and precautions can be taken in order to reduce the risk of postoperative intraocular infections. These include applying topical povidone-iodine to orbicular skin, avoiding vigorous irrigation and sealing marginal wounds postoperatively. For technical reasons and concerning controversial risks (Table 4) the use of subconjunctival or intraocular antibiotics is discouraged by most ophthalmologists. There is the possibility of combining povidone-iodine flushing with effective topical antibiotics which can penetrate the cornea and reach excellent intraocular levels (i.e. levofloxacin).^{44;61}

The combination of topical antibiotic and prophylaxis with PVI flushing has been studied. Many studies using antibiotics (neosporin, gentamicin, fusidic acid, polymyxin/B, neomycin sulfate and gramicidin) showed the additive role they play with PVI prophylaxis.^{9;14;40;48;60} Posterior studies proved the resistance of coagulase-negative *staphylococci* to these commonly used preventive antibiotics, and prompted the use of fluoroquinolones.^{47;66;67}

The use of topical antibiotics such as fluoroquinolones may also be beneficial in preventing postoperative intraocular infections.^{4;39;44} Its postoperative use should begin 1-3 days prior to surgery, and frequent dosage immediately postoperatively is recommended.⁶⁷ The newer third and fourth-generation fluoroquinolones are good agents with high bactericidal levels, which may help in addressing the emerging resistance.^{23;39}

Use of preoperative conjunctival povidone-iodine preparation is strongly supported whether prophylactic antibiotics are used or not.^{66;67} In order to decrease the conjunctival flora of patients prior to intraocular surgery, we can combine PVI and a fluoroquinolone.^{66;67} Nevertheless, there is no prospective and randomized study comparing patients treated with PVI alone against an added fluoroquinolone. Given the alarming resistance patterns, it is suggested that a broad-spectrum, highly permeable antibiotic with low toxicity like levofloxacin should be studied.^{47;61;98}

1.7. Purpose of the Study

The purpose of this study is to evaluate the effect of combining topical 0.5% levofloxacin (four times per day, one day prior to intraocular surgery) plus conjunctival flushing with 10 ml 1 % povidone-iodine (PVI), versus the effect of 10 ml 1% PVI flushing alone on the conjunctival bacterial flora.

Justification: To the best of our knowledge, there is no prospective and randomized study that compares the use of combined levofloxacin and PVI with simple PVI irrigation, in order to reduce the amount of bacterial conjunctival flora in patients scheduled for intraocular surgery. Povidone-iodine prophylaxis is considered the most justified prophylactic measure to reduce the amount of bacteria prior to intraocular surgery.^{9;14;15;67;88-90;25} The advantages of levofloxacin are its low secondary effects, its high capability amongst topical fluoroquinolones to reach effective levels in the anterior chamber, and its excellent antibacterial spectrum.⁵³

The incidence of infections after intraocular surgery is very low; as a result in analogy to reported experience^{7;14;15;48;66;67;89}, culture positivity of preoperative conjunctival swabs is used as a surrogate marker to evaluate these new prophylactic methods.

2. Material and methods

2.1 Design

The study was designed as a prospective and randomized trial.

2.2 Ethics

This is a study conducted with voluntary patients to evaluate preoperative conjunctival bacterial reduction after combining povidone-iodine (PVI) and levofloxacin, compared to PVI alone. This third-generation fluoroquinolone with a broad spectrum and low collateral effects is frequently used for lid and conjunctival infections and also after intraocular surgeries.^{4;39;56;73;85}

This study was conducted according to the World Medical Association Declaration of Helsinki⁹⁶, under the Policy of “Ethical Principles for Medical Research Involving Human Subjects”, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964. On this basis, we first asked the patients for authorization to use an extra medicine in addition to standardized povidone-iodine prophylaxis. Smears were taken from the conjunctiva with a moistened swab. This could cause discomfort and theoretically has a low risk of minor adverse effects such as small conjunctival hematoma or minor corneal excoriation.

Patients scheduled for intraocular surgery with planned anterior chamber incision or paracentesis were asked to participate in the study. Patients were over 18 years old. All patients that agreed to participate in the study were asked to sign a letter of consent before being recruited.

An application was submitted to the Ethics Commission of the Institutional Review Board at Ludwig-Maximilians-University for study approval (in German: *Ethikkommission der Medizinischen Fakultät der Ludwig Maximilians Universität München*). The research was approved by the Ethics Commission on September 28th, 2004, as Project Nr. 230/04, under the official German title:

"Effekt von topisch appliziertem 0,5 %-igem Levofloxacin auf die bakterielle Standflora der Bindehaut als Infektionsprophylaxe bei Patienten vor intraokularem Eingriff".

The act was signed by Prof. Dr. G. Paumgartner, Chairman of the Ethic Commission. The main person responsible for the project was Dr. rer. nat. Herminia Miño de Kaspar.

2.3 Patient characteristics

Participants were recruited from patients attending control or first-time appointments. They were referred to the out-patient clinic and planned for intraocular surgery, i.e. cataract surgery. The study was conducted in the Department of Ophthalmology at the University of Munich (Augenklinik der Ludwig-Maximilians-Universität, München), with recruitment initiated in November 2004 and completed in May 2005.

The design included a control group and a study group. Both groups received the standard prophylactic 10 ml povidone-iodine 1 % conjunctival flushing, while only the study group received an extra prophylactic therapy with antibiotics, 24 hours before surgery. Each group was planned to include 70 patients.

Patients were recruited, randomized and followed at the same time. The demographic characteristics were designed to be the comparable. They were randomly assigned to either study or control group.

Inclusion criteria:

- Selection was made from patients attending for the first time, or as a follow up date. The gender was irrelevant.
- The patients programmed for elective intraocular anterior chamber surgery were invited to participate in the study. There were no patients included with active systemic or local infection. Three different types of surgeries were classified:

1. Cataract surgery with intraocular lens implantation: the most frequent intraocular operation.
 2. Cataract surgery with intraocular lens implantation and pars plana vitrectomy: a frequent combination of surgery at this clinic.
 3. Other elective intraocular procedures of the anterior chamber: glaucoma surgery, penetrating keratoplasty, intraocular lens malposition, iridoplasty, etc.
- Each patient had to fully understand the characteristics and objectives of the study and to sign a consent letter.

Exclusion criteria:

- Patients who reported allergy to fluoroquinolones, iodine, some of the additional pupil- dilating eye drops or preservative agents in eye drops (i.e. benzalkonium chloride).
- Patients who had received a systemically or locally administered antibiotic within the previous 30 days.
- Patients with acute conjunctivitis, blepharitis or dacryocystitis.
- Patients under the age of 18 years.
- Patients who were not able to understand the characteristics and objectives of this investigation.

Method of randomization

At the beginning of the study, a list with 140 numbers was elaborated. The Microsoft-Office-Excel software program (Microsoft, Inc., Seattle, USA) was used to generate random numbers that were assigned to each group. The patients were randomized to either a control or study group. This randomization was distributed in sealed envelopes. Patients learned about

their group assignment from their treating ophthalmologist, who opened the envelope and explained the specific preoperative prophylactic regimen.

In order to compare similarity between both groups; demographic data such as age, sex, eye operated (right or left) and type of conducted surgery were registered.

Prophylaxis in the groups

a) Prophylaxis in all patients in control and study groups

All patients were treated as in-patients. Handling before surgery was identical. Patients were instructed not to use the medication on their fellow eye. Patients under antibacterial treatment were excluded from the study. One hour before the surgery, the patients in both groups received the standard eye drops employed to dilate the pupil: three doses of proxymetacaine hydrochloride 0.5 % and three doses of phenylephrine-hydrochloride 5 %. This was done after acquisition of the second conjunctival swab (see details in the following).

For all patients in both groups the brow, upper and lower eyelids, eyelashes, and adjacent forehead, nose, cheek, and temporal orbital area were scrubbed with 10 % povidone-



Figure 3. Orbital skin scrubbed with 10% PVI.

iodine (PVI, Braunol[®], Ratiopharm GmbH, Ulm, Germany) for 1 minute before surgery (Fig. 3). Gauze soaked with 10 % PVI was placed on the closed eye for 5 minutes after the patient was brought into the operating room (Fig. 4). Immediately before starting surgery,

the conjunctiva of the surgical eye, regardless of the assigned group, had a flushing with 10 ml 1 % PVI solution through the upper and lower fornices (Fig. 5). All excess fluid with PVI was dried up, the surgical field was draped in a sterile fashion, and a sterile lid speculum was then placed in the eye undergoing surgery (Fig. 6). After that, the surgery was performed according to the indicated procedure.



Figure 4. Gauze soaked with 10% PVI placed on the closed eye for 5 minutes.



Figure 5. Before starting surgery, upper and lower fornices are flushed with 10ml 1% PVI solution.

b) Added prophylaxis for study group only

Eyes scheduled for surgery of patients in the study group received one drop of 0.5 % levofloxacin eye drops (Oftaquix[®], Santen Oy, Tampere, Finland) 4 times a day into the conjunctival sac on the day prior to surgery and 3 applications of one drop each beginning 1 hour prior to surgery in 5 minute intervals. These drops were administered by nurses.



Figure 6. Surgical field is draped in a sterile fashion, and a sterile lid speculum is set in place.

2.4 Bacteria

Time points at which conjunctival smears for culture were acquired

Four smears of conjunctiva for the cultures were taken from each eye, at three specific time points prior to surgery, and one after the operation (Table 5). Time point T0 is at baseline 1 day before surgery, when patients were accepted for hospitalization, T1 refers to smears taken after one day of administration of topical levofloxacin for the study group, T2 and T3 represent samples obtained after iodine application. The times T0 and T1 correspond to samples taken before the patient entered the operating theater. The samples T2 and T3 were performed in the operating room, immediately before and after the operation.

The sample T1 was taken in the morning on the day of surgery. This sample had to be taken in both groups before application of topical mydriatic and vasoconstrictor, and at less 10

hours since the last application of the antibiotic in the study group. For patients of the study group, this T1 sample was taken before application of the day-of-surgery dose of levofloxacin. The T2-sample was done with lid speculum in position, 5 minutes after iodine flushing. And T3 was done at the end of surgery, before the surgeon removed the lid speculum.

Table 5. Time points at which conjunctival smears to be cultivated were obtained

Time	Definitions
T0	Baseline: 1 day before surgery and any prophylaxis
T1	At the day of surgery, before iodine flushing
T2	Just before surgery, 5 minute after iodine flushing
T3	At the end of surgery

Taking and pursuit of the cultures

The technique of taking a conjunctival smear is a simple procedure, but needs to be performed with care. Each sample must be taken using the same methodology in order to obtain an equivalent amount. Only one moistened cotton swab was used at each time point (BD-BBL™ Culture Swab™ EZ, Collection and Transport System, from *Becton, Dickinson and Company*, Sparks, MD Inc., USA). Collection of specimen was performed by completely rotating this cotton swab through the lower conjunctival sac from the temporal to the medial fornix in order to pick up specimens of all its surface parts. Special care was taken:

- Not to contact lid margins and lashes.
- Not to depress the fornix as this causes slight pain and an excessive sample.

- Not to touch the cornea as this causes slight pain in addition to the minimum risk of corneal excoriation.

The person in charge of taking the samples T0 and T1 from the control and study cases was the same person using the same technique with the identical material. At T0 and T1, cultures were obtained without topical anaesthetic to optimize bacterial growth by eliminating any preservative that might affect bacterial growth. The persons that obtained the conjunctival cultures at T0 and T1, as well as the surgeons (Fig. 7) that obtained the culture samples at T2 and T3, were masked as to whether the patient was in the control or study group.



Figure 7. With the patient dressed in sterile sheets, the surgeon took the T2 sample and can initiate the surgical procedure.



Figure 8. After taking the culture the probe is cut to 3 cm from its base and the swab is deposited in a liquid culture.

All probes were managed in a sterile fashion and cut 3 cm from their base with sterilized scissors (Fig. 8). The cotton tip was then put into thioglycolate broth. All cultures

were incubated at 37 °C for at least 10 days, and bacterial growth was identified. The swab with the cut handle was dropped in a liquid broth in a glass recipient (9 ml of Thioglycolate + Réazurine, bioMérieux[®], Marcy L'Etoile, France). The randomized number, the culture code number, and the name initials of the patients were written onto the glass recipient of the culture media with a permanent marker (Fig. 9) in order to ensure trace ability. During observation of these cultures, the growth control was carried out.



Figure 9. The cultures were incubated for 10 days.

The cultures were left to incubate at 37 °C (Mettmert[®] Incubator, Thyssen), and observed for 10 days (Fig. 10). The thioglycolate culture was considered to be of “positive growth” if the broth was cloudy within 10 days of incubation, and “sterile”, if after 10 days the medium maintained its clear and citrine transparent color. The decision of when to take a culture out of the incubator was dependent on the growth of bacteria. The bacterial growth was graded according to the volume of the liquid medium that was occupied by visible bacterial growth (Fig. 10). Colony growth patterns were graded from one cross (+), indicating barely visible small colonies, to three crosses (+++), where at least 2/3 of the medium was occupied by bacterial growth. In case of diffuse bacterial growth, the criteria ranged from slight opacity (+) to impossibility to see the finger holding the glass recipient behind the medium (+++). When positive growth of (++) or more was observed, positivity of growth was registered and bacteria were identified. If after the 10 days, a positivity of one + was found, the culture was considered positive and the bacteria identified.

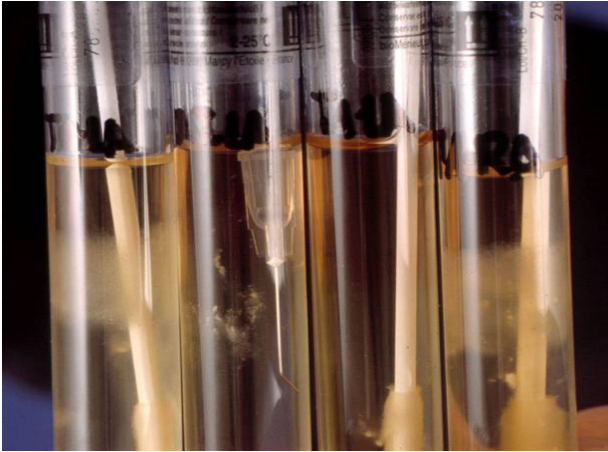


Figure 10. Incubation of the swabs in thioglycolate broth for 10 days.

(Note: The cannula cultivated in the second tube corresponds to another parallel investigation)

The persons responsible for the management and registration of positive cultures obtained from the patients' conjunctivas did not know whether the cultures under surveillance came from the control or the study group. The microbiologist responsible for isolating and identifying the bacteria was also masked as to the patients' group assignment.

Identification of coagulase-negative *staphylococci* was done by the same person performing the direct biomicroscopy and enzymatic coagulase test. The resistance to levofloxacin was registered via the Kirby-Bauer disc-diffusion technique.

The primary criteria for the outcome of this study were the measurement of positive or negative growth in cultures, as found in the thioglycolate broth. Although isolated bacteria were identified and tested for antibiotic susceptibility, a broader examination of bacterial susceptibilities to antibiotics will be presented as the main theme of another parallel medical doctoral dissertation. Nevertheless, this study presents the results related to the presence of Gram-positive bacteria, specially coagulase-negative *staphylococci* (the main cause of postoperative intraocular infections) and its resistance to levofloxacin (the antibiotic studied in this thesis).

2.5 Statistics

Demographics

To demonstrate that both groups are comparable, a demographic statistical analysis of the distribution related to gender, age, eye operated and intraocular procedures indicated for each group was performed. The method used to study these variables was the non-parametric distribution test of Wilcoxon-Mann-Whitney U (Software: BiAS[®]-2006 for Windows).

Hypothesis

Null hypothesis (H0): There is no difference in the reduction of positive bacterial growth from the cultures of conjunctival swabs in patients prior to the intraocular surgery if treatment with levofloxacin 0.5 % 1 day before the procedure is added to the 10 ml 1% povidone-iodine conjunctival flushing.

Alternative hypothesis (H1): There is a greater reduction in positive bacterial growth of conjunctival cultures taken from patients prior to surgery who were treated with levofloxacin 0.5 % 1 day before intraocular surgery and a preoperative conjunctival flushing with 10 ml 1% povidone-iodine flushing.

Method used to validate alternative hypothesis

Modified Fisher Exact Test, one-tailed *p*-value calculation (Software: BiAS[®]-2006 for Windows).

Results of positive or negative bacterial growth from cultured conjunctival swabs in both groups were obtained at different time points. Contingency tables comparing both groups at three time points before surgery (T0, T1 and T2) and one after surgery (T3) were produced. These tables are “2 X 2” type, suitable for a Fisher's Exact Test. If the variables are controlled, we can use a modified Fisher exact test in order to increase precision. The statistical comparison with a focus on the differences in positive bacterial growth in the

thioglycolate broth at time points T0 and T2 for the control and study group was the main source of validation for our alternative hypothesis.

We compared two prophylactic methods that reduce conjunctival flora. The controlled variable was an added antibiotic in the study group. In both groups, flushing with 10 ml 1% PVI was performed. As a result, we expected a reduction of bacterial growth in both groups. A two-tailed Fisher test is recommended only when the observer does not know which direction will occur in the research (greater or lesser presence of bacteria). A one-tailed test considers the expected lowering of bacteria in both groups and evaluates the hypothetical enhanced reducing effect of levofloxacin.

Simple size for each group was set to 70. Experience from earlier investigations implicated an estimate rate of positive cultures in thioglycolate broth at T1 to be around 90% in the untreated control and around 70% in the treated study group. With a given significance level of 0.05 and a predetermined power of at least 85%, needed sample size was calculated to be at least 65. Because lost to follow up was expected to be not more than 10%, sample size for each group was set to 70.

3. Results

3.1 Patient characteristics (Table 6)

The eyes of one hundred and thirty four patients scheduled to undergo anterior chamber surgery were enrolled in the study from November 2004 to May 2005 at the Department of Ophthalmology of the Ludwig-Maximilians-University in Munich, Germany. Patients were randomly assigned to control and study group ($n = 70$ each). Data acquisition was incomplete in 9 cases (6%). This was due to missed conjunctival swabs in three patients, two in the control group and one in the study group. The reasons were lack of availability of the person collecting the swab in one case, and re-scheduled surgery in two cases. In an additional two cases in the study group and one in the control group patients violated study protocol and were excluded. They had used antibiotic drugs other than study medication. Three more patients (one in study and two in control group) withdrew from study participation. All these nine cases with incomplete data were excluded from statistical evaluation. Analysis of the dropout rate between the control and study groups revealed no statistically significant difference ($P = 0.730$). As a consequence 131 of 140 patients were evaluated, comprising 66 eyes in the study group and 65 eyes in the control group (Table 6).

Table 6. Demographic data in control and study groups.

	Age in years		Gender		Operated eye		Type of surgery		
	Median (range)	Mean	M	F	RE	LE	CE/IOL	CE/IOL + PPV	Other IOAC
Study group n = 66	69 (25 – 90)	67.2 ± 14.5	22	44	33	33	50	11	5
Control group n = 65	71 (23 – 87)	68.6 ± 12.5	25	40	31	34	50	5	10
Total n = 131	70 (23 – 90)	67.9 ± 13.5	47	84	64	67	100	16	15
Statistical distribution	$P = 0.689$		$P = 0.587$		$P = 0.792$		$P = 0.914$		

M = males; F = females; RE = right eye; LE = left eye; CE/IOL = cataract extraction with intraocular lens implantation; CE/IOL + PPV = combined cataract extraction with intraocular lens implantation and pars plana vitrectomy; other IOAC = other intraocular anterior chamber procedures

No local ocular or systemic adverse reaction were observed in the patients, either after the preoperative topical application of 0.5% levofloxacin in the study group patients, or after the flushing with 10 ml 1% povidone-iodine in both, control and study groups.

There were 84 females and 47 males; the median age of all patients was 70 years (range 23-90 years) with a mean of 67.9 ± 13.5 years. In total, 64 right eyes and 67 left eyes were operated. This included cataract surgery with intraocular lens implantation ($n = 100$), combined cataract extraction with intraocular lens implantation and pars plana vitrectomy ($n = 16$), and other intraocular anterior chamber procedures ($n = 15$). Statistical analysis of the distribution of these criteria revealed no significant differences between the study and control group (age $P \geq 0.689$; gender $P \geq 0.587$; operated eye $P \geq 0.792$; type of surgery $P \geq 0.914$). Demographic details and statistical distribution related to each variable is shown in table 5. Both groups are non-parametrically distributed and are comparable (Table 6).

3.2 Bacteria

Positive cultures (Table 7)

Table 7. Results of positive bacterial cultures.

	T0		T1		T2		T3	
	Study	Control	Study	Control	Study	Control	Study	Control
Total eyes (n = 131)	66	65	66	65	66	65	66	65
Cultures taken (n = 524)	66	65	66	65	66	65	66	65
Positive cultures	55	54	50	60	8	20	5	15
Sterile cultures	11	11	16	5	58	45	61	50
Proportion of positive cultures	0.837	0.831	0.758	0.923	0.121	0.308	0.076	0.231
Proportion of sterile cultures	0.166	0.169	0.242	0.077	0.879	0.692	0.924	0.769
Statistical distribution (p value)	$P = 0.969^*$		$P = 0.009^{**}$		$P = 0.008^{**}$		$P = 0.012^{**}$	

The proportion of positive cultures in both groups at the beginning of the study (T0) is similar ($P = 0.969$). There is a difference in the proportion of positive cultures between both groups time points T1, T2 and T3 ($P = 0.009, 0.008$ and 0.012 respectively) Two-tailed Fisher Exact test; ** One-tailed Fisher Exact Test*

During the study, 524 conjunctival swabs were taken from 131 eyes to be cultured in the same numbers of thioglycolate broth (Table 7).

Positive results of cultures grown in thioglycolate broth from eyes in both groups are shown in table 7. The baseline culture results (T0) showed no statistically significant difference between groups concerning the spectrum of cultured bacteria in thioglycolate broth ($P = 0.969$). 54 of 65 samples in the control group (83.1 %) had positive cultures, similar to 55 of 66 eyes (83.7 %) in the study group ($P = 0.969$).

On the day of surgery, after one day of topical levofloxacin for the study eyes (T1), 60 of 65 eyes (92.3 %) in the control group without topical antibiotic showed positive cultures, compared with 50 of 66 eyes (75.8 %) in the study group with topical antibiotic ($P = 0.009$). The percentage of positive cultures at T0 increased from 83.1 % to 92.3 % at T1 in the control group's eyes and decreased from 83.7 % at T0 to 75.8 % at T1 in the study group's eyes. This change did not reach statistically significant levels in either the control or the study group ($P = 0.181$ and $P = 0.388$ respectively, Fig. 11)

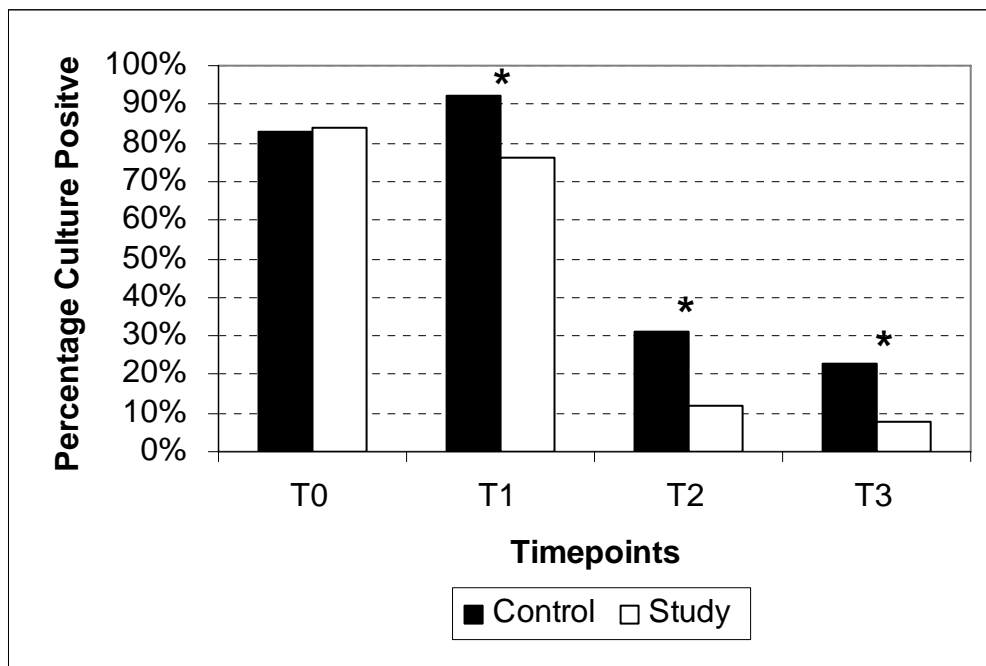


Figure 11: Percentage of positive growth in control and study groups at the four study time points. * $P < 0.05$

Immediately before surgery at T2 (5 minutes after flushing with PVI), 20 of 65 eyes (30.8 %) in the control group had positive cultures, compared with only 8 of 66 eyes (12.1 %) in the study group ($P = 0.008$). The change in the percentage of positive cultures from T1 to T2 was 92.3 % to 30.8 % in the control group ($P < 0.001$) and 75.8 % to 12.1 % in the study group ($P < 0.001$). At this time point, there was a high reduction of positive growth in both groups, which was statistically significantly more pronounced in the study group ($P = 0.008$) (Figure 11).

At T3, 15 of 65 eyes (23.1 %) in the control group and 5 of 66 eyes (7.6 %) in the study group had positive cultures ($P = 0.012$). Figure 11 shows the identified number of positive cultures in both control and study group at the four time points of conjunctival smears.

Identified bacteria (Table 8)

Table 8 shows the identified bacteria in both control and study group at the four time points of conjunctival smears. In some cases mixed cultures occurred, total amount are higher compared to culture positive results from conjunctival swabs (Table 7).

Throughout each time point, there was a progressive reduction of the total amount of identified bacteria in the study group, from 63 in T0 to 50 and 8 in time points T1 and T2. The control group showed an important reduction only at time point T1 to T2 (62 to 22). By time point T2, just before starting surgery the total amount of identified bacteria in the control and study groups was 22 and 8 respectively. The control group had 2.75 times more bacteria than the study group.

The most commonly isolated bacteria in both groups through T0 to T3 were coagulase-negative *staphylococci* (CNS); 82 of the 124 (66 %) isolated bacteria were CNS; 40 and 42 strains in the control and study group respectively at the beginning of the study at T0. The numbers decreased at T1 to 39 and 37 in both the control and the study group. The most important reduction took place after the PVI flushing, with 15 and 8 strains of CNS in the control and study group respectively. By time point T2, before starting surgery, the study group, who received levofloxacin prophylaxis, had a 53 % lower presence of CNS than the control group.

Both groups had presence of *S. aureus*, with 5 and 6 strains at T0 in the control and study group respectively. At time point T2, before starting the surgery, no *S. aureus* was detected in the study group and one strain could be found in the control group.

Table 8. Isolated bacteria from conjunctival swabs in thioglycolate broth.

	T0		T1		T2		T3	
	Control	Study	Control	Study	Control	Study	Control	Study
Coagulase-neg. staphylococci	40	42	39	37	15	8	14	4
<i>Staphylococcus aureus</i>	5	6	6	4	1	0	1	0
α-haemolytic Streptococcus	1	2	2	1	1	0	0	0
β-haemolytic Streptococcus	3	2	3	1	1	0	0	0
Streptococcus group D	1	0	1	0	0	0	0	0
<i>Corynebacterium sp</i>	3	3	3	2	0	0	0	0
<i>Propionibacterium sp</i>	5	6	6	4	3	0	0	1
<i>Micrococcus sp</i>	0	0	0	0	0	0	0	0
<i>Pseudomonas sp</i>	1	1	0	0	0	0	0	0
Other gram-negative Bacteria	2	1	2	1	1	0	2	0
Total amount of identified bacteria	61	63	62	50	22	8	17	5

(The numbers indicate the amount of bacteria identified)

Other identified bacteria were *α -haemolytic Streptococcus*, *β -haemolytic Streptococcus*, *Streptococcus Group D*, *Corynebacterium sp*, *Propionibacterium sp*, *Micrococcus sp*, *Pseudomonas sp*, and other Gram-negative Bacteria. At time point T2, just before surgery, the control group had 15 strains of CNS and 7 strains of bacteria other than CNS, including 3 strains of *Propionibacterium sp*. In contrast, at time point T2, the study group did not show growth of any bacteria other than the 8 strains of CNS.

Levofloxacin susceptibility (Table 9)

During the study, bacteria cultured in thioglycolate broth were identified and isolated. Antibiotic susceptibilities of the identified strains of CNS and *S. aureus* were evaluated (Table 9). These bacteria are those most frequently found in postoperative infections⁴³.

At the beginning of the study, at time point T0 for study and control groups, a total of 93 strains of *staphylococci* (CNS and *S. aureus*), were isolated. Amounts were similar, with 45 strains in the control and 48 in the study group. By time point T0, 82 of the isolated bacteria were susceptible to levofloxacin (88.2 %). Four (4.3 %) were intermediate-susceptible and 6 (6.4 %) were resistant. At time point T0 each group showed three strains of *staphylococci* resistant to levofloxacin. At time point T1, those three strains of resistant bacteria were again isolated in each group. The number of resistant organisms in both groups were reduced after the povidone-iodine flushing (time point T2) to one strain of CNS resistant to levofloxacin in the control group and two in the study group. At time point T3 there were still 15 strains of *staphylococci* in the control group and only 4 in the study group (all susceptible or intermediate-susceptible to levofloxacin). At T3, at the end of surgery, no bacteria resistant to levofloxacin could be isolated.

Table 9. Susceptibility of isolated *staphylococci* to levofloxacin in study and control group at the time points of the study.

	T0		T1		T2		T3	
	Control	Study	Control	Study	Control	Study	Control	Study
CNS	40	42	39	37	15	8	14	4
<i>S. aureus</i>	5	6	6	4	1	0	1	0
Total	45	48	45	41	16	8	15	4
Susceptible	41	42	40	36	15	5	14	3
Intermediate	1	3	2	2	0	1	1	1
Resistant	3	3	3	3	1	2	0	0

(CNS = Coagulase negative staphylococci)

4. Discussion

One of the goals in the prevention of infections after intraocular surgery is to reduce the number of eyelid and conjunctival bacteria that are present at the time of surgery. The source of bacteria causing postoperative endophthalmitis is thought to be the patient's own conjunctiva.^{10;90} In an attempt to minimize the risk of endophthalmitis, prophylactic measures are used to reduce the amount of bacteria in the surgical field. The topical administration of antibiotics is preferred. It has been shown that preoperative application of both topical povidone-iodine and various antibiotic agents are effective in reducing the incidence of contamination as measured by the growth of bacterial colonies in conjunctival isolates.^{7;9;14;15;19;41;48;86} Many cataract surgeons place their patients on topical antibiotic therapy in the preoperative period. Many also use intraoperative subconjunctival injections^{2;30;32;84} or intraocular infusions of antibiotics.^{59;63} Reports about toxicity of subconjunctival injections, and the associated risks have discouraged their use.⁸¹ The use of irrigating solutions containing antibiotics is likewise attended by much controversy.^{18;21;22;27-29}

In our study we did not find local or systemic collateral effects related to the use of the povidone-iodine flushing or the 0.5% levofloxacin prophylaxis. The optimal characteristic of topical antibiotics used for preoperative endophthalmitis prophylaxis includes the ability to: kill bacteria, highly permeable, bioavailability, low toxicity, broad-spectrum coverage, particularly for gram-positive bacteria and favorable susceptibility patterns. Antibiotics given before, during and after surgery can potentially reduce the ocular bacterial load. This is particularly important given the prevalence of antibiotic resistance that has resulted from widespread and prolonged use of systemic antimicrobial agents.^{9;13;30;40;48} Fluoroquinolones whose best trait are their ability to reach effective levels in the anterior segment have been shown to be one of the best options.^{4;39;44;59;66;67} It is important to characterize ocular bacterial flora and to determine their antibiotic susceptibility patterns in patients undergoing intraocular surgery.

One potential weakness of our study is that bacterial conjunctival flora must be regarded as a "dynamic" rather than a static factor, and are therefore subject to changes over time. This could result in different amounts and species detected at various time points. Though we tried to minimize the time period between the first two swabs to two days, one could argue that results at T1 as compared to T0 could have been influenced by such changes.

We would expect an equal distribution of the results in both test groups if this hypothesis were to hold true. Secondly, as long as no active inflammation is present, these changes should be minor and not relevant to the outcome of this research.

In our study the patients in the control group did not receive a placebo in the form of eye drops. One might argue that results at T1 in patients of the study group could have been caused by dilutive effects through the application of fluid alone. This is unlikely because there was not application of eyes drops ten hours before the conjunctival probing of eyes under the levofloxacin prophylaxis was done. As a result the tear was not markedly disturbed and the antimicrobial effect of levofloxacin was observed. Additionally, in a study by Isenberg *et al.*, irrigation of the conjunctiva with saline solutions alone did not reduce the bacterial flora of the conjunctiva compared to unirrigated fellow control eyes.⁴⁸ In a later study the same group found that irrigation of the conjunctiva with saline actually tended to increase the ocular flora⁸. As a result, it is commonly accepted that conjunctival bacteria flora are not significantly influenced by application of doses of fluid alone, and earlier studies evaluating the effect of topical antibiotic treatment were conducted without use of a placebo.^{9;36;39;60;66;67}

4.1 Prophylactic methods and proportion of positive cultures

Povidone-iodine (PVI)

The major reduction in the number of positive growth of bacteria in cultures from both groups with or without the antibiotic was observed after the 10 ml 1% PVI flushing prophylaxis ($P < 0.05$), but the effect was even more pronounced in eyes of the study group treated with levofloxacin ($P = 0.009$). The most widely accepted method for preoperative prophylaxis is still povidone-iodine flushing.^{7;14;15;45;55;88-90} In a review of the literature, Ciulla *et al* found PVI to have the highest evidence concerning prevention of endophthalmitis.²⁵ Schmitz *et al.* reported decreased rates of intraocular infection among those surgeons using povidone-iodine as preoperative prophylaxis.⁸¹

Isenberg *et al* compared bacterial growth from conjunctival swabs after a prophylactic regimen comprised of one or two drops of 5 % PVI with or without a three-day application of neomycin sulphate, polymyxin B sulphate and gramicidin given three times a day.⁴⁸ In their study, which included both eyes of 35 consecutive patients, the authors found the combination

of both antibiotic and povidone-iodine to be highly effective in reducing the bacterial conjunctival load. Combining PVI with antibiotics has been suggested to decrease the presence of bacteria after intraocular surgery.

Antibiotic and PVI

Topical antibiotics and iodine are used in the preoperative period to minimize the number of bacteria on the ocular surface.^{47;66;67;87;91} In this study, positive growth of bacterial cultures from conjunctival swabs in patients before intraocular surgery was used as a surrogate marker to compare prophylactic methods. After one day prophylaxis with 0.5% levofloxacin (time point T1), there were fewer positive cultures in the patients with topical antibiotic ($P = 0.009$). The results imply that topical levofloxacin significantly reduced the number of bacteria present on the ocular surface compared to the omission of the antibiotic.

However the combination of topical levofloxacin and iodine was more effective in reducing bacteria from the ocular surface just before intraocular anterior chamber surgery compared to iodine alone ($P = 0.008$). The effect is maintained until the end of surgery, as observed at T3 ($P = 0.012$). Both T2 and T3 are the most critical points, given that they represent the time immediately before and after surgery, a window of opportunity for the bacteria to gain entry into the eye.

In our design the control group did not receive any preoperative antibiotic, only the preoperative PVI irrigation, in order to evaluate additional effect of antibiotic treatment. On the morning of the surgery, patients with no prophylactic method had 92% of positive cultures (T1 control group). Those patients treated with the antibiotic as their only prophylaxis showed 76% of positive cultures (T1 study group). After povidone-iodine flushing alone we found only 31% of positive cultures (T2 control group). The strongest reduction of bacterial growth from conjunctival swabs was observed after the combined prophylaxis of levofloxacin and PVI flushing, with 12% of the cultures with positive growth (T2 study group); 2.5 times lower than with povidone-iodine flushing alone. In 1985, the study of Isenberg *et al*⁴⁸ observed the effect on the conjunctiva of 3 ml 5% povidone-iodine and a combination of prophylactic antibiotics (neomycin sulphate, polymyxin B sulphate and gramicidin) and they found 17% of positive cultures. The results of that study would be difficult to replicate due to the reported changes in resistance patterns of bacteria to old antibiotics.^{9;13;30;40;48}

In 2002 Ta *et al*, a study design very similar to this work, it had been shown that preoperative treatment with topical 0.3% ofloxacin reduced the bacterial load on the conjunctiva.⁹³ Contrary to our study, both the control and study groups received antibiotics, but for different time periods; one hour before surgery or four times a day for a three-day period previous to anterior chamber operation. After one hour of antibiotic prophylaxis and 10 ml 1% PVI flushing, there were a 34% of positive cultures in thioglycolate broth. The combination of three days 0.3 % ofloxacin therapy and 10 ml 1% PVI flushing showed 14% of positive cultures.

For the sake of comparison, Table 10 has been created to highlight the results of our study, Isenberg⁴⁸ and Ta,⁹³ however studies from different universes are not comparable. Ta used a fluoroquinolone (ofloxacin) for three days before intraocular surgery, and the positivity of cultures of 14% was similar to our percentage of 12% with only one day of levofloxacin prophylaxis. Only a prospective study comparing different regimens of levofloxacin therapy would prove whether a three day term of levofloxacin prophylaxis before intraocular surgery would be a better option.

Though our study does not provide evidence of whether additional topical treatment with levofloxacin further decreases incidence of endophthalmitis, it can be hypothesized that reduced amounts of bacteria within the surgical area lower the chances of contamination.

Table 10. Percentage of positive cultures before surgery.

Prophylactic method	Source	Percentage of Positive Cultures
No prophylaxis	Present study. T1 control group	92%
Levofloxacin 0.5 % 4 x 1 day	Present study. T1 study group	76%
Ofloxacin 0.3 % 1 hr before surgery + 10 ml 1% PVI	Ta <i>et al</i> , ⁹³ 2002	34%
10 ml 1% PVI flushing alone	Present Study. T2 control group	31%
Neomycin sulphate-polymyxin B sulphate- gramicidin + 3 ml 5% PVI	Isenberg <i>et al</i> , ⁴⁸ 1985	17%
Ofloxacin 0.3 % 4 x 3 days + 10 ml 1% PVI	Ta <i>et al</i> , ⁹³ 2002	14%
Levofloxacin 0.5 % 4 x 1 day + 10 ml 1% PVI	Present study. T2 study group	12%

PVI: Povidone-iodine.

4.2 Identified bacteria before prophylaxis

This work showed that the most common organisms colonizing the eye were coagulase-negative *staphylococci* (CNS), 66% of all isolated bacteria in time point T0, before any prophylactic method. These findings are consistent with previous published studies.^{5;51;92} CNS are implicated in approximately 70% of the cases of postoperative endophthalmitis.⁴³ The most common bacteria isolated at time point T0 from conjunctival swabs in our study were coagulase-negative *staphylococci*, *S. aureus*, *Propionibacterium acnes* and *Corynebacterium* sp. The distribution of organisms found at baseline (Table 8) was similar to that described in a report by Boltze *et al.* on normal conjunctival flora.¹⁷ An extensive explanation about isolated conjunctival bacteria will be presented in a separate doctoral thesis.

4.3 Identified bacteria in treated eyes

The patients with added antibiotic were observed to have a considerable reduction of all bacteria after the levofloxacin prophylaxis ($P < 0.05$). This was caused both as a result of decrease of *staphylococci* and other bacteria. The major reduction of conjunctival bacteria identified in both groups was observed after the povidone-iodine flushing; either diminution of *staphylococci* or other bacteria (*Streptococcus* sp, *Corynebacterium* sp and particularly with regard to *Propionibacterium* sp). The absence of *Propionibacterium* sp in the cultures from the combined therapy group coincides with the observations of Binder *et al*¹⁵. They observed the absence of growth of *Propionibacterium*, after the combined prophylaxis of PVI and antibiotic (Polymyxin B Sulfat, Neomycin sulfat and Gramicidin). They also noted, as we did, an important reduction of *staphylococci* after combined PVI and antibiotic prophylaxis.

After PVI the patients from the control group experienced a reduction in the number of identified bacteria from 62 to 22 isolates. The patients with antibiotic had an important reduction, from 55 to 8 recognized bacteria after PVI. The most remarkable difference among results from both groups after PVI flushing corresponds to the assortment of identified bacteria. Patients with levofloxacin and PVI flushing had only 8 CNS; no other kind of bacteria was identified. Patients with PVI prophylaxis alone experienced a result (15 CNS) rendering almost twice as many isolated CNS than patients with combined therapy (8 CNS). These patients with simple prophylaxis were also discovered to have had one *S. aureus*, two

streptococci, one Gram-negative rods and three strains of *Propionibacterium* sp. Comparing these results to those reported by Binder *et al*¹⁵ (combined topical Polymyxin B Sulfat/Neomycin sulfat/Gramicidin and PVI flushing) it is revealed an incremented effect of combining levofloxacin and PVI flushing in decreasing bacteria other than *staphylococci*. However, in their study it was observed after the combined antibiotic therapy an 8% of positivity to CNS, a smaller number compared to the 12% of positive CNS in our patients, after combined levofloxacin and PVI. Only a comparative study could establish if that difference might be reproducible.

4.4 Resistance of *Staphylococcus* sp to levofloxacin

Unlike antiseptics such as povidone-iodine, antibiotics do not kill bacteria within minutes of administration, but rather require a longer period of time.^{20;78} The improper use of systemic antibiotics has caused resistance to existing agents to emerge. Topical use of conjunctival antibiotics is not responsible for this resistance. According to Hodge⁴⁶ it is difficult to stay in a sub-lethal concentration in a conjunctival clinical treatment, since the tissue levels that can be achieved with topical dosing may be much higher than that typically achieved after systemic dosing. In a more recent study, Seppala *et al* found that the possibility of ocular antibiotics affecting the resistance patterns of the bacteria is unlikely.⁸³

Resistance among older fluoroquinolones has been attributed in part to inappropriate sublethal dosing, which has induced mutagenesis in once susceptible pathogens.⁵⁹ To prevent further resistance and avoid infection by resistant organisms, it is necessary to consider newer agents such as third and fourth-generation fluoroquinolones. These agents confer a dual-binding mechanism of action on gram-positive organisms, inhibiting both DNA gyrase and topoisomerase IV, which is believed to expand their spectrum of activity to inhibit bacterial strains otherwise resistant to older fluoroquinolones.^{36;64}

Fluoroquinolones are among the most frequently used topical antibiotics for endophthalmitis prophylaxis. They are bactericidal against a broad-spectrum of organisms, killing both Gram-positive and Gram-negative bacteria, but resistance has been emerging to this class of antibiotics, particularly among gram-positive organisms. Increase of resistance to ciprofloxacin and ofloxacin was recorded from 1993 to 1997 among *S. aureus*, coagulase-

negative *staphylococci*, and *Streptococcus* species, approaching 50 % of isolates examined, for some species.³⁹ A study in South Florida reported a three-fold increase in fluoroquinolone resistance among *S. aureus* isolates⁴ and there are also reports of resistance to first and second generation fluoroquinolones among Gram-negative organisms.²³

In our study levofloxacin presented at baseline (T0 from both groups) a Resistant Rate (RR) to CNS of 6.4%. This result is comparable to the study of Ta in 2003,⁹² who reported that cultured organisms were least likely to be resistant to levofloxacin. Compared with levofloxacin (RR of 6 %), the other fluoroquinolones ciprofloxacin (RR of 15%), ofloxacin (RR of 16%) and norfloxacin (RR of 15%) were associated with significantly greater rates of resistance.

At the start of the study, before any prophylaxis (T0), the number of resistant *staphylococci* was similar in both groups, observing 3 strains of bacteria resistant in each group. At time point T2, after povidone-iodine flushing, we found in the control group 16 *Staphylococcus sp* (one a *S. aureus*) and 8 in the study group. At time point T2, povidone-iodine lowered resistant and intermediate-susceptible bacteria in both control and study groups (from 5 to 1 intermediate/resistant bacteria in the control group, and from 5 to 3 in the study group). After the PVI flushing, 2 of 8 strains were resistant in the patients under combined therapy with levofloxacin (20% of identified staphylococcus) and one of 15 isolates (6%) in the patients with only PVI flushing.

One must consider the possibility that in vitro antibiotic susceptibility testing as performed in our study might not accurately reflect the true in vivo effectiveness of the antibiotics tested. The in vitro antibiotic susceptibility using the Kirby-Bauer disc diffusion technique is based on serum antibiotic concentration, which might be less than the concentration achieved with topical or subconjunctival delivery.⁹² The high concentration of commonly used antibiotics achieved with frequent topical antibiotic application or by subconjunctival injection might change the relative efficacy of the various agents in vivo. The typical concentration of topical fluoroquinolones is 3 to 5 mg/ml.⁹² The tear concentration varies, depending on the dosing regimen. Given the rise in antibiotic resistance, ophthalmologists must carefully choose the antibiotic that is most effective in minimizing ocular colonization with resistant organisms. In vitro antibiotic susceptibility testing is the most commonly cited standard and will continue to guide the ophthalmologist in antibiotic

selection. This might include choosing antibiotics that have shown the greatest effectiveness against bacteria in vitro, frequent dosing of an antibiotic over a short period of time rather than chronic use, and performing antibiotic susceptibility prevalence surveys.

5. Summary

In comparison to conjunctival flushing with 10 ml 1% povidone-iodine (PVI) alone, adding a one day presurgical prophylactic therapy with 0.5% levofloxacin eye drops significantly reduces positive bacterial conjunctival cultures prior to, and upon completion of intraocular surgery ($P = 0.008$). This is the first prospective randomized study demonstrating an enhanced effect through a combination of a topical fluoroquinolone antibiotic along with PVI compared to PVI flushing alone.

There are no conclusive scientific data showing that use of antibiotics reduces the risk of the ultimate outcome parameter: postoperative endophthalmitis.^{25;87} Only one prospective study documented efficacy in reducing endophthalmitis⁸⁹, which showed that preoperative topical 5% povidone-iodine significantly reduced the risk of endophthalmitis. The difficulty to perform a prospective controlled clinical series in today's medical-legal environment leads us to rely on indirect studies.

Coagulase-negative *staphylococci* (CNS) were the main isolated bacteria (T0) before any conducted prophylactic measure. Other bacteria were *S. aureus*, *streptococci* sp and *Propionibacterium* sp. Combinative prophylaxis with levofloxacin and PVI showed in 12% of the 66 study cultures only CNS. 24 % of the 65 patients with only PVI prophylaxis presented a CNS; additionally 10% of those same 65 patients presented other bacteria. These results parallel the findings of our positive cultures. The 6% Resistant Rate (RR) of levofloxacin to *staphylococci* at baseline (T0) is comparable to previously reported findings.⁶¹ After PVI prophylaxis alone a RR to levofloxacin of 6% was seen, demonstrating no change to baseline.

While this study did not prove that a combination of topical 0.5% levofloxacin and povidone-iodine irrigation reduces the risk for postoperative endophthalmitis, the combination showed an enhanced effect in diminishing the conjunctival bacterial flora. As this has shown to be the main origin of bacteria causing post operative endophthalmitis, it can be hypothesized that this regime reduces the risk of intraocular contamination and consequently postoperative endophthalmitis. To finally clarify this issue a large prospective randomized multi-center clinical trial is underway.⁴⁹ Until the results are published, combined prophylaxis with topical 0.5% levofloxacin and irrigation with povidone-iodine can be recommended in patients scheduled for intraocular surgery.

Zusammenfassung

Im Vergleich mit einer alleinigen Spülung der Bindehaut mit 10ml 1%-iger Povidone-Iod-Lösung (PVL) reduziert eine zusätzlich eintägig, präoperativ gegebene, prophylaktische Therapie mit 0,5%-igen Levofloxazin Augentropfen die Anzahl positiver Bakterienkulturen sowohl vor und direkt nach dem intraokularen Eingriff ($P = 0.008$). Dies ist die erste prospektiv randomisierte Untersuchung, welche diesen zusätzlichen Effekt einer Kombination aus einem topisch gegebenen Fluorochinolon Antibiotikum und einer Spülung mit PVL gegenüber einer alleinigen Spülung mit PVL nachweist.

Es gibt keine endgültigen, wissenschaftlichen Daten, die belegen, dass eine topische, antibiotische Behandlung das Risiko einer postoperativen Endophthalmitis reduziert.^{25;87} Eine prospektive Studie konnte dagegen für die präoperative Behandlung mit 5%-iger PVL ein reduziertes Risiko für eine Endophthalmitisentstehung nachweisen.⁸⁹ Die Schwierigkeit eine prospektiv, kontrollierte Studie zu diesem Thema unter den heute gegebenen medizinisch-juristischen Gegebenheiten durchzuführen, erfordert die Zuhilfenahme von indirekten Nachweisparametern.

Es wurden überwiegend Koagulase-negative Staphylokokken (CNS) unter den isolierten Bakterien zum Zeitpunkt T0, das heißt vor jedweder durchgeführten prophylaktischen Maßnahme, nachgewiesen. Andere nachgewiesene Bakterien waren *S. aureus*, *Streptococci* sp und *Propionibacterium* sp. Die kombinierte Behandlung mit Levofloxacin und PVL zeigte in 12% der 66 Studienkulturen nur CNS. In 24 % der 65 Patienten mit alleiniger PVL Prophylaxe fanden sich CNS; zusätzlich zeigten jedoch 10% dieser 65 Patienten auch andere bakterielle Erregernachweise. Diese Ergebnisse gehen einher mit unsren Nachweisen von Positivkulturen. Die 6% Resistenzrate (RR) gegenüber Levofloxacin bei Staphylokokken zum Ausgangspunkt der Studie (T0) ist vergleichbar mit den Ergebnissen vorhergehender Studien.⁶¹ Nach alleiniger PVL Prophylaxe (T2) zeigte die gefundene RR von 6% gegenüber Levofloxacin keine Veränderung of gegenüber dem Ausgangspunkt (T0).

Obwohl diese Untersuchung nicht nachweisen konnte, dass eine kombinierte Behandlung mit 0,5%-igen Levofloxazin Augentropfen und Spülung der Bindehaut mit PVL das Risiko einer postoperativen Endophthalmitis reduziert, zeigte die sie doch, dass die

kombinierte Behandlung eine verbesserte Wirkung in Hinblick auf eine Reduktion der bakteriellen Bindehautflora besitzt. Da diese als Hauptursprungsort für eine bakterienbedingte Endophthalmitis gilt, lässt sich postulieren, dass dieses Behandlungsregime das Risiko einer intraokularen Kontamination und deshalb auch das einer postoperativen Endophthalmitis vermindert. Um dies jedoch endgültig zu klären wird derzeit eine groß angelegte Multizenterstudie durchgeführt.⁴⁹ Bis deren Ergebnisse verfügbar sind, kann die kombinierte Behandlung mit 0,5%-igen Levofloxazin Augentropfen und Spülung der Bindehaut mit PVL für Patienten vor intraokularem Eingriff empfohlen werden.

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7. Resume

Full Name Israel Aguirre-Romo
Date of Birth April 18, 1973
Place of Birth Mexico City / *Estados Unidos Mexicanos*
Parents: Manuel Aguirre-Calderón
 María del Carmen Romo-Medina

Education

High School / Bachelor *Instituto Cultural Tampico*, Incorporated to the National Autonomous University of Mexico (*UNAM*), Tampico, Tam, 3 years. 1990

Graduate Degree: 6.5 years:

- Surgeon Physician. Autonomous University of Tamaulipas (*UAT*), Tampico, Mexico, 4 ½ years. 1995
- Internship: *UAT-Hospital General Regional de Tampico-Madero*, Tampico, Mexico. 1 year. 1996
- Social Service of the University: Suburban Medical Unit #113, Altamira, Mexico. 1 year. 1997

Postgraduate Studies:

- Ophthalmology. University Hospital, Autonomous University of Nuevo Leon (*UANL*). Monterrey City, Mexico. 2003
- Ophthalmology. University Fellowship in Retina and Vitreous *Ludwig-Maximilians-Universität, München, Augenklinik*. Germany. April 2004 - March 2006

Academic Examinations and Certificates

- “United States Medical Licensing Examination” (U.S.A.) Step 1. August 1996
 - “United States Medical Licensing Examination” (U.S.A.) Step 2. October 1997
 - “The Educational Commission to Foreign Medical Graduates” July 1998
 “USMLE-ECFMG Certificate” Number to practice in the U.S.A.: 0-553-954-9
-

Research Experience and Lectures

- Microbiology Laboratory, Department of Ophthalmology of the *Ludwig-Maximilians Universität München*. October 2004 - May 2006
- Department of Ophthalmology and Department of Genetics. Autonomous University of Tamaulipas. Investigation: "Mutations in the Gene GLC1-A in patients with Primary Open Angle Glaucoma". 2001 - 2003

Awards

- *Dr. Rodolfo Maya González*, Award and Academic Merit Medal; granted for the first place Graduating Class 1995 in medical studies. April 1995.

Clinical and Working Experience

- **Voluntary Medical Resident in Internal Medicine**, Department of Internal Medicine, *Hospital Médica Sur*, Mexico City. March to December 1998
- **Physician on Duty, Emergency Room**, Green Cross Emergencies Clinic. Guadalupe City, Mexico. June 1999 to January 2000

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