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INTRACAMERAL CEFUROXIME FOR PROPHYLAXIS OF
ENDOPHTHALMITIS FOLLOWING CATARACT SURGERY: A
SOUTH AFRICAN PERSPECTIVE.

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Masters of Medicine(MMed) in Ophthalmology

This research is based on original work by myself and has not been submitted for another degree at any other university. It has not been published prior to registration for the abovementioned degree.

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To Professor Colin Cook, my mentor and supervisor, and my husband Matthys, for his support.

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PART A: THE PROTOCOL

**(As approved by the Departmental Research Committee and
Faculty Research Ethics Committee)**

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PROTOCOL: INTRACAMERAL CEFUROXIME FOR PROPHYLAXIS OF ENDOPTHALMITIS FOLLOWING CATARACT SURGERY: A SOUTH AFRICAN PERSPECTIVE.

ABSTRACT

PURPOSE: Did the introduction of intracameral cefuroxime during cataract surgery reduce the rate of endophthalmitis in a hospital in South Africa? Did the results of the ESCRS study influence South African ophthalmologists, and what percentage use intracameral cefuroxime?

SETTING: Groote Schuur Hospital, Cape Town, South Africa.

DESIGN: Before-after retrospective case series, cross sectional survey

METHODS: Data will be collected over a six year period, examining all reported cases of endophthalmitis following cataract surgery and comparing the data for the three years prior to the introduction of cefuroxime, to the three years after the introduction of cefuroxime. A questionnaire, with an enclosed self-addressed envelope, will be mailed to all South African ophthalmologists.

RESULTS: Data will be analysed using the statistical program Stata Version 9.0. Variables will be described using means, medians, and proportions, as appropriate. Bivariate comparisons will be based on student t test (for means), Wilcoxon sum rank test (for medians), and Chi square or Fisher's exact test (for proportions).

CONCLUSION: A paper reporting the findings will be submitted to a peer reviewed journal for consideration for publication.

INTRODUCTION

Problem

Endophthalmitis remains one of the most devastating complications following cataract surgery, and the prognosis and successful treatment depends on timely and appropriate management, as demonstrated in the Endophthalmitis Vitrectomy Study.^{1,2}

Because the treatment of endophthalmitis can be extremely problematic in low and middle income countries where patients often present late and access to vitreoretinal services are limited, preventing the infection altogether is of utmost importance.

According to a 2006 survey in the United Kingdom among 800 consultant ophthalmologists, prophylactic measures varied widely, with only 13.6% of patients receiving intracameral antibiotics and 4.1% antibiotic infusions.³

The European Society of Cataract and Refractive Surgeons (ESCRS) recognized the need to investigate the use of antimicrobial prophylaxis. According to the findings of a prospective randomized study (announced in 2006) published in 2007, the absence of an intracameral cefuroxime prophylactic antibiotic was associated with a 4.92-fold increase in the risk for total postoperative endophthalmitis.⁴ This is the first prophylactic anti-infective regimen to be proven effective by a prospective randomized controlled study.⁵ Believing the results conclusive, the study was terminated prematurely and the routine use of intracameral cefuroxime recommended.

In January 2007 an online survey was conducted among the approximately 4000 members of the American Society of Cataract and Refractive Surgeons (ASCRS). Surprisingly 77% of surgeons still did not use intracameral cefuroxime and did not plan to use it in the near future.⁵ Almost 90% of the surgeons felt that further study was needed and 45% were concerned about the risk involved.

Further studies have confirmed the efficacy of intracameral cefuroxime in preventing endophthalmitis, without any significant adverse effects.⁶⁻⁹ Following the publication of the results of the ESCRS study, intraoperative intracameral cefuroxime was introduced as our standard practice at Groote Schuur Hospital in August 2006.

Apart from patients with known cefuroxime hypersensitivity, all patients routinely receive 1mg of intracameral cefuroxime, injected into the anterior chamber at the end of their surgery.

Justification

This study is to evaluate:

1. Whether the routine use of intracameral cefuroxime results in a decrease in the incidence of endophthalmitis in our setting.
2. The trend of endophthalmitis prophylaxis among South African ophthalmologists.

Objective

RESEARCH QUESTIONS:

- 1: Does the use of intraoperative intracameral cefuroxime reduce the risk of post-operative endophthalmitis at Groote Schuur Hospital?
- 2: Do South African ophthalmologists use intracameral cefuroxime for endophthalmitis prophylaxis following cataract surgery?

METHODS

Study design

- 1: A descriptive and analytical retrospective case series.
- 2: A cross sectional survey of all South African ophthalmologists.

Sampling strategy

Data will be collected from :

- 1.1: All patients who had cataract surgery in the 36 month period before the introduction of cefuroxime prophylaxis.

1.2: All patients who had cataract surgery in the 36 month period after the introduction of cefuroxime prophylaxis.

2: All ophthalmologists in South Africa will be surveyed, using the questionnaire in appendix two, via mail with a self-addressed envelope included.

Measurement

1. For the descriptive and analytical retrospective case series the following data will be collected:

Number of cataract surgeries performed.
Whether the patient received cefuroxime.
Number of patients admitted for presumed endophthalmitis.
Number of culture proven cases of endophthalmitis.
Number of patients receiving intravitreal antibiotics.
Number of patients requiring pars plana vitrectomy.
Visual outcome post endophthalmitis treatment.

Associated possible risk factors in endophthalmitis cases, including gender, age, race, type of surgery, surgeon experience i.e. consultant/registrar/medical officer, surgical complications and other ocular pathology.

The number of cataract surgeries done will be obtained from theatre records.

The admission records of endophthalmitis cases will be obtained from the clinicom records, specifying the number of admissions for code H44.0 between August 2003 and July 2009.

A separate data collection form will be completed for all patients who presented to the ophthalmology ward with suspected endophthalmitis.

2. For the cross sectional survey of all South African ophthalmologists the data will be collected as follows:

All ophthalmologists will be contacted via mail to their registered private practice address and asked to complete the questionnaire. A self-addressed envelope will be included. See appendix 2.

ANALYSIS

Data will be analysed using the statistical program Stata Version 9.0. Variables will be described using means, medians, and proportions, as appropriate. Bivariate comparisons will be based on student t test (for means), Wilcoxon sum rank test (for medians), and Chi square or Fisher's exact test (for proportions).

The main analysis will focus on:

1: The difference in the incidence of endophthalmitis in the patients having cataract surgery before August 2006 and not receiving intracameral cefuroxime, and in the patients having cataract surgery after August 2006 and receiving intracameral cefuroxime.

2: The proportion of South African ophthalmologists using intracameral cefuroxime for endophthalmitis prophylaxis.

All statistical tests will be two sided at $\alpha=0.05$.

ETHICS AND COMMUNICATION

Ethics

Ethical approval will be obtained from the University of Cape Town Faculty of Health Sciences ethics committee.

Reporting and implementation

A paper reporting the findings will be submitted to a peer reviewed journal for consideration for publication.

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APPENDICES

Appendix one: Patients with endophthalmitis- data collection form.

		Code
Name		
Hospital number		
Age		
Race		
Gender		
Date of surgery		
Type of surgery		
Surgeon experience		
Surgical complications		
If yes to above, specify briefly		
Intracameral cefuroxime		
Other ocular pathology		
If yes to above, specify briefly		
Date of admission for presumed endophthalmitis		
Culture positive		
Specify organism		
Administration of intravitreal antibiotics		
Specify type of antibiotic		
Pars plana vitrectomy		
Final visual acuity		

Appendix two: survey of endophthalmitis prophylaxis.

**DIVISION OF OPHTHALMOLOGY, GROOTE SCHUUR HOSPITAL: SURVEY OF ENDOPHTHALMITIS
PROPHYLAXIS IN CATARACT SURGERY IN SOUTH AFRICA**

PLEASE INDICATE WHICH OF THE FOLLOWING PERIOPERATIVE MEASURES ARE USED BY YOU
DURING CATARACT SURGERY.

NAME (FOR STATISTICAL PURPOSES ONLY, YOUR ANSWERS WILL BE ANONYMOUS)

-
1. INTRACAMERAL CEFUROXIME
2. INTRACAMERAL MOXIFLOXACIN
3. INTRACAMERAL VANCOMYCIN
4. VANCOMYCIN ADDED TO IRRIGATION FLUID
5. SUBCONJUNCTIVAL GENTAMICIN
6. SUBCONJUNCTIVAL CEFUROXIME
7. TOPICAL MOXIFLOXACIN (VIGAMOX)
8. OTHER(PLEASE SPECIFY) _____

THANK YOU.

DR JUNET VAN DER MERWE: Registrar, Department Ophthalmology,
Groote Schuur Hospital,
Observatory, Cape Town

Appendix three: coding form.

	Code
Name	
Hospital number	
Age	Age in years
Race	White : 1 Black: 2 Asian: 4 Coloured: 3 Unspecified: 5
Gender	Male: 1 Female: 2
Date of surgery	
Type of surgery	Phacoemulsification: 1 Extracapsular cataract extraction :2 Unspecified: 3
Surgeon experience	Consultant: 1 Junior registrar: 3 Senior registrar: 2 Medical officer: 4
Surgical complications	Yes: 1 No: 2
If yes to above, specify briefly	Posterior capsule tear: 1 Phaco-conversion: 5 Vitrectomy: 2 Iris damage: 6 Dropped lens/ fragment: 3 Zonular dehiscence: 7 Aphakic: 4 Unspecified: 8
Intracameral cefuroxime	Yes: 1 No: 2
Other ocular pathology	Yes: 1 No: 2
If yes to above, specify briefly	Diabetes: 1 Previous trauma: 7 Glaucoma: 2 Previous uveitis: 8 Corneal opacity: 3 Retinal detachment: 9 Corneal guttatae: 4 Previous ocular surgery: 10 Blepharitis: 5 Ocular surface disease: 11 Pseudoexfoliation: 6 Unspecified: 12
Date of admission for presumed Endophthalmitis	
Culture positive	Yes: 1 No: 2

Specify organism	Gram negative bacilli: 1 Gram positive bacilli: 2 Gram negative cocci: 3 Gram positive cocci: 4	Filamentous bacteria: 5 Mycobacteria: 6 Fungal: 7 Unspecified: 8
Administration of intravitreal antibiotics	Yes: 1 No: 2	
Specify type of antibiotic	Ceftazidime plus Vancomycin: 1 Other: 2	
Pars plana vitrectomy	Yes: 1 No: 2	
Final visual acuity	6/6 or better: 1 6/7.5 - 6/18: 2 6/24 – 6/60: 3 Count fingers: 4 Hand movement: 5 Perception of light: 6 No perception of light: 7	

University of Cape Town

PART B: THE LITERATURE REVIEW

University of Cape Town

LITERATURE REVIEW

INTRODUCTION

Endophthalmitis remains one of the most devastating complications following cataract surgery, and the prognosis and successful treatment depends on timely and appropriate management, as demonstrated in the Endophthalmitis Vitrectomy Study.¹ The treatment of endophthalmitis can be extremely problematic in low and middle income countries where patients often present late and access to vitreoretinal services are limited. Preventing endophthalmitis is therefore important.

The optimal regime for endophthalmitis prophylaxis remains a controversial issue. Endophthalmitis fortunately is a rare occurrence but this makes it difficult to conduct adequately powered studies.^{2,3} The incidence of presumed infectious endophthalmitis is low, with reported rates of 0.05% to 0.36% and an overall estimate of 0.13%.⁴⁻⁶

The only evidence based method of endophthalmitis prophylaxis shown to be effective in the past, was the use of povidone-iodine 5% in the conjunctival sac before surgery.⁷

Many different techniques are being used without reliable scientific evidence. The incidence of endophthalmitis is so low, that a very large study is needed to provide statistically significant evidence to detect a reduction in the incidence of endophthalmitis.^{2,3}

Most surgeons use an antibiotic prophylactically. Some use vancomycin either in the irrigation fluid or by intracameral injection. This practice is not recommended because vancomycin is reserved for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) endophthalmitis and other MRSA infections.⁸ Both the American Academy of Ophthalmology and the Center for Disease Control and Prevention in the USA advise against its use in cataract surgery.

RESULTS OF THE ESCRS MULTICENTER STUDY

There existed a need to find scientific evidence for the most appropriate endophthalmitis regime. The European Society of Cataract and Refractive Surgeons (ESCRS) initiated a large scale, randomized partially masked prospective placebo-controlled multicenter study across Europe including Austria, Belgium, Germany, Italy, Poland, Portugal, Spain, Turkey and the United Kingdom.

The main objective of the study was to determine whether a perioperative antibiotic helps prevent subsequent endophthalmitis and additionally to collect data which would be helpful in identifying risk factors for endophthalmitis. In this study two drugs were chosen for the trials. Cefuroxime was chosen for intracameral use because of the Swedish study in which efficacy and safety was established.^{9,10} Levofloxacin, a third-generation fluoroquinolone was chosen because it is well absorbed into the anterior chamber¹¹ and showed enhanced anti-bacterial activity compared to ciprofloxacin and ofloxacin.

Patient recruitment was started in September 2003. There were 16 603 patients recruited, 324 were lost to follow-up and 68 were omitted because they did not have the planned surgery or withdrew their consent.¹² The study was scheduled to continue recruiting patients until 31 March 2006, but was terminated early in January 2006 after it became clear that intracameral cefuroxime reduced the risk to approximately one-fifth the value observed without prophylaxis.¹³

The patients were recruited into one of four groups. Group A received placebo vehicle drops x five and no intracameral injection. Group B received placebo vehicle drops x five and intracameral cefuroxime. Group C received levofloxacin drops 0.5% x five and no intracameral cefuroxime. Group D received levofloxacin drops 0.5% x five and intracameral cefuroxime.

The incidence of endophthalmitis was highest in group A where the total rate was 0.345%, and for proven endophthalmitis 0.247%. The lowest incidence was in group D with a rate of 0.049% for total endophthalmitis and 0.025% for proven endophthalmitis.¹²

In group B the total rate was 0.074% and the proven rate was 0.049%, indicating that adding levofloxacin was not of major benefit.

In the intent-to-treat patient population that received intracameral cefuroxime (Group B and D), the endophthalmitis rate was only 0.062%. The rate in the groups that did not receive cefuroxime (Group A and C) was five times higher (0.296%).

The endpoint of the study was the diagnosis of endophthalmitis, but not all the cases identified as endophthalmitis had positive cultures. Endophthalmitis was diagnosed in 29 patients, 20 proven and nine unproven. The median time to presentation was 4.5 days. There was no case of early-onset (one-three days) endophthalmitis in the two groups that received intracameral cefuroxime. The early onset cases were associated with rapid and severe onset of symptoms. These cases included six isolates of streptococcal species and two isolates of *Staphylococcus epidermidis*.¹⁴ There were a total of eight proven streptococcal infections, all in the groups that did not receive cefuroxime, and five of the eight patients had a final visual acuity of 20/200 or worse.¹⁴ Streptococcal endophthalmitis resulted in earlier onset and worse outcomes than staphylococcal infections. This trend has also been demonstrated in other studies.^{15,16}

INTRACAMERAL ANTIBIOTICS: QUESTIONS IN THE UNITED STATES

In January 2007, 4000 members of the American Society of Cataract and Refractive Surgery (ASCRS) were asked to participate in an online survey about endophthalmitis prophylaxis. A total of 1312 members responded. The majority of respondents (69%) were from the United States.¹⁷

Most surgeons used topical antibiotics, and fourth-generation fluoroquinolones were preferred by 81%. Only 30% of respondents used intracameral antibiotics which included vancomycin, cephalosporins and quinolones. Vancomycin was used by 61% which is interesting because as mentioned earlier, the American Academy of Ophthalmology advises against it.

The publication of the ESCRS study appeared not to have a significant impact on the respondents of the survey. Only 7% started or planned to use intracameral cefuroxime in the near future and 77% did not have any plans to use intracameral cefuroxime.¹⁷ A variety of reasons were stated for not using it. Most surgeons (89%) felt that further study was needed and 45% were concerned about the risks involved which might include dilution errors, or toxic anterior segment syndrome. However, 80% would inject intracameral antibiotics if a commercially approved preparation were available at reasonable cost.

The Mayo clinic published an article in 2008 highlighting the concerns in the United States regarding intracameral cefuroxime.¹⁸ The rate of endophthalmitis in the intracameral cefuroxime group in the ESCRS study were similar to rates reported in other studies in the U.S. where only topical antibiotics were used pre- and postoperatively.^{19,20}

The authors felt that the actual benefit of cefuroxime may be less if compared with the perioperative use of topical antibiotics in the U.S. However, there are no large evidence based studies to prove this statement. The actual rate of endophthalmitis might be even less in the U.S. if cefuroxime were introduced.

Another factor to be considered is the duration of protective effect from intracameral antibiotics. It is short, probably fewer than 24 hours. The risk of contamination from the surface of the eye is not addressed by the use of intracameral antibiotics. This risk remains until the wound heals.¹⁸

The choice of cefuroxime was questioned as well. It has only average coverage of gram-positive and gram-negative organisms, does not cover MRSA, and has time dependent action, taking several hours to be effective, therefore dilution may occur before effectiveness.^{19,21} Despite the above concerns, cefuroxime has been proven to be effective and the concerns remain speculation until studies prove otherwise.

Swedish ophthalmologists have a low rate of endophthalmitis and use intracameral antibiotics and not pre- or postoperative antibiotics. They also found that perioperative topical antibiotics had minimal or no additional benefit.^{22,23}

Almost all surgical specialities, except ophthalmology, have published joint guidelines for antibiotic prophylaxis of postsurgical infection.²⁴ There are no large randomized controlled prospective studies evaluating the effectiveness of antibiotics in the irrigation fluid or topical antibiotics pre- and postoperatively. The only way to have consensus will be to launch a large cross-continental study to address all the issues raised.

SAFETY PROFILE OF CEFUROXIME

One of the most quoted reasons for not using cefuroxime is concerns about the safety profile. Numerous studies have been published evaluating the safety of cefuroxime. One of the first studies was done in Sweden at St. Eriks Hospital where cefuroxime was added to the prophylactic program in January 1996.¹⁰ Cefuroxime was evaluated in a nonrandomized observer-masked best-case trial. Cefuroxime did not have a statistically significant effect on endothelial cell loss, postoperative visual acuity or inflammation compared with non-administration of cefuroxime. Cefuroxime hypersensitivity was also evaluated. Only three positive skin prick tests were found in 5813 screened

cataract patients. Therefore it is safe to conclude that IgE-dependent hypersensitivity to cefuroxime is very rare.

Macular thickness after cataract surgery was evaluated in a prospective randomized double-masked clinical study in 2004.²⁵ The study group received 1mg of intracameral cefuroxime and the control group received intracameral balanced salt solution (BSS). Twenty-three patients in the cefuroxime group and 17 patients in the BSS group had OCT performed four to six weeks postoperatively. Intracameral cefuroxime did not have a statistically significant effect on macular thickness.

The dose dependent risk of cefuroxime and corneal endothelial cell death has also been evaluated.²⁶ Human corneal endothelial cells were exposed to various concentrations of cefuroxime and vancomycin. Reduction in cell viability was observed in concentrations higher than 2.75 mg/ml for cefuroxime and 5.0 mg/ml for vancomycin. The current cefuroxime dose of 1 mg diluted in 0.1 ml BSS results in a final concentration of nearly 2.75 mg/ml and no adverse effects were detectable at that dose.

A randomized controlled trial on the safety of intracameral cephalosporins confirmed the above findings.²⁷ A 1mg dose of intracameral cefuroxime, cefazolin and ceftazidime were evaluated in the randomized trial. Central endothelial cell density (ECD) and retinal centre point thickness (CPT) were measured before and three months after surgery. None of the cephalosporins had any significant effect on ECD or CPT.

COMPLICATIONS ASSOCIATED WITH CEFUROXIME

There are reports in the literature of complications associated with the use of intracameral cefuroxime. A severe anaphylactic reaction in a patient with known penicillin allergy has been reported. The patient recovered well after immediate resuscitation.²⁸

Dilution errors remain a potential risk factor. There are no commercially available preparations and the cefuroxime has to be diluted prior to theatre according to a dilution protocol so that the final concentration is 1mg in 0.1 ml. Even while following the protocol, variability in the final concentration may occur possibly because of inadequate mixing in small volume syringes.²⁹

Several cases of intraocular inflammation have been reported after injection of very high doses of intracameral cefuroxime.³⁰ Six patients received 40-50 mg of intracameral cefuroxime instead of 1 mg because of a dilution error. The patients had moderate anterior chamber inflammation, extensive macular oedema, diffuse leakage on fluorescein angiogram and abnormal electroretinograms (ERG) indicating alteration of the rod photoreceptors. The patients were observed without surgical intervention and the final visual outcome was satisfactory in all cases. Modifications in central corneal thickness (CCT) and endothelial cell density (ECD) were similar to those observed after uneventful phacoemulsification. Long-term retinal function was not evaluated though.

Severe cystoid macular oedema with subretinal fluid accumulation has been reported in two patients who received 2mg of cefuroxime in 0.1 ml.³¹ The oedema occurred on day one after the surgery. Cystoid macular oedema typically takes 4 to 12 weeks to develop after cataract surgery, and the rapidity of onset of oedema in these two patients, increased the probability that it was due to the cefuroxime.

Despite the risk of dilution error, cefuroxime even at doses 40-50 times the recommended dose, appeared to have no long-term side effects, but that needs to be confirmed with repeated ERG testing. The fact that ECD did not appear to be adversely affected indicates that cefuroxime may be less toxic to endothelial cells than indicated by in vitro testing.²⁶

FURTHER STUDIES ADVOCATING THE USE OF CEFUROXIME

In 2002 the Department of Ophthalmology at St. Eriks Hospital in Sweden published data from a retrospective observational study to compare the rate of endophthalmitis from 1990 to 1995 with the rate from 1996 to 2000. Cefuroxime was added to the prophylactic program in January 1996 because the rate of endophthalmitis was considerably higher than reported rates in North America.⁹

The rate of endophthalmitis dropped from 0.26% to 0.06%. (from 89 cases in 34 102 operations to 20 in 32 180 operations). Coagulase-negative staphylococci, streptococci with the exception of enterococci, and *S aureus* virtually disappeared as causative organisms, indicating that cefuroxime is highly effective against its targeted spectrum.

A cause for concern was the fact that cefuroxime was less effective against gram negative bacteria and enterococci, indicating that there were shortcomings in the antibacterial spectrum of cefuroxime.

Since the publication of the ESCRS study results, numerous other studies have followed, showing similar results, with a significant decrease in the incidence of endophthalmitis after adding cefuroxime to the prophylactic regime.

In Dar es Salaam, Tanzania, the rate has dropped from 0.24% (12 cases in 5000 operations) to 0% (none in 21 000 operations).³² The University Hospital of Getafe in Madrid, Spain showed a reduction of 0.5% to 0.11% (five cases) where two of the five did not receive cefuroxime due to a penicillin allergy and *S epidermidis* was isolated from the vitrectomy cassette in both cases.³³

Another unit in Madrid, University Hospital Fundación Alcorcón, reported a reduction of 0.59% to 0.043%.³⁴ In the group that did not receive cefuroxime, the leading causative organisms were coagulase-negative staphylococci (*S epidermidis*) and *S aureus*.

A retrospective analysis performed by Yu-Wai-Man P, et al, at the University of Sunderland, United Kingdom, showed that intracameral cefuroxime resulted in a three-fold reduction in the rate of presumed infectious endophthalmitis when compared to subconjunctival cefuroxime.³⁵ The incidence of presumed infectious endophthalmitis was 0.046% in the intracameral group and 0.139% in the subconjunctival group which was statistically significant.

In all the studies discussed above, a significant reduction in the rate of endophthalmitis is apparent. These are all retrospective observational studies, with all the limitations associated with these studies, but the results are strikingly similar and cannot be ignored.

DID THE USE OF INTRACAMERAL CEFUROXIME INCREASE AFTER THE PUBLICATION OF THE ESCRS STUDY RESULTS?

In 2005, before the publication of the results of the ESCRS study, a large survey of 800 consultant cataract surgeons in the United Kingdom showed that 66.4% gave subconjunctival cefuroxime and 10% gave intracameral cefuroxime.³⁶ Vancomycin was used as a bolus by 3.6% of surgeons and as an infusion in 4.1%. Only 2% of surgeons prescribed fluoroquinolone drops in the postoperative period.

In June 2008, approximately 250 consultant members of the United Kingdom and Ireland Society of Cataract and Refractive Surgeons (UKISCRS) were surveyed with a 39% response rate (98 members).³⁷ The main criticisms of the ESCRS study were the lack of a subconjunctival cefuroxime treatment arm (68%), the high control group rate of endophthalmitis (13%), statistical analysis queries (13%) and the choice of cefuroxime (6%).

More surgeons used intracameral antibiotics, with 55% using intracameral cefuroxime and 5% using vancomycin. Thirty-seven percent of respondents used no intracameral antibiotic at all. Of the surgeons using cefuroxime, 48% switched after publication of the ESCRS trial. The increased rate of intracameral cefuroxime use in this study might not be a true reflection of current practices in the U.K. because of the small number of surgeons surveyed. (98 of approximately 900 cataract surgeons in the U.K.)

The perioperative patterns of prophylaxis in Canada were published in 2007, after a survey was conducted between November 2004 and January 2005.³⁸ Of the 800 ophthalmologists surveyed, 239 responded (30% response rate) of which 216 performed cataract surgery. Only 15% of surgeons used intracameral antibiotics with vancomycin the most commonly used intracameral antibiotic (87%). Postoperative topical antibiotics were used by 97% with moxifloxacin being the most common postoperative topical antibiotic (30%).

Subsequently to the ESCRS study, a retrospective analysis of the incidence of endophthalmitis in a high volume unit in Canada, showed that none of the 25 surgeons operating in that unit, used intracameral antibiotics, and 76% used fourth-generation fluoroquinolones in the post-operative period.³⁹ The incidence of endophthalmitis was 0.043% in this unit (six of 13931 surgeries). The authors concluded that very low rates of endophthalmitis can be achieved without the routine use of intracameral antibiotics and that the use of it would introduce other potential risks such as toxic anterior segment syndrome.

ALTERNATIVES TO INTRACAMERAL CEFUROXIME

The most commonly used prophylactic agents in the United States and Canada are fourth-generation fluoroquinolones, such as moxifloxacin (Vigamox) and gatifloxacin (Zymar), of which moxifloxacin is used most often. Moxifloxacin has also been used intracamerally, and studies evaluating intracameral moxifloxacin showed it to be safe in terms of endothelial cell counts, corneal pachymetry and anterior chamber reaction.^{40,41}

Moxifloxacin is commercially available as a self-preserved ophthalmic solution and it eliminates the risks of using an antibiotic that needs to be prepared prior to surgery.

Recent reports of emerging antibiotic resistance to fluoroquinolones are worrying.^{42,43} Resistance is also being reported in the fourth-generation fluoroquinolones. As much as 85% of methicillin-resistant *S Aureus* isolates are resistant to ophthalmic fluoroquinolones, including gatifloxacin and moxifloxacin. The important question is whether ophthalmologists are contributing to the emerging resistance patterns by using fluoroquinolones as prophylaxis.

SUMMARY

The European Society of Cataract and Refractive Surgeons (ESCRS) recognized the need to investigate the use of antimicrobial prophylaxis. According to the findings of a prospective randomized study published in 2007, the absence of an intracameral cefuroxime prophylactic antibiotic was associated with a 4.92-fold increase in the risk for total postoperative endophthalmitis.¹² This is the first prophylactic anti-infective regimen to be proven effective by a prospective randomized controlled study. Believing the results conclusive, the study was terminated prematurely by the investigators, and the routine use of intracameral cefuroxime was recommended.

In January 2007 an online survey was conducted among the approximately 4000 members of the American Society of Cataract and Refractive Surgeons (ASCRS). Surprisingly 77% of surgeons still did not use intracameral cefuroxime and did not plan to use it in the near future.¹⁷ Almost 90% of the surgeons felt that further study was needed and 45% were concerned about the risk involved.

Further studies have confirmed the efficacy of intracameral cefuroxime in preventing endophthalmitis, without any significant adverse effects.^{10,25,33,44} Dilution error and ocular toxicity after high doses of cefuroxime however, have been reported.³⁰

Ophthalmologists need to standardize the prophylaxis of endophthalmitis and it has to be evidence based. Ophthalmologists should try to avoid using the same antibiotics for treatment and prophylaxis, as this could cause further resistance, especially vancomycin which is used to treat MRSA as mentioned earlier.

In middle and low income countries cefuroxime is much more cost-effective than moxifloxacin, and for that reason remains the more logical choice. The lack of a commercially available preparation seems to be a major issue amongst ophthalmologists not using cefuroxime. Unfortunately the manufacturing of such a product would most certainly increase the cost of using cefuroxime significantly and would make it less attractive in middle and low income countries.

Dilution errors remain a problem, but if a strict protocol is followed and the nurses and doctors responsible for the preparation of the intracameral antibiotics receive adequate training, the risk should be negligible.

The most effective mode of prophylaxis will probably change as bacterial resistance patterns emerge, and the studies of the last five years might become irrelevant. It remains the clinician's responsibility to determine what is best for the patient with the current resources available.

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PART C: ARTICLE FOR PUBLICATION

ABBREVIATED FORM ACCEPTED FOR PUBLICATION IN THE JOURNAL OF CATARACT AND REFRACTIVE SURGERY

INTRACAMERAL CEFUROXIME FOR PROPHYLAXIS OF ENDOPHTHALMITIS FOLLOWING CATARACT SURGERY: A SOUTH AFRICAN PERSPECTIVE.

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INTRACAMERAL CEFUROXIME FOR PROPHYLAXIS OF ENDOPTHALMITIS FOLLOWING CATARACT SURGERY: A SOUTH AFRICAN PERSPECTIVE.

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ABSTRACT

PURPOSE: Did the introduction of intracameral cefuroxime during cataract surgery reduce the rate of endophthalmitis in a hospital in South Africa? Did the results of the ESCRS study influence South African ophthalmologists' practice, and what percentage use intracameral cefuroxime?

SETTING: Groote Schuur Hospital, Cape Town, South Africa.

DESIGN: Before-after retrospective case series, cross sectional survey

METHODS: Data were collected over a six year period, examining all reported cases of endophthalmitis following cataract surgery and comparing the data for the three years prior to the introduction of cefuroxime, to the three years after the introduction of cefuroxime. A questionnaire, with an enclosed self-addressed envelope, was mailed to all South African ophthalmologists.

RESULTS: There was a significant reduction in the rate of endophthalmitis following the introduction of intracameral cefuroxime, from 0.55% to 0.08% ($p=0.0013$). Of the 23 cases prior to cefuroxime, 16 eyes were culture positive (69.6%), 13 were gram positive cocci and three were gram positive bacilli. There were no culture positive eyes in the cefuroxime group. The response rate to the questionnaire was 74%. Of the 245 respondents, 74 ophthalmologists (30%) reported using cefuroxime as part of their prophylactic regime.

CONCLUSION: Prophylaxis with intracameral cefuroxime is effective in our setting. South African ophthalmologists should be encouraged to use intracameral cefuroxime as endophthalmitis prophylaxis.

INTRODUCTION

Endophthalmitis remains one of the most devastating complications following cataract surgery, and the prognosis and successful treatment depends on timely and appropriate management, as demonstrated in the Endophthalmitis Vitrectomy Study.¹ The treatment of endophthalmitis can be extremely problematic in low and middle income countries where patients often present late and access to vitreoretinal services are limited. Preventing endophthalmitis is therefore important.

The optimal regime for endophthalmitis prophylaxis remains a controversial issue. Endophthalmitis fortunately is a rare occurrence but this makes it difficult to conduct adequately powered studies.^{2,3} The incidence of presumed infectious endophthalmitis is low, with reported rates of 0.05% to 0.36% and an overall estimate of 0.13%.⁴⁻⁶

In the past, the only evidence based method of endophthalmitis prophylaxis shown to be effective, was the use of povidone-iodine 5% in the conjunctival sac before surgery.⁷

Many different techniques are being used without reliable scientific evidence. The incidence of endophthalmitis is so low, that a very large study is needed to provide statistically significant evidence to detect a reduction in the incidence of endophthalmitis.^{2,3}

Most surgeons use antibiotic prophylaxis. Some use vancomycin either in the irrigation fluid or by intracameral injection. This practice is not recommended because vancomycin is reserved for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) endophthalmitis and other MRSA infections.⁸ Both the American Academy of Ophthalmology and the Center for Disease Control and Prevention in the USA advised against its use in cataract surgery.

The European Society of Cataract and Refractive Surgeons (ESCRS) recognized the need to investigate the use of antimicrobial prophylaxis. According to the findings of a prospective randomized study published in 2007, the absence of an intracameral cefuroxime prophylactic antibiotic was associated with a 4.92-fold increase in the risk for total postoperative endophthalmitis.⁹ This is the first prophylactic anti-infective regimen to be proven effective by a prospective randomized controlled study. Believing the results conclusive, the study was terminated prematurely by the investigators, and the routine use of intracameral cefuroxime was recommended.

In January 2007 an online survey was conducted among the approximately 4000 members of the American Society of Cataract and Refractive Surgeons (ASCRS). Surprisingly 77% of surgeons still did not use intracameral cefuroxime and did not plan to use it in the near future.¹⁰ Almost 90% of the surgeons felt that further study was needed and 45% were concerned about the risk involved.

Further studies have confirmed the efficacy of intracameral cefuroxime in preventing endophthalmitis, without any significant adverse effects.¹¹⁻¹⁴ Dilution error and ocular toxicity after high doses of cefuroxime however, have been reported.¹⁵

Following the publication of the results of the ESCRS study, intraoperative intracameral cefuroxime was introduced as our standard practice at Grootte Schuur Hospital in August 2006. Apart from patients with known cefuroxime hypersensitivity, all patients routinely receive 1mg of intracameral cefuroxime, injected into the anterior chamber at the end of their surgery.

The objective of this study was to evaluate whether the routine use of intracameral cefuroxime resulted in a decrease in the prevalence of endophthalmitis in our setting and if the results of the ESCRS study influenced the trend of endophthalmitis prophylaxis among South African ophthalmologists.

METHODS

The study received ethical approval from the Research Ethics Committee of the University of Cape Town. The study designs consisted of a descriptive and analytical retrospective case series and a cross sectional survey of all South African ophthalmologists during 2010 and 2011.

All ophthalmologists in South Africa were surveyed, using a questionnaire that was sent via mail to their registered address. They were requested to return the questionnaire in an enclosed self-addressed envelope. The questionnaire was publicised at a national meeting of the Ophthalmology Society of South Africa.

For the case series data were collected from the records of patients who had cataract surgery in the 36 month period before the introduction of cefuroxime prophylaxis and compared to the data of patients who had cataract surgery in the 36 month period after the introduction of cefuroxime prophylaxis.

For each period, the following data were collected: number of cataract surgeries performed; number of patients admitted for presumed endophthalmitis; whether the patient with suspected endophthalmitis received cefuroxime; number of culture proven cases of endophthalmitis; the organism cultured; number of patients receiving intravitreal antibiotics; number of patients requiring pars plana vitrectomy; visual outcome post endophthalmitis treatment; associated possible risk factors in endophthalmitis cases, including gender, age, race, type of surgery, surgeon experience i.e. consultant/registrar/medical officer; surgical complications and pre-existing ocular pathology.

The number of cataract surgeries performed in the six year period from August 2003 until July 2009 was obtained from theatre records. The admission records of endophthalmitis cases were obtained from the clinicom records, specifying the number of admissions for code H44.0 (the diagnostic code for endophthalmitis) between August 2003 and July 2009. A separate data collection form was completed for all patients who presented to the ophthalmology ward with suspected endophthalmitis after cataract surgery.

Data were analysed using the statistical program Stata Version 9.0. Variables were described using means, medians, and proportions, as appropriate. Bivariate comparisons were based on Fisher's exact test.

RESULTS

Survey

At the time of the survey there were 330 ophthalmologists in South Africa of which 245 responded to the questionnaire resulting in a 74.2% response rate. The ophthalmologists were asked to document their perioperative antibiotic practices and all modalities of antibiotic administration used. Table 1 summarises the results of the questionnaire.

Table 1: Primary method of endophthalmitis prophylaxis used by South African ophthalmologists

Primary method of prophylaxis	number of surgeons	percentage
Intracameral cefuroxime	74	30.2%
Intracameral moxifloxacin	52	21.2%
Intracameral vancomycin	4	1.6%
Irrigation fluid vancomycin	36	14.7%
Irrigation fluid gentamicin	4	1.6%
Subconjunctival cefuroxime	12	4.9%
Subconjunctival gentamicin	21	8.6%
Subconjunctival lincomycin	8	3.3%
Subconjunctival clindamycin	6	2.4%
Subconjunctival other	3	1.2%
Topical moxifloxacin	14	5.7%
Topical other	6	2.4%
No antibiotics	5	2%
	245	100%

152 surgeons used only one agent as prophylaxis. The remaining 93 surgeons used two or more agents. The two agents used most frequently as second agent were topical moxifloxacin (51 surgeons) and subconjunctival gentamicin (23 surgeons).

Case series

There were 23 of 4219 (0.55%) cases of endophthalmitis in the pre-cefuroxime group and 3 of 3971 (0.08%) cases of endophthalmitis in the cefuroxime group. The reduction in the proportion of cases of endophthalmitis following the introduction of cefuroxime was significant ($p=0.0013$). The relative risk reduction was 86% (95% CI 53.9-95.8%), the absolute risk reduction was 0.47% (95% CI 0.2-0.7%), and the number needed to treat was 212 (95% CI 133-419).

Table 2: Results from endophthalmitis cases

Clinical endophthalmitis	Organism cultured	Surgical complications	Surgeon experience	Final visual acuity
PRIOR TO CEFUROXIME				
Patient 1	None	Torn rhexis, PC intact	Consultant	6/24
Patient 2	<i>Strep pneumoniae</i>	None	Registrar	NPL
Patient 3	<i>Strep pneumoniae</i>	None	Consultant	NPL
Patient 4	None	None	Consultant	6/5
Patient 5	<i>Strep pneumoniae</i>	None	Registrar	NPL
Patient 6	<i>Staph epidermidis</i>	None	Registrar	6/18
Patient 7	<i>Bacillus species</i>	None	Registrar	6/9
Patient 8	None	None	Registrar	6/9
Patient 9	<i>Bacillus species</i>	None	Registrar	6/12
Patient 10	<i>Staph epidermidis</i>	None	Registrar	6/6
Patient 11	<i>Staph aureus</i>	None	Registrar	NPL
Patient 12	<i>Bacillus cereus</i>	Zonular dehiscence	Registrar	NPL
Patient 13	<i>Staph epidermidis</i>	Unstable ant. chamber	Registrar	HM
Patient 14	<i>Staph aureus</i>	None	Consultant	6/18
Patient 15	<i>Staph epidermidis</i>	None	Consultant	NPL
Patient 16	None	None	Registrar	6/12
Patient 17	<i>Micrococcus species</i>	PC tear, vitreous loss	Registrar	NPL
Patient 18	<i>Streptococcus mitis</i>	PC tear, vitreous loss	Registrar	HM
Patient 19	None	None	Registrar	NPL
Patient 20	None	None	Consultant	6/5
Patient 21	<i>Staph epidermidis</i>	Incomplete rhexis	Consultant	CF
Patient 22	<i>Staph epidermidis</i>	None	Registrar	6/9
Patient 23	None	No clinical notes	Unknown	6/18
POST CEFUROXIME				
Patient 1	None	None	Registrar	6/9
Patient 2	None	None	Registrar	6/9
Patient 3	None	None	Registrar	NPL
		Posterior capsule(PC)		Count fingers(CF) Hand movement(HM) No perception of light(NPL)

Table 2 shows the culture results in the endophthalmitis cases. Of the 23 cases prior to cefuroxime, 16 eyes were culture positive (69.6%) and seven were culture negative. All three cases of endophthalmitis after introduction of cefuroxime were culture negative. Of 16 culture positive eyes, 13 were gram positive cocci and three were gram positive bacilli. Infection was caused by *Staphylococcus epidermidis* in six eyes, *Staphylococcus aureus* in two eyes, *Streptococcus pneumonia* in three eyes, *Streptococcus mitis* in one eye, *Micrococcus species* in one eye and *Bacillus species* in three eyes. Absence of cefuroxime is more likely to result in culture positive result (69.6% of cases with $p=0.046$)

Possible risk factors for worse visual outcome were analysed. There was no statistically significant difference in final visual acuity (V/A) between the cefuroxime and non-cefuroxime groups (Fisher exact $p=1.00$). There was no statistically significant difference in final V/A between the different organisms cultured (Fisher exact $p=0.812$), although notably all three patients with *Streptococcus pneumonia* had a final V/A of No Perception of Light (NPL). There was a statistically significant difference in final V/A between cases with and without surgical complications. Patients with surgical complications ended with Count Fingers vision or worse, except for one patient with 6/24 vision, where 11 of 19 patients without complications had 6/18 or better vision (Fisher exact $p=0.003$).

DISCUSSION

South African ophthalmologists use a wide variety of antibiotic prophylactic measures. Cefuroxime is the preferred method, with 30% of ophthalmologists using it as prophylaxis, but topical moxifloxacin and intracameral moxifloxacin is also used by a large proportion of ophthalmologists. The number of ophthalmologists (14.7%) using vancomycin in the irrigation fluid as the primary method of prophylaxis, is cause for concern, because we should try to avoid using the same antibiotic for treatment and prophylaxis, as this could cause further resistance, especially vancomycin which is used to treat methicillin-resistant *Staphylococcus aureus*.

In middle to low income countries cefuroxime is much more cost-effective than moxifloxacin, and for that reason remains the logical choice. The lack of a commercially available preparation seems to be a major issue amongst ophthalmologists not using cefuroxime. Unfortunately the manufacturing of such a product would most certainly increase the cost of using cefuroxime and would make it less attractive in middle to low income countries.

Many surgeons fear drug hypersensitivity in penicillin allergic patients. In a study conducted in Sweden, 5813 patients undergoing cataract surgery were screened and 233 had skin prick testing with cefuroxime if they reported possible hypersensitivity to β -lactam antibiotics. Only three tests were positive.¹³ Subsequently, four of five patients with known cefuroxime hypersensitivity had

cefuroxime instilled in the anterior chamber after being pre-treated with oral antihistamine. No adverse effects were observed. Hypersensitivity should constitute no limitation to its use as endophthalmitis prophylaxis.

Our study has a number of weaknesses. Part of this study was a retrospective case series and non-controlled, which makes it a less adequately powered study than a prospective randomised controlled trial would be, however the results were the same as previously reported by similar studies.^{11,16,17,18} Only 74% of ophthalmologists responded to our survey therefore the endophthalmitis prophylaxis patterns may not be a true reflection of the current practices used. We did not ask what the reasons might be for not using intracameral cefuroxime, and this information would be useful.

At our institution the endophthalmitis rate was reduced from 0.55% to 0.08% after the introduction of cefuroxime. The number to treat is fairly large, with 212 patients receiving cefuroxime to prevent one case of endophthalmitis, but the cost of treatment needed for endophthalmitis and its associated morbidity would easily negate the cost of cefuroxime for 212 patients.

The organisms cultured in the pre-cefuroxime group confirmed that cefuroxime is a very effective choice for prophylaxis. Cefuroxime is less effective against gram negative bacteria, but no gram negative organisms were cultured in our study. Surgical complications during surgery increased the risk of poor visual outcome in patients who developed endophthalmitis in the pre-cefuroxime group. The prognosis for visual recovery is very poor in this group of patients, and endophthalmitis must be prevented as far as possible.

The most effective mode of prophylaxis will probably change as bacterial resistance patterns emerge, and the studies of the last five years might become irrelevant. It remains the clinician's responsibility to determine what is best for the patient with current resources available.

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PART D: SUPPORTING DOCUMENTS

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