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TITLE PAGE

Title: Adherence to European Society for Cataract and Refractive Surgery recommendations amongst Italian cataract surgeons: a survey

Running title: Adherence to ESCRS recommendations amongst Italian cataract surgeons

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ABSTRACT

Title: Adherence to European Society for Cataract and Refractive Surgery recommendations amongst Italian cataract surgeons: a survey

Running title: Prevention of endophthalmitis after cataract surgery in Italy

PURPOSE: To survey the surgical routines with regards to prophylactic strategies in a sample of Italian Hospitals and compare these with the European Society for Cataract and Refractive Surgery (ESCRS) guidelines.

SETTING: clinical-based study.

DESIGN: questionnaire-based survey, retrospective study

METHODS: Six private and 18 public Hospitals participated to this Survey.

Patient or study population: the overall volume of cataract operations in the 24 centres in 2013 was 43553.

Intervention or Observation Procedure(s): cataract surgery

Main outcome measures: Incidence of endophthalmitis per 1000. An incidence of less than 0.13% was considered acceptable.

RESULTS: Our study provides the first Italian data on the use of intracameral antibiotics in cataract surgery, as recommended by the ESCRS. Thirteen centres (54%) used intracameral cefuroxime at the end of surgery. Of the 13 centers that used cefuroxime, 8 (62%) had an incidence of endophthalmitis less than 0.13%. Of the 7 (29%) centres that did not use intracameral cefuroxime, all had an endophthalmitis rate of greater than 0.13%. This difference was statistically significant ($p < 0.05$). Among the 4 centers not included, 2 have used vancomycin, one a quinolone, and the last a combination of antibiotics. The majority of surgeons (79%) did use preoperative antibiotic eyedrops and 63% of them have recommended topical fluorquinolones but this measure was not shown protective. No differences in the incidence of post-cataract endophthalmitis between high and low-volume sites was demonstrated.

CONCLUSIONS

Only little more than half of the centers surveyed in this study adhered to the recommendations of the ESCRS and routinely employed prophylactic intracameral cefuroxime. An incidence of endophthalmitis greater than 0.13% was encountered significantly more frequently amongst centres that did not employ intracameral cefuroxime.

INTRODUCTION

Endophthalmitis remains one of the most challenging and devastating complications faced by the ophthalmologist.¹⁻⁸ Post-cataract endophthalmitis (POE) incidence ranges from 0.04% to 0.13% with differences in regional microbiological spectrum.⁹⁻¹⁶

The European Society for Cataract and Refractive Surgery (ESCRS) has recently updated its recommendations for prevention and management of post-cataract endophthalmitis.^{17, 18} Since the routine introduction of intracameral injection of cefuroxime 6 years ago, the rate of endophthalmitis has been significantly reduced.¹⁹⁻²⁵ Furthermore, a commercially available formulation of cefuroxime (Aprokam[®]) approved for intracameral prophylaxis was introduced to the European market in 2013.

Recently, the Italian Society of Ophthalmology issued recommendations to prevent endophthalmitis following cataract surgery but left antibiotic use to the individual surgeon's discretion.²⁶

What the “choosing wisely” paradigm in medicine would imply for perioperative prophylaxis in cataract surgery remains controversial,²⁷ because surgical settings, techniques and preferences may be different in various settings. Topical preoperative antibiotics remain popular despite the recognition that overuse and repeated exposure to topical antibiotics can lead to the emergence of bacteria that do not respond readily to available treatments. Mounting evidence suggests that ocular surface organisms are becoming more resistant to fluoroquinolones, with up to 30% of cultured ocular isolates being resistant.²⁸⁻³² Also, the efficacy and safety profile of intracameral cefuroxime during cataract surgery remain controversial since there are conflicting results in the literature about the additional protective effect of cefuroxime when added to the standard of care.^{17,18,33,34}

The purpose of our study was to conduct a survey to collect data on the attitudes and methods used to prevent post-cataract endophthalmitis in a list of selected Italian hospitals and to compare practice with ESCRS guidelines and best available evidence.

METHODS

A multiple choice questionnaire-based survey was designed to get a broad cross-section of different settings across the country: six private and 18 public Italian Hospitals participated to this Survey.

Among public hospitals, 10 were teaching hospitals. Institutional Review Board approval was obtained at the single institution for retrospective review of identified patient records.

The incidence of endophthalmitis was established from a retrospective analysis of a coding database at the respective institution (number of postoperative endophthalmitis codes/number of cataract surgery codes at that institution). An incidence of post cataract endophthalmitis of less than 0.13% was chosen as an acceptable level of endophthalmitis,³⁵ since a systematic review found an aggregate incidence of endophthalmitis occurring after cataract surgery of 0.13%.¹³

The purpose of the first part of the questionnaire was to collect information about the surgical routines with regards to prophylactic strategies.

The purpose of the second part of the questionnaire was to determine the incidence of endophthalmitis after cataract surgery in the year 2013 in each Hospital and to assess whether the ESCRS recommendations with regards to intracameral cefuroxime were adhered to. Furthermore, allergic or toxic reactions with intracameral cefuroxime were inquired about.

Statistical Analysis The results were analyzed using the StataMP11 statistical software (Stata Corp., College Station, TX, 2011). Firstly, a descriptive analysis of the centres was conducted, considering the annual cataract volume, the number of infectious endophthalmitis cases per 1000 cataracts, the geographic area and the hospital type. Results were expressed in frequencies and percentages. Endophthalmitis incidences at the various participating institutions were dichotomized as $< 0.13\%$ versus $> 0.13\%$. A descriptive analysis of the use of perioperative antibiotics and/or intracameral antibiotics, the use of antimicrobial drugs at the end of surgery,

possible side effects and the use of postoperative antibiotics, was then carried out.

Finally, a multivariate analysis was performed in order to highlight which outcomes were related with a rate of endophthalmitis higher or less than the expected acceptable value of 0.13%. For all analyses the alpha level was set at 0.05.³⁶

RESULTS

Our survey mirrors the preferred practice patterns to prevent post-cataract endophthalmitis among a spectrum of private and academic settings with varying surgical volumes in 2013.

The overall volume of cataract operations in the 24 centres in 2013 was 43,553.

Centres' characteristics are shown in Table 1: 8 hospitals were public, 10 were academic and 6 private operating within the Italian National Health System. In the table we provide readers with volume of cataract operations. Eleven centres showed an incidence of post-cataract endophthalmitis lower than 0.13% and 13 centres showed an incidence higher than 0.13%.

Table 2 shows the methods used to prevent post-operative endophthalmitis. All surgeons declared to use preoperative conjunctival povidone-iodine. The use of subconjunctival antibiotics was not reported and only in two centres vancomycin was used in the infusion bottle. The majority of surgeons (79%) did use preoperative antibiotic eyedrops and 63% of them have recommended to start a perioperative topical antibiotic 3 days before the scheduled cataract surgery. Fluorquinolones were the preferred preoperative topical antibiotics for cataract surgery (ofloxacin, ciprofloxacin and levofloxacin, in order of frequency). Thirteen centres (54%) used intracameral cefuroxime at the end of surgery. Surgeons declared to have used more than one antibiotic as a post-operative prophylaxis according to local microbiological surveillance (chloramphenicol + fluoroquinolones, netilmicin + fluoroquinolones). The majority of cataract surgeons did not taper antibiotics during follow up.

Table 3 shows the association of endophthalmitis by therapy used. Thirteen centres (54%) used intracameral cefuroxime at the end of surgery. Of the 13 centers that used cefuroxime, 8 (62%) had an incidence of endophthalmitis less than 0.13%. Of the 7 (29%) centres that did not use intracameral

cefuroxime, all had an endophthalmitis rate of greater than 0.13%. This difference was statistically significant ($p < 0.05$). Among the 4 centers not included, 2 have used vancomycin, one a quinolone, and the last a combination of antibiotics. In the centres where vancomycin was used the incidence of endophthalmitis was lower than 0.13% only in one. In the centre where a fluoroquinolone was used and in the centre where a combination of cefuroxime + vancomycin was used the incidence of endophthalmitis was found lower than 0.13%.

The incidence of endophthalmitis was not associated with the use of preoperative antibiotics nor with a specific molecule. Our data showed no differences in the incidence of post-cataract endophthalmitis between high and low-volume centres.

DISCUSSION

We present information on current prophylactic antibiotic use for cataract surgery in Italy.

Despite the existence of internationally validated standardized protocols, there is heterogeneity regarding the surgeon's attitudes to prevent endophthalmitis in the real world. All surgeons agree on the use of topical 5% povidone-iodine solution to prepare the conjunctiva for three minutes before surgery and povidone-iodine for the skin. In a recent prospective clinical study it was shown that ocular surface preparation using povidone-iodine 5% alone in the absence of postinjection topical antibiotics does not promote bacterial resistance or changes in conjunctival flora.²⁸

However, it is controversial whether preoperative antibiotics or intracameral cefuroxime play a role in the routine prophylaxis of post-cataract endophthalmitis.²⁷⁻³⁴ The majority of Italian cataract surgeons use topical fluoroquinolones in the perioperative period. In our survey, the use of perioperative antibiotics does not have a protective effect. The overuse and repeated exposure to antibiotics may lead to the emergence of bacteria that do not respond readily to available treatments. Mounting evidence suggests that ocular surface organisms are becoming more resistant to fluoroquinolones,²⁷⁻³² with up to 30% of cultured ocular isolates being resistant. In the era of “choosing wisely” and “antimicrobial stewardship” paradigms,²⁷ the importance of appropriate

antibiotic use needs to be emphasized: according to a recent study topical antibacterial therapy was equally effective in reducing the conjunctival bacterial load whether given 1 day or 1 hour before surgery.³⁷

Our survey provides the first Italian data on the use of intracameral antibiotics in cataract surgery. There is already strong evidence that intracameral prophylaxis with cefuroxime may be effective in lowering the incidence of endophthalmitis.^{17-25, 38} The ESCRS has been recommending to administer cefuroxime in the anterior chamber in all cases of cataract surgery since 2007.¹⁷⁻¹⁹ However, the additional protective role of cefuroxime over the standardized protocols is still a matter of debate. In our survey, cefuroxime does seem to have a protective effect. Given the low rate of incidence of endophthalmitis, it is difficult to demonstrate a greater efficacy of a preventive protocol that includes intracameral cefuroxime versus a prophylactic protocol that does not include cefuroxime: however, when the ESCRS guidelines are followed, 62% of centres that routinely use intracameral cefuroxime had an incidence of post-cataract endophthalmitis lower than the acceptable 0.13% and similarly acceptable rates were found significantly less frequently amongst centers that did not routinely employ intracameral cefuroxime. Nevertheless, in 5 centres that routinely used intracameral cefuroxime the incidence of post-cataract endophthalmitis was higher than 0.13%. There may have been other factors other than just intracameral antibiotics that contributed to higher endophthalmitis rates: the use of perioperative topical antibiotics (type of molecule and duration of prophylaxis), and the clinical characteristics of the patients operated. In the sample of selected hospitals included in this survey only thirteen centres (54%) used intracameral cefuroxime at the end of surgery. However, with pre-formulated cefuroxime now being readily available, the number of Italian cataract surgeons who use cefuroxime is increasing as shown in table 2. The intracameral use may have gained slow acceptance by surgeons in Italy over other ways of administration of antibiotics (subconjunctival or in the infusion bottle)^{9,10} for technical reasons (risk of dilution errors, and bacterial contamination) and concerns about endothelial corneal toxicity.

The important clinical question is whether cefuroxime may be the antibiotic of choice to prevent post-cataract endophthalmitis. The identification of cefuroxime as ideal prophylactic antibiotic to cover the most frequent microbiological pathogens derive from the conclusion of the Endophthalmitis Vitrectomy Study (1995).³⁸ Microbiological surveillance is mandatory to understand the current role of cefuroxime. When we compare the microbiological surveillance³⁹⁻⁴⁴, among different studies in US and Europe, the list of germs involved is quite stable and similar with the majority of them belonging to Gram +: *coagulase-negative Staphylococci*, *Staphylococcus aureus*, *alpha-hemolytic streptococci*, and *Streptococcus pneumoniae*. Among Gram - *Pseudomonas spp*, *enterobactriaceae*, *Haemophilus influenzae*, *Moraxella*, and *Klebsiella*.

Microbiological variations in infectious agents are secondary to differences in climate (i.e fungal infections) or organization (different health systems). In a previous report of ESCRS in 2007 only Gram + germs were isolated.¹⁷ A recent microbiological review³⁵ of all culture proven cases of endophthalmitis in the last 25 years at one large institution appears to support cefuroxime versus cefazolin and/or other antibiotics that have higher resistant rates. Endophthalmitis isolates have had a significant trend toward both increasing resistance to cephalosporins and Methicillin and decreasing resistance to aminoglycosides and Imipenem. On the other hand Vancomycin has been shown to be effective towards Gram + germs but ineffective towards Gram – germs. Therefore Vancomycin⁴² should be used as second line agent, also because it is effective against resistant strains of *Staphylococcus aureus* (MRSA). As far the allergic or toxic reactions are concerned it was recently reported⁴⁵ that a patient developed an anaphylactic reaction several minutes after intracameral injection of cefuroxime at the end of uneventful phacoemulsification and intraocular lens implantation surgery. In our survey 50% of surgeons were concerned about toxic or allergic reactions.

Choosing wisely also is a patient specific choice. For example, elderly patients with blepharitis, poor tear film, anticipated prolonged surgery, may be more prone to infection and therefore good candidates for intracameral or preoperative antibiotics.

There is a growing debate on the definition and the inclusion of immunocompromised patients, such as those with diabetes, cancer or long term treatment with steroids, history of trauma or previous ocular surgery: it would be of clinical interest investigate whether a correlation between specific types of germs and immunodepression may be demonstrated.

Cost-effectiveness analyses are also warranted. A retrospective study carried out at University of Udine, Italy in 2013 showed that the use of commercially available intracameral antibiotics is not cost-effective in the prevention of post-cataract endophthalmitis compared to the costs of vitrectomy for endophthalmitis, given the rare occurrence of post-cataract endophthalmitis. (*Prof. P. Lanzetta and coworkers personal communication, Pordenone, Italy, September 2014*).

Strengths of our study are the enrollment of a variety of private, public, and academic settings across Italy. This is the first Italian survey on the subject to employ email interviews for data collection. The method offers advantages over postal surveys and telephone interviews, as direct dialogue between the epidemiologists (FB, RG, RS), the principal investigator (AG) and cataract surgeons (complete list reported in the appendix) allows clarification of answers, additional queries and leaves time for a better retrospective analysis. Each centre involved in the survey was totally blind regarding the participation of the other centres.

Limitations include the retrospective nature of our study. There may have been other factors than just intracameral antibiotics that contributed to lower endophthalmitis rates. Randomized controlled trials, with rare outcomes require very large sample sizes and are costly or even cost-prohibitive to conduct. Further we could not perform a Health Technology Assessment analysis given the absence of uniform data and sufficient studies. We are aware that case control studies or models should have provided more solid scientific data than a survey. A high cut point for an "acceptable" level of endophthalmitis was decided (0.13%): in a systematic review an aggregate incidence of endophthalmitis occurring after cataract surgery of 0.128% was found.¹³ Further the cut-off decided in our survey was lower than the level found in the Cefuroxime study.¹⁷ We are aware that

it would have been desirable to have a lower than reported average level of endophthalmitis: however dealing with rare clinical events the choice of lower cut point may have weakened the association.

In conclusion, when we compare the routine clinical practice in the sample of Italian hospitals enrolled in this survey with ESCRS guidelines and best available evidence, the use of cefuroxime at the end of surgery was lower than expected. Our survey shows that a greater proportion of centers that use cefuroxime have an acceptable incidence of endophthalmitis. The majority of surgeons in our survey (83%) said they would use cefuroxime if a preformulated preparation of cefuroxime for intracameral use were commercially available, according to the literature.⁴⁶

We cannot recommend or discourage the use of preoperative antibiotics, since no significant association were found in our survey,: however, when it was decided to use preoperative antibiotics fluoroquinolones were chosen.

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WHAT WAS KNOWN

- Although the ESCRS guidelines recommend to use cefuroxime at the end of surgery as a direct injection in the anterior chamber since 2007, its use gained slowly acceptance by the

scientific community in Italy, also correlated to the difficulties in preparing the antibiotic (risk of dilution errors, risk of bacterial contamination).

- Pre-formulated cefuroxime commercially available “on label” formulation of cefuroxime were introduced in the European market since 2013.
- However it is not clear whether the use of cefuroxime should be offered routinely to all patient undergoing cataract surgery or based on a risk assessment (local and systemic factors).

WHAT THIS PAPER ADDS

- Our Survey is the wider completed in Italy to collect information about the surgical routines with regards to prophylactic strategies and it is the first to report data about the use of cefuroxime in the anterior chamber in Italy.
- Our Survey shows that a greater proportion of centers that use cefuroxime have an acceptable incidence of endophthalmitis (lower than 0.13%)
- As no significant association were found in our Survey, we cannot recommend or discourage the use of preoperative antibiotics: however, when it was decided to use preoperative antibiotics fluoroquinolones were chosen.

Appendix

List of centres examined by Region (from North to South)

NHS: National Health System

Piemonte

- Torino (NHS and University): Claudio Panico MD, Francesco Faraldi MD and Savino D'Amelio MD
- Borgomanero (NHS): Vito Belloli MD, Vincenzo Ferrara MD

Lombardia

- Milano (University): Paolo Nucci MD, Edoardo Villani MD
- Brescia (University): Francesco Semeraro MD
- Milano (University): Matteo Cereda MD
- Brescia (private hospital operating with NHS): Barbara Parolini MD
- Milano (private hospital operating with NHS): Mario Romano MD

Veneto

- Venezia (NHS): Antonella Franch MD
- Verona (University): Giorgio Marchini MD, Piero Ceruti MD
- Treviso (NHS): Giuseppe Scarpa MD
- Negrar (private hospital operating with NHS): Grazia Pertile MD, Guido Prigione MD

Emilia Romagna

- Reggio Emilia (NHS): Luigi Fontana MD
- Ravenna (NHS): Cesare Forlini MD
- Parma (University): Nicola Ungaro MD

Marche

- Ancona (University): Cesare Mariotti M

Toscana

-Pisa (NHS): Stanislao Rizzo MD, Francesco Barca MD

-Pisa (University): Michele Figus MD

Umbria

-Perugia (NHS): Tito Fiore MD

Lazio

-Roma (NHS): Tommaso Rossi MD

Campania

-Acerra (private hospital operating with NHS): Aldo Gelso MD

-Napoli (private hospital operating with NHS): Otello Gallo MD

- Napoli (NHS): Beniamino Mastursi MD

- Pompei (private hospital operating with NHS): Dario Furgiuele MD

Calabria

-Catanzaro (University): Vincenzo Scorgia MD

Sardegna

-Sassari (University): Francesco Boscia MD

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