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# Preoperative gentamicin eye drops and chlorhexidine solution in cataract surgery.
## Experimental and clinical results

*P.G. MONTAN[1], H. SETTERQUIST[1], E. MARCUSSON[2], M. RYLANDER[2], U. RANSJÖ[2]*

[1] Department of Ophthalmology, St Erik's Hospital, Stockholm
[2] Department of Clinical Microbiology, Karolinska Hospital, Stockholm - Sweden

PURPOSE. *1) To evaluate the effects on the conjunctival flora of gentamicin ophthalmic eye drops 0.3%, given four times in 45 minutes, and a conjunctival rinse with 10 ml chlorhexidine 0.05% solution. 2) To investigate retrospectively the rate of endophthalmitis after cataract operations when these antimicrobials were applied preoperatively.*
METHODS. *Seventy-six patients undergoing standard phacoemulsification operations were enrolled in the experimental part of the study. Cultures were taken preoperatively, 5 minutes after prophylaxis with either chlorhexidine or gentamicin. To assess the combined effects of chlorhexidine and gentamicin, cultures were taken after the cataract operation. Hospital charts were reviewed for cases of endophthalmitis in 1994 and 1995, when this prophylactic protocol was used at the St Erik's cataract surgery department.*
RESULTS. *The conjunctival microflora was significantly suppressed by chlorhexidine rinsing alone (p = 0.001), while no other significant anti-bacterial effects were observed with the experimental prophylaxis. The endophthalmitis rate was 32/12. 806 operations (0.25%).*
CONCLUSIONS. *Topical rinsing with chlorhexidine solution suppresses conjunctival flora in the short term. Combined topical chlorhexidine and gentamicin prophylaxis does not eliminate postoperative endophthalmitis caused by gram-positive bacteria. (Eur J Ophthalmol 2000; 10: 286-92)*

KEY WORDS. *Postoperative endophthalmitis, Prophylaxis, Gentamicin, Chlorhexidine*

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## INTRODUCTION

Postoperative endophthalmitis remains a major concern in intraocular surgery. Despite advances in its treatment (1), a high proportion of patients suffer major loss of vision, particularly if infected with highly virulent bacteria such as streptococci (2, 3). The main source of contamination is the indigenous microflora of the ocular surface and adjacent skin (4, 5). Antimicrobials are therefore commonly used before, during, or after the intervention. The value of these treatments, however, remains uncertain, mainly because of the lack of comparative randomised studies.

In January 1994, we abandoned our previous prophylaxis of gentamicin 20 mg subconjunctival injection, on account of poor results (3). It was replaced by gentamicin eye drops and chlorhexidine solution given preoperatively. The same program for ocular preparation had been in use for the preceding four years at the ophthalmic department of the Sahlgrenska Hospital in Gothenburg, Sweden, with apparent efficacy and no local adverse reactions (personal communication, Dr. Gun Lindgren).

The aim of this study was twofold: to evaluate how this regimen influenced the conjunctival microflora and to assess the endophthalmitis rate in the two years when this prophylactic program was uniformly used.

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## MATERIALS AND METHODS

### *Experimental culture studies*

Cataract patients were enrolled, after giving informed consent. Their mean age was 75 years (range 42 - 96 years), 73% were women. Exclusion criteria were diabetes, systemic treatment with any antibiotic or immunosuppressant, any topical treatment in either eye, previous ocular surgery, and signs of ocular infection or inflammation. The local antibacterial efficacy of the prophylactic protocol was investigated in three experimental trials. In two studies (I and II), the immediate preoperative effects were assessed. In a third study (III), the effects at the end of cataract surgery were evaluated.

*Study I.* One drop of non-preserved gentamicin 0.3% ophthalmic solution (Gentamicin Sulfate™, Chauvin Pharmaceuticals Ltd, Romford, England) was administered four times in 45-minutes into the lower conjunctival fornix in one eye of 20 subjects. Five minutes after the last application the eyes were anesthetised with one drop of non-preserved tetracain 1% (Amethocaine™, Chauvin Pharmaceuticals Ltd, Romford, England). Conjunctival cultures were taken bilaterally with the untreated fellow eye serving as a control.

*Study II.* Ten ml of chlorhexidine solution 0.05% (Pharmacia Pharmaceuticals, Uppsala, Sweden) was used to irrigate one eye of 20 subjects. After five minutes both eyes were anesthetised and cultured as in study I.

*Study III.* Thirty-six subjects who had been operated with an uneventful phacoemulsification procedure were included. Eighteen treatment patients received the combined prophylactic regimen of gentamicin 0.3% given four times in 45 minutes and chlorhexidine solution 0.05% 10 ml irrigation 5 minutes before the start of the operation. Eighteen control patients received no preoperative prophylactic treatment. The pupil was dilated with an eye-drop combination of cyclopentolate hydrochloride 0.75% and phenylephrine hydrochloride 2.5% preserved with benzalkonium chloride 0.01%, given three times. Topical application of non-preserved tetracain 1%, followed by a subtenon injection of lidocain 2%-adrenalin 0.00125% 1.5 ml (Xylocain® adrenalin, Astra, Södertalje, Sweden) were used for anesthesia. The peri-ocular skin was disinfected with chlorhexidine alcohol 0.5% (Pharmacia Pharmaceuticals). Cultures were taken at the conclusion of surgery, just before insertion of the lens.

Study III was conducted in 1996, incorporating an amendment to our prophylaxis protocol, and all subjects were given an injection of cefuroxime 1 mg (Zinacef™, Glaxo Wellcome, Mölndal, Sweden) into the capsular bag after implantation of the intraocular lens, i.e. after the conjunctival sample had been obtained. The non-operated and untreated fellow eyes of the 18 treatment subjects were also cultured after topical administration of non-preserved tetracain 1%. These data had no relevance to the analysis of study III but were included in the compilation of the normal material.

### *Sample collection and culture techniques*

The culture specimens were collected with absorbent polyvinyl alcohol (PVA) foam pads (a gift from Mölnlycke Clinical Products AB, Mölnlycke, Sweden), with a diameter of 10 mm (6). They were grasped with sterile forceps and moved back and forth twice over the conjunctival surface in both the inferior and superior fornices. The pads were immediately placed in sterile test tubes containing 2 ml sterile peptone water 0.1%. The samples were coded and taken to the Department of Clinical Microbiology, Karolinska Hospital, and handled no later than 4h after collection. The tube was vortexed for 1 minute. Ten µl were taken with a sterile plastic loop and 100 µl were collected with a calibrated pipette. The fluid samples were plated (incubation time and atmosphere in brackets) on blood agar (air 2d), hematin ($CO_2$ for 2d), and anaerobic blood agar (anaerobic jar 4d). Colony counts were made on the solid media growing 30-100 colonies if possible and expressed in colony forming units (CFU) per pad. Bacteria were identified according to current methods (7).

### *Clinical data*

The preoperative preparation before cataract surgery in 1994 and 1995, apart from dilating eye drops, consisted of gentamicin eye-drops 0.3% given 4 times in 45 minutes and chlorhexidine solution 0.05% 10 ml irrigation of the conjunctiva 5 minutes before the start of the operation. The periocular skin was disinfected with chlorhexidine alcohol 0.5%. No other anti-infective drugs were given. The lid margins were

draped with a sterile plastic cover (Johnson & Johnson, Arlington, TX, USA).

The follow-up program for all our cataract patients included two visits in the hospital, the last about a week after the operation. The final postoperative examination was done 1 - 2 months later by the referring ophthalmologist.

Records of all patients having undergone cataract surgery at our facility in 1994 and 1995, who presented suspected endophthalmitis, i.e. ocular findings including a hypopyon and/or vitreous clouding together with a deterioration of visual acuity, were analysed for study eligibility. No maximum interval was set between the surgery and the diagnostic procedures. The mandatory management of presumed postsurgical endophthalmitis included hospitalisation, intraocular culture sampling and treatment with intravitreal and intravenous antibiotics. Systemic steroids and vitrectomy were employed in approximately half the cases.

Anterior chamber and vitreous body samples were sent to the Department of Clinical Microbiology, Karolinska Hospital. The specimens were incubated as follows (incubation time and atmosphere in brackets): on hematin agar ($CO_2$ for 4 - 6d), on blood agar (anaerobic jar 4 - 6d), in Brain Heart Infusion broth (Difco Labs, Detroit, Michigan, USA) supplemented with hemin, isovitalex, and albumin (air 2 - 4d), and in PeptoneYeast Glucose Broth (anaerobic jar for at least 6d). All incubations took place at 36°C. If the solid plates yielded no growth, broths showing turbidity were subcultured on hematin agar in $CO_2$ and air for 2 days and on blood agar in an anaerobic atmosphere for 4 days. Isolates were identified according to standard procedures (7).

If cultures were negative and the patient had full recovery of vision within one week after the diagnostic sampling, the condition was diagnosed as sterile postoperative inflammation (2 cases). Four culture-negative cases were excluded since the intraocular inflammation was considered secondary to a superficial wound infection. Three cases attributable to cataract wound dehiscence were excluded.

*Statistical methods*

Continuous parameters were evaluated with non-parametric methods since data were not normally distributed. Paired data (experimental studies I and II) were analysed with the Wilcoxon signed-rank test, and independent variables (experimental study III) were evaluated with the Mann-Whitney U test. Categoric variables were analysed with the Yates' corrected chi square test, using Statistica Software (StatSoft Inc. 1995, Tulsa, OK, USA).

P values below 0.05 were considered significant.

## RESULTS

The normal flora of the conjunctiva in unoperated and untreated control eyes of 58 cataract patients is listed in Table I. Thirty-nine patients (67%) had at least one isolated species, 25 had two, 11 three and 3 four species or strains in their cultures. Coagulase-negative staphylococci (CNS) were the main isolates (58%) followed by propionebacteria (25%). Only three of 44 CNS isolates found in control eyes were resistant to isoxazolylpenicillin and two had lowered sensitivity. One CNS isolate was resistant to gentamicin.

Tables II and III present the results of the experimental treatment studies. The chlorhexidine solution wash of the ocular surface significantly reduced conjunctival bacterial colonisation, both qualitatively ($p = 0.004$) and quantitatively ($p = 0.001$). The gentamicin treated eyes had lower bacterial counts than control eyes but the difference was not statistically significant. In eyes cultured after the cataract extraction, assessing the combined effect of gentamicin and chlorhexidine, there was no significant difference in bacterial numbers between treated and untreated patients (Tab. II).

The overall frequency of endophthalmitis was 0.25% or 32 cases in 12,806 operations. This was practically identical to the rate observed using subconjunctival gentamicin in 1990-1993 (3). The median delay between the operation and the diagnostic procedure was 7 days. Fifty percent of the cases were culture positive. Table IV displays causative organisms and visual outcomes.

No adverse effects of the study treatment were noted in the experimental or in the clinical parts of the study.

## DISCUSSION

Many prophylaxis regimens have been proposed for cataract surgery following experimental studies (8, 9)

**TABLE I -** BACTERIA ISOLATED IN 58 UNTREATED, UNOPERATED EYES

| Species | Isolate 1 | Isolate 2 | Isolate 3 | Isolate 4 | Total |
|---|---|---|---|---|---|
| CNS | 20 | 20 | 3 | 1 | 44 |
| *Staphylococcus aureus* | 1 | | | | 1 |
| Micrococci | 1 | | | | 1 |
| Alphahemolytic streptococci | | 1 | 1 | | 2 |
| Anaerobic streptococci | | 1 | 1 | | 2 |
| Propionebacteria | 11 | 1 | 6 | 1 | 19 |
| Corynebacteria | 6 | | | 1 | 7 |
| | | | | | 76 |

CNS = Coagulase Negative Staphylococci

**TABLE II -** QUANTITATIVE DATA OF EXPERIMENTAL STUDIES

| Study | Culture site | CFU median (range) | P value in Wilcoxon (I and II) or Mann-Whitney (III) |
|---|---|---|---|
| I Gentamicin | Treated eyes n = 20 | 0 (0-320) | 0.08 |
| | Control eyes n=20 | 35 (0-1220) | |
| II Chlorhexidine | Treated eyes n = 20 | 0 (0-400) | 0.001 |
| | Control eyes n = 20 | 250 (0-11200) | |
| III Gentamicin + Chlorhexidine | Operated and treated eyes, n = 18 | 0 (0-640) | 0.22 |
| | Operated and untreated eyes, n = 18 | 20 (0-5040) | |

CFU = Colony-Forming Units

**TABLE III -** QUALITATIVE DATA OF EXPERIMENTAL STUDIES

| Study | Culture site | Positive culture | CNS | Propionebacteria | P values* |
|---|---|---|---|---|---|
| I Gentamicin | Treated eyes n = 20 | 8 (40%) | 5 (25%) | 5 (25%) | 0.21 |
| | Control eyes n = 20 | 13 (65%) | 12 (60%) | 6 (30%) | |
| II Chlorhexidine | Treated eyes n = 20 | 6 (30%) | 4 (20%) | 3 (15%) | 0.004 |
| | Control eyes n = 20 | 16 (80%) | 14 (70%) | 3 (15%) | |
| III Gentamicin + Chlorhexidine | Operated and treated eyes n = 18 | 8 (44%) | 4 (22%) | 3 (17%) | > 0.5 |
| | Operated and untreated eyes n = 18 | 10 (56%) | 6 (33%) | 4 (22%) | |

* Yates' corrected chi-square test comparing proportions of eyes with any positive culture.
CNS = Coagulase-Negative Staphylococci

**TABLE IV -** ENDOPHTHALMITIS CASES, CAUSATIVE MICRO-ORGANISMS AND VISUAL OUTCOME

| Species | Total no. of subjects | No. of subjects with visual result ≥ 2/20 |
|---|---|---|
| CNS | 11 | 8 |
| *S. aureus* | 3 | 1 |
| Streptococci | 2 | 0 |
| Culture negative | 15* | 14 |
| Not cultured | 1 | 1 |

*One patient was lost to follow-up

but clinical studies of their efficacy are few. In the present study, we assessed the immediate antibacterial effects and the clinical consequences of a topical pre-operative antimicrobial prophylaxis.

The choice of regimens was based on the proven efficacy of gentamicin against conjunctival commensals (10) and the broad *in vitro* activity against both gram-positive and gram-negative species described for chlorhexidine (11). We are not aware of any published report describing conjunctival rinsing with chlorhexidine solution as a prophylactic method for intraocular surgery. Chlorhexidine in the concentration we used proved safe for the epithelium in a rabbit model (12) and we did not observe any adverse effects. Damage to the corneal endothelium has, however, been reported with a weaker solution of chlorhexidine mistakenly used for intraocular irrigation in cataract surgery (13). The reasons for designing a short-term treatment to be given immediately before the operation were to circumvent possible compliance problems and to achieve as high a concentration as possible of the antimicrobials during surgery (14).

In the experimental study, the bacterial flora consisted only of gram-positive bacteria. From this point of view, our regimen appeared well designed, but an antibacterial effect was shown only for chlorhexidine solution while that of the gentamicin eye drops could not be statistically proven. Our study model with the fellow untreated eye serving as a control is based on the known concomitance of conjunctival commensals in both eyes of healthy individuals (15). In theory, sterilising effects of the gentamicin eye drops in the present study could have been more difficult to demonstrate, since the control eyes in trial I had lower colony counts than in trial II. This is unlikely to be the case, however, since the bacterial counts in the control eyes did not differ significantly between trial I and II ($p = 0.06$). With an antibacterial effect equal to that of the chlorhexidine rinsing, the gentamicin regimen would actually have achieved significance from a statistical point of view.

Suppression of the ocular adnexal flora has been found after short-term applications of ciprofloxacin (8), and povidone-iodine (9). None of these studies ascertained the duration of the anti-bacterial effects throughout a cataract operation, as in the present investigation. We did not find any differences in postoperative bacterial counts between treated and untreated eyes but the reason for this inadequate effect of our prophylaxis is not known. The peroperative continuous irrigation of the ocular surface may dislodge bacteria both from the angular lid margins, which are difficult to drape completely, and from the fornices. Irrigation with saline has been shown experimentally to increase the bacterial yield from the conjunctiva (9). Moreover, cultures of the aqueous humour at the conclusion of the cataract intervention have revealed substantial contamination, 24-43%, despite previous preparation with povidone-iodine and in many cases topical antibiotics (16-18). The local microbial load towards the end of the intervention, when the intraocular implant is inserted, is probably crucial for the development of endophthalmitis. Therefore, postoperative cultures of the conjunctiva or, even better, of aqueous aspirates seem indicated as parameter of efficacy in the validation of any suggested anti-infective regimen in intraocular surgery.

Epidemiological studies of postoperative endophthalmitis may be flawed by an underestimation of cases, since infected patients might report to institutions other than the study centre. During the period of our clinical study, hospitalisation was mandatory in the management of presumed endophthalmitis. Since St Erik is the only eye clinic in the Stockholm area for inpatient care, we can assume that no patient with postoperative intraocular infection escaped our attention.

As causes of endophthalmitis, only gram-positive bacteria were isolated. In the prevention of infection, topical gentamicin and chlorhexidine was no better than our previous regimen with subconjunctival gentamicin (3), and clearly inferior to a protocol involving intracameral antibiotics described in a Canadian

report (19). Comparing infection rates from different centres may be difficult, since case definitions may differ. For postoperative endophthalmitis, there are no accepted principles regarding the classification of culture-negative cases. Our rate would have been 0.12%, had we based our analysis solely on culture-positive cases. Like us, other investigators have presented fairly large numbers of culture-negative cases (1, 20). The clinical grounds for suspecting endophthalmitis are undue inflammatory reaction coupled with severe visual loss. Fifty percent of our culture-negative subjects had perception of hand movements or light while the rest had less than 0.25 vision at admission. These patients must be considered as infected when no other satisfactory explanation of the condition was found. Negative cultures may result from inadequate sampling or bacterial death before the sample is taken. In an animal model, a self-sterilising capacity of the vitreous has been demonstrated for CNS (21). The course of culture-negative endophthalmitis resembles that of endophthalmitis caused by CNS in that both usually have a favourable visual outcome.

In summary, a short-term preoperative treatment with chlorhexidine solution suppressed the microbial flora of the conjunctiva in cataract patients. The combination of gentamicin eye drops and chlorhexidine solution did not provide a cleaner environment in the conjunctiva at the time of lens insertion than no preoperative treatment at all. This was paralleled by the unsatisfactory rate of gram-positive endophthalmitis seen in the clinical investigation. Our data cannot be generalised to a more extended dosing schedule of the present anti-microbials or to other preoperative prophylactic agents such as povidone-iodine. Still, we are not aware of any other recent report of a good clinical effect when pre-operative disinfectant measures were used alone. To achieve the necessary bactericidal concentration, the drug may well have to be delivered into the eye (19). To us, it is evident that the study treatment cannot be solely relied upon if endophthalmitis caused by gram-positive species is to be effectively prevented. In view of its apparent anti-bacterial capacity in the opening phase of the operation, its low cost and good safety profile, chlorhexidine solution has been kept in our protocol as an adjunct to a cephalosporin given intracamerally at the end of the intervention.

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Reprint requests to:
Per G. Montan, MD
Department of Ophthalmology
St Erik's Hospital
Polhemsgatan, 50
S-112 82 Stockholm, Sweden

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