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Bacteriology and cefuroxime resistance in endophthalmitis following cataract surgery before and after the introduction of prophylactic intracameral cefuroxime: a retrospective single-centre study

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SUMMARY

Background: Intracameral cefuroxime as prophylaxis against postoperative endophthalmitis (POE) following cataract surgery was introduced in 1996 at St Erik Eye Hospital. Soon after the introduction of intracameral cefuroxime, the rate of POE fell dramatically and a shift in the aetiology was noticed.
Aim: To analyse bacteriology and susceptibility to cefuroxime before and after the introduction of intracameral cefuroxime.
Methods: All culture-proven cases of endophthalmitis at St Erik Eye Hospital after cataract surgery performed over a 20-year period were included in a retrospective observational study.
Findings: Sixty-two cases of endophthalmitis occurred in 34,390 (0.18%) cataract surgeries before the introduction of intracameral cefuroxime (Period 1), while 33 cases occurred in 75,144 (0.044%) operations after the introduction of intracameral cefuroxime (Period 2), showing a significant difference between the periods ($P < 0.001$). The incidence of coagulase-negative staphylococci (1/1400 vs 1/15,000; $P < 0.001$), *Staphylococcus aureus* (1/2000 vs 1/30,000; $P < 0.001$), streptococci other than enterococci (1/2500 vs 1/25,000; $P < 0.001$) and *Propionibacterium acnes* (1/16,000 vs 0/75,000; $P = 0.04$) fell sharply in Period 2. Cefuroxime-sensitive strains became less frequent in Period 2 ($P < 0.001$). Enterococci became the predominant species, albeit not significantly ($P = 0.13$), whereas the rate of cefuroxime-resistant strains almost reached significance ($P = 0.05$) in Period 2.
Conclusions: Intracameral cefuroxime leads to a reduction of the rate of endophthalmitis after cataract surgery, and brings about a shift in pathogens from cefuroxime-sensitive to cefuroxime-resistant organisms.

Introduction

Cataract surgery is generally safe and improves vision for the majority of patients [1,2]. Complications are rare, but postoperative endophthalmitis (POE) represents one of the worst, carrying a high risk for visual damage and increased costs for society [3,4]. In several publications from St Erik Eye

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Hospital, incidence, risk factors and the role of infection prophylaxis have been analysed in POE following cataract surgery [5,6]. Since 1998, this work has continued within the Swedish National Cataract Register, harbouring a nationwide endophthalmitis registry [7–9]. Both study settings have demonstrated the superiority of intracameral cefuroxime over topical regimens in preventing POE [6–8], which has been confirmed by numerous international studies [10–14]. Consequently, the uptake of intracameral antibiotic prophylaxis, predominantly cefuroxime, has been 99% among cataract surgeons in Sweden for approximately 10 years [8].

The bacteriology of POE after cataract surgery differs considerably between patients who are given and patients who are not given intracameral cefuroxime [6,8,9,15–18], with a particular reduction in *Staphylococcus aureus* and most streptococci in the former group. This shift has, to date, only been subject to a preliminary analysis from the study institution [6], and the authors are not aware of any comprehensive studies presenting the sensitivity data of POE pathogens in cases given prophylactic intracameral cefuroxime.

Methods

All culture-positive cases of endophthalmitis identified in the nosocomial infection records of St Erik Eye Hospital after uncombined cataract operations performed from February 1990 to November 2009 were included. This time period was divided into Period 1 (before the introduction of intracameral cefuroxime) and Period 2 (after the introduction of intracameral cefuroxime).

POE was defined as any inflammatory condition after cataract surgery warranting intraocular sampling from the aqueous humour and vitreous fluid, and simultaneous administration of intravitreal antibiotics. Cultures were performed according to standard methods [19], mainly in the contracted microbiology laboratory at Karolinska Hospital. Sensitivity patterns were determined by standard disc-diffusion methods, and minimum inhibitory concentration (MIC90) breakpoints were given as defined by the Swedish Reference Group for Antibiotics (www.sls.se/raf). Patient age and sex, causative organisms, susceptibility to cefuroxime and visual impairment (defined as best corrected visual acuity less than 20/200 examined approximately three months after infection) were analysed and compared between patients who were given and patients who were not given intracameral cefuroxime.

From 1990 to 1993, prophylaxis consisted of subconjunctival gentamicin 20 mg postoperatively. In 1994–1995, gentamicin drops 0.3% were given four times in 45 min pre-operatively, followed by conjunctival chlorhexidine 0.05% rinsing before placing the lid speculum. From January 1996, 1 mg intracameral cefuroxime in 0.1 mL saline was added postoperatively. By June 1998, gentamicin drops were discontinued but chlorhexidine rinsing was kept. These policies were followed universally. Povidone iodine was not used.

During the study period, cataract surgery changed from the extracapsular technique to phaco-emulsification; this transition was completed by 1995.

Medical treatment of POE included intravitreal injection of cefuroxime 1 mg in surgeries from 1990 to 1993. From then on, cases were treated with intravitreal injection of ceftazidime 2.27 mg and vancomycin 1 mg following recommendations from the ongoing Endophthalmitis Vitrectomy study (EVS) [3]. From 1995, when the EVS results were made public, a standard oral dose of prednisone 60 mg for five days was included, and indications for vitrectomy were adopted according to the study conclusions [3].

Statistical analyses were performed using Statistica Version 13.0 (Statsoft Inc., Bedford, UK). For categorical data, Pearson's Chi-squared test was used. $P < 0.05$ was considered to indicate significance.

Results

During the study period 1990–2009, 95 cases of culture-positive endophthalmitis occurred in 109,534 cataract operations.

Sixty-two cases of culture-positive endophthalmitis occurred in 34,390 cataract operations before the introduction of cefuroxime (1990–1995; Period 1), corresponding to a rate of 0.18%, while 33 cases of endophthalmitis were diagnosed in 75,144 cataract operations after the introduction of cefuroxime (1996–November 2009; Period 2), yielding a rate of 0.044%. In Period 1, 33 infected patients underwent extracapsular cataract extraction (ECCE) and three patients underwent intracapsular cataract extraction, giving a joint incidence of POE of 0.24% in 14,925 non-phaco-emulsification surgeries, while 26 POE cases occurred after phaco-emulsification, signifying a rate of 0.13% in 19,465 operations. The 33 patients who sustained endophthalmitis in Period 2 all underwent phaco-emulsification. The POE rate was significantly lower ($P < 0.001$) when operations were performed with intracameral cefuroxime (Period 2), regardless of whether comparisons were made with the entire cohort, non-phaco-emulsification procedures or phaco-emulsification procedures in Period 1.

The proportion of POE cases aged $\geq$85 years was greater (24%) than in the control cohorts in the respective periods (17.2% and 16.8%) without being significantly different. The female ratio in the study population decreased from 66% in Period 1 to 57.5% in Period 2, paralleling a similar trend in the control population (from 69.7% to 64.5%). Neither of these differences were significant.

The risk of severe visual loss per prophylaxis period, defined as final visual acuity worse than 20/200, was approximately one in 1400 operations in Period 1 (i.e. 0.073%, 25 cases out of 62). The corresponding figures for Period 2 were one in 5300 surgeries (i.e. 0.018%, 14 cases out of 32, data missing for one case). The difference between the periods was significant ($P < 0.001$).

Significant changes in incidence were noted for almost all Gram-positive species between the periods. Coagulase-negative staphylococci (CoNS) caused significantly fewer cases of POE after the introduction of cefuroxime (1/1400 vs 1/15,000; $P < 0.001$). Similar differences were found for *S. aureus* (1/2000 vs 1/30,000; $P < 0.001$), streptococci other than enterococci (1/2500 vs 1/25,000; $P < 0.001$), and *P. acnes* (1/16,000 vs 0/75,000; $P = 0.04$) (Table I and Figure 1). Enterococci (mostly described as *Enterococcus faecalis* but occasionally as *Enterococcus* spp.) became the predominant species in Period 2 (1/5800 in Period 2 vs 1/17,200 in Period 1), but the difference was not significant ($P = 0.13$).

In an attempt to find specific traits for cases infected with enterococci, systemic immunosuppression and diabetes mellitus were investigated in the entire study cohort. Only eight

Table I
Cefuroxime resistance and sensitivity among causative strains

Causative strains	Period 1 ($N = 34,390$)	Period 2 ($N = 75,144$)	P-value
Cefuroxime-resistant coagulase-negative staphylococci	1	4	0.58
Cefuroxime-sensitive coagulase-negative staphylococci	25	1	<0.001
Cefuroxime-resistant enterococci[b]	2	13	0.13
Cefuroxime-sensitive *Staphylococcus aureus*[a]	17	2	<0.001
Cefuroxime-sensitive streptococci[a]	13	3	<0.001
Cefuroxime-resistant Gram-negative bacteria[c]	2	10	0.27
Cefuroxime-sensitive *Propionibacterium acnes*[a]	2	0	0.04

Period 1, before the introduction of cefuroxime; Period 2, after the introduction of cefuroxime.
[a] No cases of resistant bacteria.
[b] No cases of sensitive bacteria.
[c] No cases of sensitive bacteria. Period 1: *Morganella morgani* $N = 1$, *Pseudomonas aeruginosa* $N = 1$. Period 2: *Agrobacter radiobacter* $N = 3$, *Alcaligenes xylosoxidans* $N = 2$, *Serratia marcescens* $N = 2$, *Pseudomonas aeruginosa* $N = 2$, *Pseudomonas mendocina* $N = 1$.

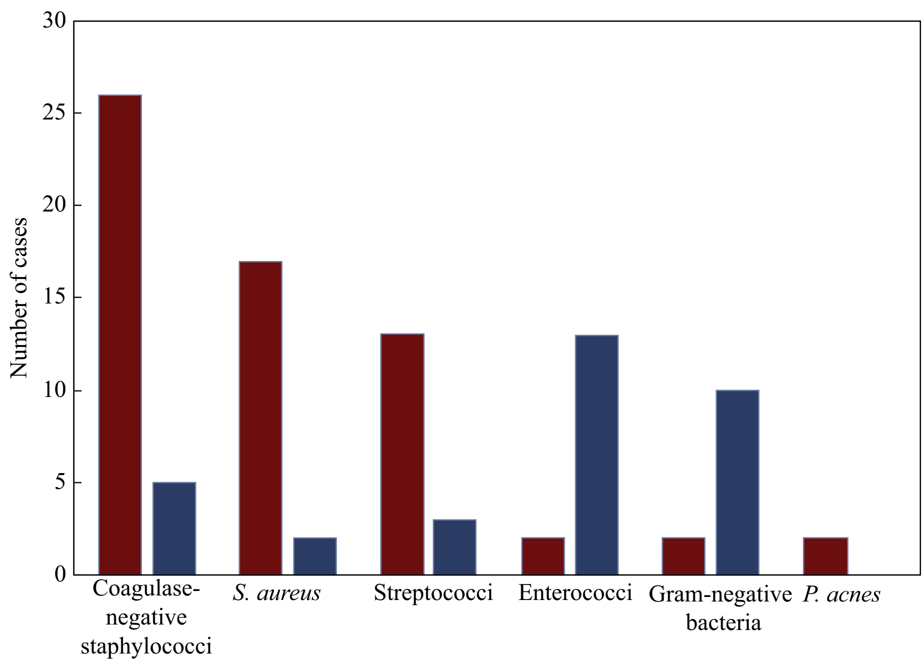

Figure 1. Bacterial aetiology before ($N = 34,390$ operations, 1990–1995, red bars) and after ($N = 75,144$ operations, 1996–2009, blue bars) the introduction of intracameral cefuroxime. *S. aureus*, *Staphylococcus aureus*; *P. acnes*, *Propionibacterium acnes*.

cases in Period 1 and nine cases in Period 2 had these characteristics. Enterococcal infection was no more frequent (12.5% and 22%, respectively) in these subgroups.

Gram-negative infections were conspicuous in Period 2 among causative strains, but not significantly more frequent ($P = 0.27$). Two epidemics caused by rare Gram-negative bacteria occurred in Period 2. Two cases of *Alcaligenes xylosoxidans* operated on successively were identified, as were three consecutively operated cases infected with the same *Agrobacterium* sp. The second event could be attributed to a contaminated water tank involved in cleaning the phaco-emulsification hand pieces. A similar mechanism of contamination was likely responsible for the first epidemic [6]. Fortunately, the infections were mild and patients ended up with fairly good vision.

In Period 1, five cases were infected with a cefuroxime-resistant organism, while in Period 2, 27 cefuroxime-resistant organisms were identified ($P = 0.05$) (i.e. just above the defined level of significance). Conversely, the rate of cefuroxime-sensitive strains was significantly higher before the introduction of intracameral cefuroxime than after ($P < 0.001$) (Table I). No meticillin-resistant *S. aureus* (MRSA) was found, while five meticillin-resistant, and accordingly cefuroxime-resistant, CoNS were detected, 80% of them in Period 2. For these CoNS strains, the median visual outcome was 20/30, while the corresponding visual outcome for cefuroxime-sensitive strains was 20/40. All enterococci were resistant to cefuroxime, but sensitive to vancomycin and ampicillin. The median visual acuity after enterococcal infection was counting fingers.

Discussion

This retrospective study clearly demonstrates that the explanation behind the evident prophylactic effect of cefuroxime, a second-generation cephalosporin, lies in its effective targeting of micro-organisms found to be the common culprits in POE following cataract operation (e.g. coagulase-negative staphylococci, *S. aureus*, and streptococci except enterococci)

[15,16]. When intracameral cefuroxime was initiated in 1996, its choice, besides being backed by reassuring safety data, was based on sensitivity analyses of previous POE pathogens in the study institution [6,20] (Table I). After the change in the prophylactic protocol, cefuroxime-sensitive Gram-positive bacteria were reduced considerably, causing one infection in 12,500 procedures compared with one in 580 procedures before intracameral cefuroxime, a convincing improvement ($P < 0.001$). These results are similar to those in the prospective randomized study of the European Society for Cataract and Refractive Surgery, where an elimination of causative *S. aureus* and streptococci was demonstrated in the cefuroxime-treated group comprising 6836 operations [17]. The conclusion is that the injection technique, and the type and dose of antibiotic, provide effective prevention against relevant strains, although not infallibly [20]. Conversely and logically, cefuroxime-resistant strains became the predominant cause of POE once cefuroxime was instituted, causing POE in one out of 2750 cases, compared with one in 6600 in Period 1 (Table I). It should be noted that Period 2 is burdened with two epidemic POE outbreaks with five cases infected by Gram-negative bacteria, where cefuroxime could not be blamed *per se* [6]. Still, it is conceivable that the use of a highly concentrated and broad-acting antibiotic in the aqueous humour may favour the outgrowth of any present resistant bacterium if other competing contaminants are eradicated. In an analysis on organisms causing POE in Kaiser Permanente, California, 37–50% resistance to the given topical fluoroquinolone prophylaxis among CoNS was demonstrated, which may indicate a selection mechanism on the ocular surface when topical antibiotics are given pre-operatively [18]. The main concern is the emergence of enterococci as the most frequent isolate in Period 2. Enterococci are inherently resistant to cefuroxime and other cephalosporins, and like other streptococci, they are a virulent cause of POE [7,8,21–23]. The frequency of POE due to enterococci is low in the absence of prophylactic intracameral cefuroxime, in line with the present findings in Period 1 [15,16,18]. A higher rate has been reported from East Asia, but no information was provided about the prophylactic regimen [23], and it is not known if enterococcal infection is on the rise in European countries where intracameral cefuroxime is presently in use [24]. Enterococci are present in the conjunctiva in 2% of patients scheduled to undergo cataract surgery, according to a culture study from Spain including 8300 samples [25]. The authors demonstrated that diabetic patients were more prone to be colonized with enterococci. In the present study, as in the Swedish registry studies [7,8], it was not possible to single out diabetes or other patient characteristics that would signal an increased risk of an enterococcal infection. Interestingly, enterococci is well recognized as a general problem in nosocomial infections, and patients suffering from malignancies are particularly vulnerable [26]. Another decisive factor for the occurrence of enterococcal infections seems to be the use of cephalosporins in health care in general, identified 20 years ago in Spain and more recently in Denmark [27,28]. In Sweden, the use of intravenous cefuroxime for initial treatment of serious respiratory and upper urinary tract infections was commonplace in the 1980s. This practice went on until approximately 10 years ago, when Swedish microbiologists (www.mikrobiologi.net) warned against the use of cefuroxime, referring to its inferior performance to penicillins, cloxacillins or third-generation cephalosporins against relevant pathogens.

Whatever the relationship with widespread use of cefuroxime for general infection, the most recent data from the Swedish POE registry (manuscript in preparation) demonstrate that enterococci are still a leading cause of POE.

CoNS were the most common pathogenic organisms in Period 1, but were reduced significantly in Period 2. Meticillin-resistant CoNS were found occasionally, which was not unexpected as they are quite frequent in the conjunctiva [5,29,30]. From the limited material, these infections did not appear to be particularly virulent, as opposed to a report by the French Institutional Endophthalmitis Study Group [31].

S. aureus was reduced even more markedly than CoNS after the introduction of intracameral cefuroxime. The two detected strains were, in fact, sensitive to cefuroxime. In contrast, MRSA was not found in either period. Statistics from the Swedish Centre for Disease Control (www.folkhalsomyndigheten.se) provide clues as there were only 1478 cases, mostly carriers of the strain, in 2009 in a population of nine million; this is a low figure despite a considerable increase from the 35 reported cases in 1995.

Retrospective studies on surgical complications have limitations related to changes over time in operative techniques and indications. In this study, the periods differ in terms of surgical methods, with ECCE being prominent in Period 1. There is a possible bias generated by the larger incision in ECCE, which could lead to a higher rate of contamination relative to the small-incision phaco-emulsification procedure in use throughout Period 2, but the literature is contradictory in this respect [32–34]. An even more important issue is the incidence of capsule rupture, a strong determinant for POE [7,8] which is suspected to have been higher in Period 1 [32]. Data from the study hospital are not easily accessible to clarify this factor prior to 2002, when nationwide reporting of this intra-operative complication to the Swedish National Cataract Register was instituted [35]. Nonetheless, in a case–control investigation from the authors' clinic encompassing 1994–2000, thus bridging the shift in prophylaxis, non-use of cefuroxime emerged as the most important risk factor for POE in a multi-variate analysis [32]. In addition, an almost identical effect of intracameral cefuroxime on the POE rate demonstrated herein has been shown in other retrospective comparative studies [12,14,36], in the prospective randomized study of the European Society of Cataract and Refractive Surgery, and the Swedish prospective registry studies [7,8,10], supporting the validity of the present results.

In summary, intracameral cefuroxime not only achieves a reduction in the rate of endophthalmitis after cataract surgery, but also brings about a shift in pathogens from cefuroxime-sensitive to cefuroxime-resistant organisms.

Conflict of interest statement

None declared.

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