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A case-control study of post-operative endophthalmitis diagnosed at a Spanish hospital over a 13-year-period

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SUMMARY

A retrospective case-control study of patients who had undergone cataract extraction at a Spanish hospital over a 13-year period was conducted to identify the risk factors for developing post-operative endophthalmitis (POE). During the study period, the type of antibiotic prophylaxis was changed from subconjunctival gentamicin to the addition of both vancomycin and gentamicin to the irrigating solution. The overall incidence of POE was 0·19% (35 cases/18 287 operations). For the period prior to the change in antibiotic prophylaxis, the incidence rate of POE was 3·4 cases/1000 operations while in the latter period the incidence rate decreased to 0·34 cases/1000 operations. All patients who presented a virulent microorganism had a final visual acuity worse than 20/200. The only significant risk factor identified was the type of prophylaxis used (odds ratio 1·97, 95% confidence interval 0·94–4·14, $P = 0·07$). There were no significant differences between cases and controls although choice of surgeon approached significance.

Key words: Antibiotics, eye infections, prevention.

INTRODUCTION

Post-operative endophthalmitis (POE) is an infrequent, but serious complication associated with intraocular surgery [1, 2]. In the majority of cases, the source of the bacteria involved is the patient's own periocular flora, with a predominance of coagulase-negative staphylococci (CNS) [3–5]. The visual prognosis for such patients may be predicted from the visual acuity (VA) upon presentation and the virulence of the causal microorganism [2, 6].

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Strategies for reducing the incidence of POE include careful attention to pre-operative preparation of the surgical site with antiseptic agents such as povidone iodine (PI) [7] and the use of selected prophylactic antibiotics, a practice that remains controversial among ophthalmologists. The most commonly used prophylactic antibiotics are topical fluoroquinolones [8, 9], either subconjunctival injection of gentamicin [10] or intracameral injection of cephalosporins at the end of the surgery [1, 2, 10–13], and the addition of antibiotics such as vancomycin and/or gentamicin to the irrigating solution during surgery [14].

The aim of this study was to estimate the incidence of POE and the risk factors associated with its development after cataract extraction.

MATERIALS AND METHODS

Design

A retrospective, observational, matched case-control study was undertaken of patients who had undergone cataract extraction in the Department of Ophthalmology at La Mancha Centro General Hospital (MCGH), Spain, during the period 1996–2008. This matched design coupled with appropriate analysis, allowed for the control of confounding caused by the matching variables.

Patient selection and data extraction

Cases were patients with a clinical and/or microbiological diagnosis of POE who had been treated at MCGH. For controls two patients were matched to each case who underwent the same type of intraocular surgery at the same hospital and with the same prophylactic protocol within a week of their case's index date (on the same day if possible). Two controls were chosen for each case in order to allow the detection of odds ratios (ORs) $\geqslant 2$, with a power of 80% and an alpha risk of 5% [95% confidence interval (CI)].

Data were extracted independently by two observers from the patients' clinical histories and the database of the hospital microbiology laboratory. Variables related to endophthalmitis were start of infection (time), affected eye, sample sent to the microbiology laboratory, isolated microorganism, susceptibility to antimicrobials, treatment and administration routes, and visual prognosis. Independent variables were age, sex, underlying diseases [comorbidity scale of the American Society of Anesthesiologists (ASA)], duration of surgery, choice of surgeon, and prophylaxis regimen.

Risk indicators of surgical infection

Two indicators of risk were used. The National Nosocomial Infections Surveillance (NNIS) scale which assigns a score of between 0 and 3 to each patient in ascending order of risk with regard to the following variables: (i) type of surgery (0 points for clean or clean-contaminated surgery, 1 point for contaminated surgery), (ii) duration of surgery (0 points if the duration is below the 75th percentile, 1 point if above), and (iii) underlying patient risk (0 points for ASA I and II, 1 point for $\geqslant$ASA III).

The second scale, the Study on the Efficacy of Nosocomial Infection Control (SENIC), uses both patient and surgical data to assign a score of between 0 and 4 to each patient in order of increasing risk with regard to the following variables: (i) comorbidity (0 points if there are $\leqslant 2$ associated diagnoses, 1 point if there are >2 associated diagnoses), (ii) surgery type (0 points for clean or clean-contaminated surgery, 1 point for contaminated surgery), (iii) duration of operation (0 points if <2 h, 1 point if $\geqslant 2$ h), and (iv) site of surgery (1 point for abdominal surgery, 0 points for other locations).

Surgical technique

From 1996 to 1999, both phacoemulsification (Phaco) and extracapsular cataract extraction (ECCE) were routinely performed at our hospital. However, after 1999, Phaco virtually replaced ECCE. In fact, after that year only two ECCE procedures were performed, generally due to complications that arose during Phaco. From 1998 onward, hydrophobic acrylic intraocular lenses were used and all incisions were corneal. All the operations in our series were performed by 13 experienced ophthalmologists.

Protocol for outpatient surgery

Preparation of the site of surgery involved the instillation of 5% PI drops in the conjunctival sac with subsequent washing of the entire periocular area with a solution of 10% PI (or 0·5% chlorhexidine in allergic patients). The antibiotic prophylaxis used in our hospital varied over two main periods. In the first period, from January 1996 to April 2003, the protocol consisted of a single subconjunctival injection of 0·5 ml gentamicin (Gentamicin Braun® 80 mg/ml, B. Braun Medical, Spain) upon completion of surgery, while in the second period, from May 2003 to December 2008, a mixture of 5 mg vancomycin (Vancomycin Normon® EFG, Spain) and 4 mg gentamicin (B. Braun Medical) added to 500 ml balanced salt solution (BSS; Alcon Cusí, Spain) was used to irrigate the eye during surgery. In both periods, upon completion of surgery, patients were given eye drops with aminoglycosides and dexamethasone (Colircusí Gentadexa® or Tobradex®, Alcon Cusí) for 7 days, after which they continued with a corticosteroid for a further 4 weeks. All patients were examined by the attending ophthalmologist 1 day after surgery and again 1 month later unless complications arose.

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Diagnosis

Clinical diagnosis of endophthalmitis was based on decreased VA along with the degree of inflammation and fibrin in the anterior chamber between day 1 and week 6 after surgery and classified as acute infection or up to 1 year later as chronic infection. Intraocular samples (five aqueous humors and 35 vitreous humors) were taken from suspected endophthalmitis cases for microbiological analysis. Microbes were identified and antimicrobial susceptibility determined by standard methods.

Treatment

Intravitreal medications administered at the time of diagnosis included vancomycin, ceftazidime, and dexamethasone for all eyes. If the clinical course was unsatisfactory, intravitreal injections were repeated (two cases). Subsequent pars plana vitrectomy (PPV) was performed in 26 patients.

Analytical strategy

Descriptive phase. The cumulative incidence of endophthalmitis was calculated as the ratio between the number of detected cases and the number of patients operated on during the same period. For the bivariate analysis, the response variable (case/control) was related to each of the independent variables by constructing contingency tables. For each table we estimated the statistical significance (using either the χ^2 test or Fisher's exact test if the expected number of events was <5) and measured the magnitude of association as an OR with 95% CIs. For the multivariate analysis, all independent variables associated with the response variable with a significance of $P \leqslant 0{\cdot}20$ (according to the criteria of Maldonado & Greenland [15]) formed part of the multivariate models of conditional logistic regression. Statistical calculations were made using Stata v. 11.0 (StataCorp LP, USA), and EPIDAT v. 3.1 (OPS, Xunta de Galicia, Spain).

RESULTS

Of the 18 287 intraocular operations performed at our hospital, POE occurred in 35 cases, giving an incidence rate of 1·91 cases/1000 operations (95% CI 1·25–2·57 cases/1000 operations). To match the 35 cases, 70 controls were selected, two for each case. The median age of patients was 62 years (range 22–91 years), and the POE incidence was higher (62%) in men. The number of days from the initial surgical procedure to the time of endophthalmitis diagnosis ranged from 1 to 120 days (median 6 days).

Table 1. *Risk for surgical site infection according to the NNIS and SENIC scales*

	n		%	
Score	NNIS	SENIC	NNIS	SENIC
0	27	25	49·1	45·5
1	26	29	47·3	52·7
2	2	1	3·6	1·8
Total	55	55	100·0	100·0

NNIS, National Nosocomial Infections Surveillance; SENIC, Study on the Efficacy of Nosocomial Infection Control.

Post-operative infection risk factors

The majority (71·4%) of patients exhibited either ASA II or ASA III (ASA I 28·6%, ASA II 36·5%, ASA III 34·9%). Half of the patients had more than two diagnoses, ranging from no comorbidity (15·9%) to eight concomitant diseases. The surgical infection risk as measured by NNIS and SENIC indicators was <1 in 27 cases (49·1%) for the former and, <1 in 25 cases (45·5%) for the latter (Table 1).

The median length of surgery was 30 min (range 15–88 min), with one cataract extraction combined with keratoplasty. The most commonly used technique was sutureless clear corneal Phaco (80%). Eight patients (22·8%) developed intraoperative complications (Supplementary Table S1); of these, five (14·3% of the total) suffered posterior capsule rupture (PCR) with vitreous loss, so all of them underwent an intraoperative anterior vitrectomy, with three cases achieving a final VA of $\geqslant$20/40.

Antibiotic prophylaxis

For the period prior to the change in antibiotic prophylaxis (from subconjunctival injection of gentamicin to vancomycin and gentamicin in irrigation), the incidence rate of POE was 3·4 cases/1000 operations; this decreased in the latter period to 0·34 cases/1000 operations.

Microbiological analysis and clinical outcome

Twenty-four positive cultures were obtained from 35 cases (culture yield of 69%), with one mixed infection

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in which two microorganisms were identified. Data for each patient, such as the specific microorganism isolated and any underlying diseases are given in the Supplementary Table S1. Gram-positive bacteria (GPB) were predominant, with CNS being the most commonly isolated bacteria (48%), especially *Staphylococcus epidermidis* (36%). Seventy-five percent of eyes with CNS had a final VA of ⩾20/40, but in all cases in which a virulent microorganism was isolated (e.g. *Staphylococcus aureus*, streptoccci, or *Enterococcus faecalis*), the final VA achieved was <20/200. All GPB isolates were typical in their antimicrobial susceptibility profile (vancomycin susceptible, variable susceptibility to cefuroxime: 68%, ciprofloxacin: 80%, and gentamicin: 75%). All Gram-negative isolates were susceptible to ceftazidime, ciprofloxacin and aminoglycosides.

Overall, 13 (39%) patients achieved a final VA of ⩾20/40, but six (18%) patients presented a final VA worse than 20/200, including three eyes with no light perception and one evisceration.

Risk factors for POE

The distribution of risk factors in cases and controls showed no significant differences between groups, although the association with infection almost reached statistical significance for one of the 13 surgeons (Table 2). In the conditional multivariate analysis, the only factor associated with a higher risk for POE was not performing (or at least the absence of a record of performing) pre-operative prophylaxis (OR 1·97, 95% CI 0·94–4·14, $P=0·07$).

Table 2. *Bivariate analysis of the risk factors for post-operative endophthalmitis*

	Cases ($n=35$)	Controls ($n=70$)	P
Age (years)	66·9 ± 14·0	71·1 ± 11·4	0·20
Sex			0·89
Male	21 (60%)	43 (61·4%)	
Female	14 (40%)	27 (38·6%)	
Duration of operation (min)	48·7 ± 50·5	45·9 ± 35·4	0·75
ASA			0·24
I	6 (17·1%)	10 (14·3%)	
II	14 (40%)	36 (51·4%)	
III	15 (42·9%)	20 (28·6%)	
IV	0	4 (5·7%)	
NNIS			0·84
0	18 (51·4%)	40 (57·1%)	
1	15 (42·9%)	27 (38·6%)	
2	2 (5·7%)	3 (4·3%)	
SENIC			0·96
0	13 (37·1%)	24 (34·3%)	
1	21 (60%)	44 (62·9%)	
2	1 (2·9%)	2 (2·9%)	
Diabetes mellitus			0·58
No	28 (80%)	59 (84·3%)	
Yes	7 (20%)	11 (15·7%)	
COPD			
No	31 (88·6%)	61 (87·1%)	
Yes	4 (11·4%)	9 (12·9%)	
Povidone iodine*			0·68
No	17 (48·6%)	31 (44·3%)	
Yes	18 (51·4%)	39 (55·7%)	
Surgeon			
2	7 (15·6%)	9 (9·4%)	0·28
7	4 (8·9%)	2 (2·1%)	0·08
9	9 (20%)	12 (12·5%)	0·24

ASA, American Society of Anesthesiologists; NNIS, National Nosocomial Infections Surveillance; SENIC, Study on the Efficacy of Nosocomial Infection Control; COPD, chronic obstructive pulmonary disease.
* Not recorded in clinical histories.

DISCUSSION

We found that the incidence of POE could not be associated with the majority of risk factors for surgical site infection. Comorbidity and other indicators validated for various types of surgery, such as those included in the NNIS and SENIC indexes, were not related to the occurrence of endophthalmitis. Indeed, the only factors that could be associated with the incidence of this post-operative complication in our series were the prophylaxis used and surgical expertise.

The European Society of Refractive Cataract Surgery has observed that the risk of POE is twice as high among more experienced surgeons [13], which may be due to the fact that the latter tend to operate on patients with greater complications. By contrast, many studies indicate that PCR is one of the most important risk factors for the development of endophthalmitis and less experienced surgeons may be more likely to attend to such cases [16]. In our series, the ophthalmologist associated with the most cases of POE was an experienced surgeon.

A study published in 2012 by Tan *et al*. showed a significant decrease in the endophthalmitis rate when they changed from subconjunctival gentamicin to intracameral cefazolin [10]. Similarly, the majority of our POE cases occurred when subconjunctival

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gentamicin was used. However, while intracameral injection of either cefazolin or cefuroxime at the end of Phaco has proven effective in preventing POE [1, 2, 10–13], several studies point to the disadvantages of using the latter, including its allergenic or toxicity problems stemming from extemporaneous compounding [17, 18] and its ineffectiveness against enterococci, methicillin-resistant staphylococci and *Pseudomonas aeruginosa*. In our series, the overall resistance to cefuroxime was 32%, which for our hospital makes it inappropriate antibiotic prophylaxis against POE. For its part, cefazolin is a more effective antimicrobial for prevention of infections caused by GPB, with its use in recent years showing an associated incidence of POE ranging from 0·047% to 0·01% [10–12] and thus reducing the risk of endophthalmitis in one study by 88·7% [11]. However, it does not lower the risk of infection by Gram-negative bacteria (GNB).

Our prophylaxis regimen of adding vancomycin and gentamicin to the irrigating solution, recommended by Gills in the 1980s [14], led to a POE incidence rate of 0·034%, similar to that found by other authors using intracameral cephalosporins [1, 2, 12, 13]. The main disadvantages of prophylactic vancomycin are its toxicity, mostly due to dilution or dosage errors in BSS preparation [17], and the possible emergence of vancomycin-resistant enterococci [19]. However, use of prophylactic vancomycin in short surgical procedures does not provide the necessary selection pressure to promote resistance [20]. Furthermore, there are several therapeutic alternatives such as linezolid [8] and daptomycin [21], which offer better penetration than vancomycin to treat serious infections due to GPB. In our series, all isolated GPB and GNB were susceptible to vancomycin and gentamicin, respectively.

One of the main limitations of retrospective case-control studies is the increased risk of selection and information bias, especially in the selection of the controls. We therefore chose controls which were treated closest in time to the cases, thereby controlling those factors that might be associated with surgical technique, choice of surgeon, and the various prophylactic methods used. We can thus assume that such bias does not invalidate the associations observed. Nevertheless, we feel strongly that prospective multicentre studies assessing the efficacy of the principal prophylactic antimicrobials used in ophthalmology are necessary to establish the optimum prophylactic regimen and delivery route. In the USA, some authors have noted the effectiveness and safety of intracameral moxifloxacin in preventing POE, which has the added advantage of being available in a self-preserved formulation [22, 23] Despite the controversy surrounding the use of antibiotic prophylaxis in ophthalmology, our study supports the role of antibiotic prophylaxis in preventing endophthalmitis after intraocular surgery. Other risk factors commonly associated with POE, such as underlying diseases or duration of the intervention, did not appear to be relevant to the development of infection in our patients and likewise, surgical risk scores did not serve as useful predictors of endophthalmitis.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S095026881400034X.

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DECLARATION OF INTEREST

None.

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