Endophthalmitis is defined by an intraocular inflammation, due mainly to infection. Peri-ocular skin flora from the patient plays a significant role in causing the intraocular infection, and Staphylococcus epidermidis accounts for 81.9% of all cases of endophthalmitis.\(^1\)

Endophthalmitis infection is an infrequent but devastating consequence of cataract surgery; in fact, cataract surgery is the leading cause of endophthalmitis. Infection after cataract surgery leads to increased health costs\(^2\) and also causes devastating clinical consequences, even blindness. This has led to frequent medical lawsuits.\(^3\) Despite advances in microsurgical techniques, a recent population-based study reviewing Medicare claims in the US revealed that endophthalmitis following cataract surgery is becoming more prevalent.\(^4\) The incidence of endophthalmitis rose from 1.79 cases per 1,000 in 1994 to 2.49 cases per 1,000 in 2001 – an overall increase of 37%.

To date, the best approach to or surgical regimen for cataract surgery to reduce the risk of endophthalmitis remains unclear. The European Society of Cataract and Refractive Surgery (ESCRS) Endophthalmitis Study examined the impact of intracameral cefuroxime and topical levofloxacin on post-operative infection. This article outlines risk factors for endophthalmitis, summarises the ESCRs Endophthalmitis study and discusses the implications of the study results on the future of endophthalmitis prevention within the context of cataract surgery.

Risk Factors Identified Prior to the Study
Risk factors for endophthalmitis are largely the same in both Asian and Western populations.\(^5\) Two reports have noted that diabetes mellitus increases the likelihood of developing staphylococci.\(^6,7\) Diabetes causes alterations in immunity and consequently leaves sufferers with a higher susceptibility to developing an infection after surgery. In addition, visual prognosis after endophthalmitis treatment is poor in diabetic patients in comparison with non-diabetic patients. Systemic or topical immunosuppressant drugs also alter the immune response, leading to an increased risk of endophthalmitis.\(^8\) Patients on antimitabolites or corticosteroids also have a higher incidence of endophthalmitis.

Certain procedures and materials used in cataract surgery have also been found to alter the risk of endophthalmitis.\(^9,10\) One study has suggested that the implantation of a heparinised intraocular lens (IOL) and the creation of a tight seal may protect the patient from infection.\(^10\) The type of IOL material and the location of the incision were examined in 5,797 small-incision cataract patients at Toyama Medical and Pharmaceutical University Hospital from March 1998 to March 2001.\(^9\) The results suggested that temporal corneal incisions may lead to an increased risk of endophthalmitis. Lens material had no effect on risk of endophthalmitis.

Other risk factors identified include infectious respiratory or skin agents from surgeons or other healthcare personnel present in the operating room (OR) coming into contact with the patient’s eye.\(^10\) In addition, the cleanliness of the OR air affects the incidence of endophthalmitis.\(^10\) Finally, the longer the duration of surgery, the higher the infection rates, most likely due to increased exposure of the eye.\(^11\)

Prior to the ESCRs Endophthalmitis Study, there were no relevant scientific data examining the most effective antibiotic for preventing endophthalmitis following cataract surgery.

Study Rationale
Prior to the ESCRs Endophthalmitis Study, there were no relevant scientific data examining the most effective antibiotic for preventing endophthalmitis following cataract surgery. In 2003, the ESCRs initiated a Europe-wide study, which included 24 hospitals across nine EU countries. The study included four treatment arms. All groups were given povidone–iodine 5% pre-surgery and drops of levofloxacin every six hours for six days after surgery (povidone–iodine was given universally as it is the only prophylaxis with evidence-based efficacy).\(^12\) The variables in the study were 1mg cefuroxime injection into the anterior chamber immediately after surgery, and pre- and post-operative levofloxacin drops – one hour and 30 minutes before surgery, and three drops at five-minute intervals after surgery. The four study groups were as follows:

- Group A was the control group, which received no topical levofloxacin or intracameral cefuroxime;
- Group B did not receive topical levofloxacin, but was intracameral injected with cefuroxime;
- Group C was given the additional topical levofloxacin and placebo injections; and
- Group D was the double-positive group and received both cefuroxime and levofloxacin.\(^13\)

Cefuroxime was the intracameral antibiotic of choice used in the study. It was administered in an off-label preparation that had
previously been proved to be effective and safe in more than 40,000 patients in a Swedish study conducted between 1999 and 2001.14,15 Cefuroxime is effective against the majority of bacteria that cause endophthalmitis.16 Additionally, the effects of topical levofloxacin – a third-generation fluoroquinolone – were examined in the study. Levofloxacin was selected because of its enhanced antibacterial activity over ciprofloxacin and ofloxacin and because it is well absorbed into the anterior chamber.17 The study was essentially designed to test the potential prophylactic effects of intracameral cefuroxime in the presence or absence of topical levofloxacin on post-operative endophthalmitis after cataract surgery. Secondary to this, the study aimed to provide an accurate estimate of the rate of endophthalmitis and to identify any specific risk factors.

The study planned to reach 35,000 participants, which would have given each of the four planned treatment arms 8,750 participants. However, recruitment into the study was terminated early – on 13 January 2006 – as the mentors of the trial noted a significant positive trend with the use of intracameral antibiotics.18 At this stage a total of 15,971 patients had been recruited. The mean age of the participants was 74 years. The physicians used an IOL of their preference.

Cefuroxime and Levofloxacin Results

Suspected cases of endophthalmitis in the study were confirmed using cultures, Gram-stain testing and polymerase chain reaction (PCR). In Groups B and D, which were both treated with intracameral cefuroxime, a total of five presumed cases and three proven cases of endophthalmitis were reported. In comparison, in the groups that were not administered cefuroxime there were 23 presumed cases and 16 proven cases of endophthalmitis. These results demonstrate that patients receiving cefuroxime benefit from an almost five-fold reduced risk of developing endophthalmitis.18

The highest rate of endophthalmitis – 0.38% – was seen in Group A, which received no pre-operative therapeutics.14 The use of levofloxacin alone reduced the rate of infection from 0.30% to 0.33%, but this was not statistically significant. Group D, which received both levofloxacin and cefuroxime, had the lowest rate of endophthalmitis, with only two presumed cases – a prevalence rate of 0.05%. The use of both topical levofloxacin and intracameral cefuroxime did not appear to have a significant synergistic advantage and decreased the rate of endophthalmitis by only 0.03%.

In the proven cases of endophthalmitis, there were 11 cases where the infective agent was identified as staphylococci, eight cases of streptococci, two cases of Propionibacterium acnes, one complex of salmonella, Escherichia coli and E. shigella and, finally, one case of Gemella haemolytica.14 Of the 11 cases of staphylococci, only three occurred in the cefuroxime-treated groups. The visual outcome of these patients ranged from 20/20 to 20/80. None of the patients was pronounced legally blind. All eight cases of streptococci occurred in the non-injected groups; their visual acuity ranged from 20/20 to no light perception. Five patients in this group were classed as legally blind after infection. This is a powerful result and shows that cefuroxime provides protection from streptococci, which are the cause of the most severe cases of infection and often lead to blindness.19
Cataracts

Risk Factors Identified by the Study

In the ESCRs Endophthalmitis Study, the type of IOL used was a free choice decided by the surgeon. This allowed the study co-ordinators to determine the risk factors of using different materials for the IOL. Interestingly, they discovered that silicone IOLs increased the risk of presumed endophthalmitis by over three-fold and proven endophthalmitis by approximately six-fold.18 Acrylic lenses, according to this study, are by far the least risky material and may reduce the risk of developing infection. Additionally, clear corneal incisions increased the likelihood of endophthalmitis by almost six-fold in comparison with a scleral tunnel incision. However, only two of the 23 centres tested in the study used the scleral tunnel technique; therefore, the difference could result appears to be significant.

Implications of the Study Results

The magnitude of the ESCRs Endophthalmitis Study is extremely impressive and the results are highly significant at a clinical level. They suggest that the application of povidone–iodine to the skin surrounding the eye and to the eye itself before surgery combined with a post-operative intracameral injection of cefuroxime is the best way to prevent infection.12 According to the study results, cefuroxime could reduce the risk of endophthalmitis to four cases per 10,000 each year from the current prevalence of 2.49 cases per 1,000. In total, this would reduce the number of cases in Europe by 60,000 per year.19

To complete the study using the 1mg dose of cefuroxime, an exemption was required to be obtained; this expired when the study stopped recruiting patients. Currently, cefuroxime is not available from manufacturers in the dose used in the study. Therefore, if it were used in a clinical setting, physicians would be required to undertake the dilution themselves. This raises concerns that errors in dilution would occur upon administration. In the past, the off-label use of other intracameral antibiotics – such as vancomycin – has led to devastating effects of toxic anterior segment syndrome (TASS).22 However, the dilution of cefuroxime is a relatively simple technique and should not cause a problem if an appropriate drug-dilution mechanism is set up. The method of dilution in this study was the same as in the Swedish study, and it worked well in both.

It could be argued that an alternative intracameral agent or a different drug-delivery mechanism is superior to cefuroxime in terms of reducing infection post-cataract surgery. However, extensive clinical trials and safety tests would need to be completed to prove any superiority; this may be superfluous given that cefuroxime can achieve a 0.05% rate of endophthalmitis.

It must also be noted that cefuroxime is not currently licensed in Europe for intracameral application. Physicians can, however, make the judgement to use it off-label at their own risk, and are doing so in increasing numbers. In addition, steps are being taken to get cefuroxime on to the market in the correct dose for use in cataract patients in order to protect them from the devastating consequences of endophthalmitis.

Summary

Endophthalmitis can be a devastating effect of cataract surgery, leading to enormous healthcare costs. Recently, endophthalmitis rates have been on the rise despite improvements to surgical techniques. The ESCRs Endophthalmitis Study set out to demonstrate the potential prophylactic effects of intracameral cefuroxime in the presence or absence of topical levofloxacin. The results show that cefuroxime reduces endophthalmitis rates from 0.38 to 0.05%. Secondary observations of the study identify two distinct risk factors: first, the use of silicone IOLs increases the risk of infection three-fold; and second, the use of clear corneal incisions instead of the scleral tunnel technique also increases the risk of endophthalmitis.