ESCRLS ENDOPHTHALMITIS STUDY UPDATE

Additional studies confirm intracameral cefuroxime reduces incidence of endophthalmitis after cataract surgery

by Roibeard O'hEineachain

Since Ignaz Semmelweis first proposed that obstetricians wash their hands before attending to women in childbirth, hygiene protocols in a clinical setting have been a recurring source of controversy. In cataract surgery, there is now general agreement regarding sterile technique, but somewhat less of a consensus regarding endophthalmitis prophylaxis. However, following publication of the ESCRS Endophthalmitis Study in 2006 an increasing number of surgeons, particularly in Western Europe, have adopted the practice of injecting antibiotics intracameraly at the conclusion of surgery.

The ESCRS initiated the ESCRS Endophthalmitis Prophylaxis study in 2003. The study’s investigators, chaired by Peter Barry FRCs, Dublin Ireland, originally designed the trial to include 35,000 cataract patients who were to be randomised to receive intracameral cefuroxime or no intracameral antibiotic. However, in a dramatic turn of events, by the time 16,000 patients had been recruited the data showed that those receiving the intracameral antibiotic had a five-fold reduction in endophthalmitis.

Following the publication of the ESCRS study, the ESCRS adopted new guidelines for cataract surgery advising the use of intracameral cefuroxime. The American Academy of Ophthalmology (AAO), for their part, also state in their preferred practice guidelines for cataract surgery that “only intracameral antibiotics at the end of the case guarantees suprathreshold antibiotic levels for an extended period of time”.

The evidence The inspiration for the ESCRS Endophthalmitis Study came from a report on the results achieved with intracameral cefuroxime in Sweden, as reported by Per Montan MD of St Erik’s Eye Hospital in Stockholm, Sweden in the June 2002 issue of the Journal of Cataract and Refractive Surgery.

“The Swedish registry data provided strong evidence of its efficacy and the safety but it was nonetheless anecdotal in statistical terms. So the ESCRS study aimed at proving the efficacy and safety of cefuroxime in a randomised trial,” Dr Barry told EuroTimes in an interview.

A survey of ASCRS and ESCRS members which David Leaming MD carried out in 2011 showed that 60 per cent of ESCRS respondents used intracameral antibiotics, compared to only 20 per cent of American respondents.

The Swedish retrospective study showed that the incidence of endophthalmitis occurring in patients included in the Swedish Cataract registry fell from 0.48 per cent to 0.06 per cent after the Swedish ophthalmologists adopted the use of intracameral cefuroxime in 1996. That is, from 1990 through 1995 there were 18 cases of postoperative endophthalmitis among 3,742 eyes that underwent cataract procedures, compared to only 11 cases in 12,245 procedures performed during the years 1996 to 2000 (p <0.001). The Swedish Registry patients included virtually all cataract procedures performed during the years under study.

The use of intracameral antibiotics by Swedish cataract surgeons was in turn inspired by a study by Howard Gimbel MD, who reported achieving a very low incidence of endophthalmitis after he adopted the use of intracameral

Cataract surgeons in Sweden chose to use cefuroxime instead of vancomycin, because it is active against most of the bacteria that had caused endophthalmitis in cataract patients in the Swedish Cataract Registry during previous years and because of a general feeling they had that vancomycin should be reserved for treatment rather than prophylaxis.

Cefuroxime is a second-generation cephalosporin antibiotic. It was FDA-approved for oral and parenteral use in 1983. It is effective against most staphylococcus and streptococcus species, many Gram-negative organisms, p. acne and the diptheroids. Its use in endophthalmitis prophylaxis has been solely on an off-label basis until last year, when a new single-dose preparation of cefuroxime (Aprokom®, Thea) for intracameral use received approval in several European countries.

Study mirrors registry results. The ESCRS Endophthalmitis Study adopted the Swedish protocol for their randomised controlled study. They randomised patients into four groups, two groups received intracameral cefuroxime and two groups received no intracameral antibiotics. As an additional measure, one group each of the intracameral antibiotic and no intracameral antibiotic also received postoperative topical treatment with the third-generation antibiotic levofloxacin.

The trial commenced on September 15, 2003 in 24 centres in eight European countries. It was planned to include a total of 35,000 cataract patients undergoing phaco cataract surgery. However, the ESCRS Endophthalmitis Study’s investigators terminated the trial early, on January 13, 2006, when they detected a trend in favour of intracameral antibiotics. The registry findings showed that during the years 2005 to 2010 the rate of endophthalmitis following cataract surgery among 464,996 operated eyes was only 0.029 per cent. That compares to an incidence of 0.048 per cent during the years 2002 through 2004 (P<.001). (Friling et al, Journal of Cataract & Refractive Surgery 2013: 39:15-21.)

“That has probably been due to improvements in surgical technique, such as smaller incisions, shorter operating times and the fact that patients in Sweden now undergo cataract surgery when they are healthier and at a younger age than was previously the case,” said Anders Behndig MD, Umeå University, Umeå, Sweden.

Gram-positive species accounted for 70 per cent of cases. The numbers of endophthalmitis cases caused by strains resistant to intracameral had not increased in Sweden over the years although such strains now account for a higher proportion of cases.

“The resistant bacteria we see in Sweden have been resistant all along and we don’t appear to have really induced any resistance to bacteria by using the antibiotic prophylaxis,” Dr Behndig said.

He noted that in a few rare instances patients did not receive intracameral cefuroxime, generally for fear of an allergic reaction. In those cases the rate of endophthalmitis was seven times higher.

Centres outside of Sweden which participated in or adopted the protocol of the ESCRS Endophthalmitis Study have also reported a sustained reduction in the incidence of endophthalmitis.

A study conducted at a University Hospital in Madrid, Spain showed that among 13,652 patients who underwent cataract surgery from 1999 to December 2008, the rate of endophthalmitis fell from 0.59 per cent during the years 1999 to 2005 to 0.043 per cent after surgeons at the centre adopted the routine use of cefuroxime in 2006. (Garcia-Sanchez et al, J Cataract, Refract Surg 2010; 36: 203-207.)

Jorge Alio MD, PhD, Alicante Spain, who participated in the ESCRS Endophthalmitis Study said that his centre has continued to have a low incidence of endophthalmitis following the study’s completion.

“Intracameral cefuroxime has been proven in post-cataract patients and is shown to reduce the incidence of endophthalmitis five-fold and even ten-fold in other studies and more than 10 studies support the use of cefuroxime. No randomised clinical study has been published that could demonstrate the efficacy of any other antibiotic in preventing endophthalmitis,” Dr Alio said.

The moxifloxacin alternative. On the other hand, many cataract surgeons have chosen not to adopt the prophylactic use of intracameral cefuroxime. They include some who accept the findings of the ESCRS Endophthalmitis Study but maintain that other agents might be more suitable.

“I think that the ESCRS Endophthalmitis Study has made a revolutionary change not only in my practice, but also many practices in India,” Keiki Mehta MD, Cullen Eye Institute, Baylor College of Medicine, Texas, US.

However, he noted that he has been using the fourth-generation fluoroquinolone, moxifloxacin, rather than cefuroxime, as his intracameral antibiotic. He added that he prefers the agent to cefuroxime because it has a longer half-life and unlike cefuroxime, intracameral administration achieves levels that are effective against MRSA, if only for a few hours.

He noted that moxifloxacin is also easier to use than cefuroxime and possibly less risky as well. Since it can be used without dilution its use does not entail any risk of
The future of endophthalmitis prophylaxis

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“Prior to the ESCRs Endophthalmitis Study, I had been using intracameral vancomycin based on Howard Gimbel’s reported outcomes in more than 20,000 cases. Because of the success and safety of using 1mg of vancomycin in 0.1ml for my own patients, I have continued this practice ever since,” said ASCRS president, David Chang MD.

“We have the increasing threat of methicillin resistant staph aureus (MRSA) in the US, and vancomycin is one of the few agents that multi-drug resistant organisms are sensitive to. Unlike with systemic vancomycin administration, I do not believe that direct injection of 0.2ml into the sterile anterior chamber poses any risk of inducing vancomycin drug resistance. Finally, an important British study has validated the pharmacokinetic rationale of using a single intracameral injection of 1mg of vancomycin.”

He noted that in a survey of ASCRS members conducted in 2007, approximately one year after the ESCRs Endophthalmitis Study, around three-fourths of the more than 1,300 respondents were still not injecting intracameral antibiotics. However, 82% per cent said that they would do so if a reasonably priced commercial preparation were available.

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He noted that the ESCRs study did not compare intracameral cefuroxime to the most common American practice pattern for endophthalmitis prophylaxis, namely, the prophylactic use of pre- and postoperative topical 4th generation fluoroquinolone antibiotics. In addition, the ASCRS survey indicated that the lack of a commercially available antibiotic for intracameral injection in the US raised significant concerns over the risks of mixing “homemade” antibiotic solutions.

“In light of these perceived risks, I suspect that many American surgeons won’t switch unless IC antibiotics are shown to be superior to what they are already doing,” Dr Chang said.

In some parts of the world, previously established protocols stand in the way of wider use of intracameral antibiotics.

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certainly increase the adoption of intracameral antibiotics by cataract surgeons in the United States. “Any delay in the availability of a product such as this in the US is inexcusable,” he added.

Keiki Mehta MD in India told EuroTimes that he has had a similar experience with moxifloxacin.

“The ESCRs Endophthalmitis Study has made a revolutionary change not only in my practice, but also many practices in India. The use of intracameral moxifloxacin has become routine,” he said in an interview.

He noted that he and his associates at his centre have been using intracameral moxifloxacin for close to 16 months and during that time they have encountered only one case of endophthalmitis out of around 6,000 cases. In previous years they had about two cases per year out of 4,500 cases of cataract surgery, he said.

“The changes are most dramatic in eye camps where infection was previously quite a problem but now that we use moxifloxacin the incidence has plummeted to almost zero,” he added.

With regard to cefuroxime, Dr Mehta expressed concern that the agent might leak into the vitreous, particularly in older eyes where the zonules may have lost some of their integrity. The effect of cefuroxime on the retina has yet to be fully elucidated, he said. Moxifloxacin, on the other hand has a proven track record of retinal safety, since it is frequently used intravitreally for the treatment of endophthalmitis.

However, Dr Behndig told EuroTimes that Swedish cataract surgeons currently use cefuroxime in eyes with posterior capsule ruptures and it has so far proved completely safe in such cases.

Vancocymin as first resort

Some cataract surgeons meanwhile have adhered to the use of intracameral vancomycin as originally suggested by Howard Gimbel MD. Vancomycin, a glycopeptides antibiotic, is generally regarded as an antibiotic of last resort.

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dilution errors. On the other hand, like cefuroxime, until very recently, and vancomycin, it is not available in single dose units and must be prepared in batches.

“The issue in the United States is the lack of availability of antibiotics that are premixed at the dosages that are required for intracameral use, particularly antibiotics such as cefuroxime and vancomycin. That means you have to rely on a compounding pharmacy or your own pharmacy in order to prepare these intracameral injections,” Dr Koch noted.

He added that the availability of an approved product such as Aprokam, the new cefuroxime preparation, would...