A Review of Antibiotic Prophylaxis for Post-operative Endophthalmitis

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Abstract

The purpose of this review is to summarise all available evidence regarding antibiotic prophylaxis for post cataract surgery endophthalmitis as some prophylactic measures add significantly to the cost of surgery, are routinely used and yet their benefit to cataract patients has not been proven. Use of Povidone Iodine before starting the surgery is one of the most effective means of reducing the incidence of postoperative endophthalmitis. Intracameral cefuroxime is another important measure advocated by many studies. Intracameral moxifloxacin may be considered as an alternative to cefuroxime. Although pre and post-operative systemic or topical antibiotics, subconjunctival antibiotics and antibiotics in the irrigating solution have not been proven to decrease post-operative endophthalmitis, they have not been shown to be detrimental and hence surgeons may consider their use according to personal preferences and a cost-benefit analysis of their healthcare system.

Keywords: prophylaxis, complication, endophthalmitis, cataract surgery, antibiotics

Cataract extraction is by a wide margin the most common intraocular surgery performed worldwide, with more than 5.1 million patients undergoing cataract surgery annually in India alone. Postoperative endophthalmitis is a rare but dreaded complication of cataract surgery. In most cases, this complication is unforeseeable and with the potential to cause a devastating visual outcome. The reported rates of post cataract surgery endophthalmitis have reduced from 0.3-0.5% in the 1990s to 0.04-0.41% in the present day scenario.2,4 The patient’s own ocular surface flora is the most common source of infection following cataract surgery with contaminated surgical instruments and an unsterile operating room environment contributing to the remaining cases.5 The most commonly implicated organisms causing endophthalmitis worldwide are coagulase negative staphylococci (33-77%), staphylococcus aureus (10-21%), streptococci (9-19%), gram negative bacteria including pseudomonas aeruginosa (6-22%) and fungi (up to 8%).3 However in India, rates of gram negative infections have been seen to be as high as 53% and of fungal infections up to 16%.6 The antibiotics that have been used for endophthalmitis prophylaxis include cephalosporins, fluoroquinolones, vancomycin and aminoglycosides. Cefazolin is a first generation cephalosporin with good activity against gram positive organisms while cefuroxime is a second generation cephalosporin which also has activity against some gram negative bacteria.4 Ciprofloxacin, ofloxacin and levofloxacin are second generation fluoroquinolones that are mainly active against gram negative bacteria. Moxifloxacin and gatifloxacin are fourth generation fluoroquinolones with excellent activity against gram positive and negative bacteria.7 Vancomycin is used mainly against gram positive bacteria resistant to the above drugs, including methicillin resistant staphylococcus aureus (MRSA).8 Cataract surgeons must continue to operate in a sterile, efficient operating room with proper aseptic techniques. Some prophylactic measures that add significantly to the cost of surgery, are routinely used and yet their benefit to cataract patients has not been proven. Also, new evidence continues to reveal a lot of promising strategies to prevent post-operative endophthalmitis. Cataract surgery is already a major social and economic burden in developing countries.9,10 Therefore, to keep cataract surgery safe, cost effective, and affordable on a global scale, it is important to measure outcomes and to periodically review and revise operating protocols based on the best available evidence. The existing controversies in prophylaxis of endophthalmitis include the role of topical antibiotics, the role of intracameral antibiotics, the choice of intracameral antibiotic and, the role of subconjunctival and systemic antibiotics. The purpose of this review is to summarise all available evidence regarding antibiotic prophylaxis for post cataract surgery endophthalmitis.

Pre-operative Measures

Topical fluoroquinolones:
The rationale behind their use is that antibiotic levels exceeding the minimal inhibitory concentrations (MIC) of bacteria in the aqueous humour would prevent infection.11 Unfortunately, there is no clear answer to whether topical antibiotics should be started pre-operatively. As per the American Society of Cataract and Refractive Surgery (ASCRS) survey of 7767 members carried out in August 2014, 85% of ASCRS surgeons initiated topical antibiotics preoperatively, with 48% starting antibiotics 3 days before surgery, 32% starting antibiotics one day prior to surgery, and 20 % on the day of the surgery.12 A retrospective analysis of the case records of 42426 eyes of all patients who had cataract surgery at Aravind Eye Hospital, Pondicherry, during January 2007 to August 2008
was performed. On the day before surgery, patients received ciprofloxacin 0.3% eye drops 6 to 8 times in the operative eye. Systemic antibiotic agents were not used. With the use of only topical fluoroquinolones, without intracameral or subconjunctival antibiotic agents, the overall 0.09% incidence of presumed infectious endophthalmitis was comparable to that in the prospective multicentre multinational ESCRs study subgroup receiving intracameral antibiotics (0.075%).\textsuperscript{13}

Ta et al concluded that a 3 day pre-treatment with topical ofloxacin reduced bacterial conjunctival flora as compared to treatment starting 1 hour prior to surgery.\textsuperscript{14}

Data from the European Society of Cataract and Refractive Surgeons (ESCRs) group illustrated that the placebo group demonstrated an increase in the risk of laboratory confirmed endophthalmitis compared to the group receiving two drops 0.5% levofloxacin 1 hour prior to cataract surgery. However, this finding was not statistically significant.\textsuperscript{13,15} In the ESCRs postoperative endophthalmitis study designed in 2002, levofloxacin was selected as the antibiotic for use in the topical preoperative prophylaxis arm for all patients and for prevention of postoperative infection. This was based on data demonstrating that it achieved anterior chamber penetration and offered broader spectrum coverage than the earlier generation fluoroquinolones (ciprofloxacin and ofloxacin) that were available for ophthalmic use at that time. The study however did not assess the role of pre-operative endophthalmitis prophylaxis using topical levofloxacin.\textsuperscript{15}

The fourth-generation fluoroquinolones offer several advantages over levofloxacin that would theoretically favour their use in endophthalmitis prophylaxis.\textsuperscript{16} The benefits include a broader spectrum of antibacterial activity and greater potency against gram-positive pathogens, superior ocular penetration characteristics, and reduced susceptibility to resistance development. Moxifloxacin may be regarded as a superior choice over gatifloxacin based on differences in potency and penetration, which are the two major determinants of antibiotic efficacy. In addition, unlike gatifloxacin, moxifloxacin does not contain the preservative benzalkonium chloride.\textsuperscript{17} Statistical comparisons of antibacterial activity based on MIC values showed moxifloxacin was significantly more potent than levofloxacin and the second-generation fluoroquinolones against fluoroquinolone-resistant coagulase-negative staphylococci.\textsuperscript{17} Similar results favouring moxifloxacin were reported in a study testing the in vitro susceptibility of 77 bacterial endophthalmitis isolates to the ophthalmic fluoroquinolones.\textsuperscript{18} In addition, the ocular concentrations of moxifloxacin achieved were consistently much higher than those occurring with topically instilled gatifloxacin, ciprofloxacin, ofloxacin or levofloxacin ophthalmic solutions.\textsuperscript{19–21}

In 2008, Vasavada et al compared 2 moxifloxacin regimens for pre-operative cataract prophylaxis. Group A had moxifloxacin instilled 4 times a day 1 day before surgery plus 1 drop 2 hours before surgery and Group B had moxifloxacin instilled 2 hours before surgery and then every 15 minutes for 1 hour. Both dosing regimens produced substantially higher aqueous concentrations than the known minimum inhibitory concentration for Staphylococcus epidermidis. Group B achieved significantly higher aqueous concentrations than Group A.\textsuperscript{22} In addition, both regimens were also found to reduce the amount of conjunctival bacterial flora.\textsuperscript{23} Unfortunately, this was not correlated to endophthalmitis rates but the authors hypothesised that the above regimens would confer a lower endophthalmitis complication rate post-operatively.

A systematic review by Ciulla et al concluded the efficacy of preoperative topical antibiotic prophylaxis was not yet scientifically proven.\textsuperscript{24} The ESCRs 2007 guidelines cite preoperative topical antibiotic prophylaxis as an option to consider,\textsuperscript{25} while the French 2011 guidelines do not recommend it.\textsuperscript{26}

Systemic Antibiotics:
Schmitz et al surveyed more than 300000 eyes undergoing cataract surgeries and noted that addition of systemic antibiotics did not result in a significantly lower rate of post-operative endophthalmitis.\textsuperscript{27} In general, the use of oral or systemic antibiotics as prophylaxis for endophthalmitis is controversial and not recommended.\textsuperscript{28}

Peri-operative Measures

Povidone Iodine:
It is believed that the source of bacteria causing endophthalmitis is usually the patient’s own microbial flora from the conjunctiva, eyelids and nose.\textsuperscript{29,30} Also it is reasonable to assume that since a certain number of bacteria would be required to produce endophthalmitis, decreasing the hosts microbial flora would reduce the incidence of endophthalmitis.\textsuperscript{31}

In a study conducted in Aravind Eye Hospital, Pondicherry, the incidence of endophthalmitis was 38 in 42426 cataract surgeries performed (0.09%). The protocol used at the above mentioned centre was pericocular scrubbing with 10% povidone iodine 1 day prior to surgery and then again on table just before commencement of surgery. 5% and 10% povidone iodine was also instilled in the conjunctival sac before starting the procedure and at the end of it respectively. No antibiotics were used in the irrigating solution, as direct intracameral injections or subconjunctivally.\textsuperscript{1} The rate of endophthalmitis achieved (0.09%) was comparable to that seen in developed countries.\textsuperscript{32,33} Hosseini et al concluded that using povidone iodine 5% solution for 15 minutes or 10% for 5 minutes can prevent the growth of most post cataract surgery endophthalmitis bacterial isolates in vitro.\textsuperscript{34} Ciulla et al in an evidence-based review of the literature on endophthalmitis prophylaxis, concluded that preoperative povidone–iodine prophylaxis was the single most effective means for reducing the risk for postoperative endophthalmitis.\textsuperscript{24}

Wykoff et al in a study from 2002 to 2009 used povidone iodine (5%) and achieved a lower rate of endophthalmitis (0.025%).\textsuperscript{35} Nentwich et al studied the incidence of endophthalmitis from 1990 to 2009 at a single academic institution in Munich. With the use of 10% pre-operative
betadine scrubs and topical application of 1% povidone iodine 1 minute prior to surgery, the endophthalmitis rate was 0.170%. The rate of endophthalmitis fell to 0.065% when in the above regimen, instead of topical drops; irrigation of the fornices with 1% povidone iodine was done 1 minute before surgery. No intracameral antibiotics were used. These rates are comparable to the group that received intracameral cefuroxime in the ESCRS study. The above two studies thus found reduced incidence of endophthalmitis with increasing volumes and concentrations of povidone iodine. This is in accordance with studies that have used reduced conjunctival bacterial load as a surrogate marker for reduced post-operative endophthalmitis.

**Antibiotics in the irrigating solution**

Sobaci et al studied the outcomes of more than 600 patients who underwent cataract surgery with or without antibiotics (vancomycin and gentamycin) in the irrigating solution. No cases of endophthalmitis were seen in the antibiotic group with 2 cases (0.62%) in the plain irrigating fluid group. Studies have also shown that switching from plain BSS to vancomycin/BSS for irrigation maintains the vancomycin concentration greater than the MIC for 6 hours leading to effective endophthalmitis prophylaxis. Mixing vancomycin in the irrigating solution also dilutes its concentration and minimizes the risk of toxic anterior segment syndrome due to toxins, contaminants or formulation errors as compared to direct intracameral injections.

Schelonka and SaBell studied more than 57000 patients who underwent cataract surgery with 20mcg/ml vancomycin in the irrigating solution. They found a significant decrease (p=0.0015) in the rate of endophthalmitis with the use of vancomycin in the irrigating solution as compared to balanced salt solution (BSS) without vancomycin. However, as per the 2014 ASCRS survey of more than 7600 members, of the 90% surgeons using peri-operative antibiotics, only 14% used them in the irrigating solution with the remaining preferring the direct intracameral route. This shows a decreasing trend of the use of antibiotics in the irrigating solution which was 48% in the 2007 ASCRS survey.

**Intracameral antibiotics**

Montan et al found a low rate of endophthalmitis (0.06%) in more than 32000 patients with the use of intracameral cefuroxime (1mg in 0.1ml). A similar study from Sweden of more than 1.5 lakh patients showed the rate of endophthalmitis in patients receiving intracameral cefuroxime to be 0.053%. The ESCRS Endophthalmitis Study Group recruited more than 16000 patients undergoing cataract surgery from 2003 to 2006 and divided them into 4 groups: no perioperative antibiotics, perioperative topical levofloxacin, intracameral cefuroxime and both topical levofloxacin and intracameral cefuroxime. The results showed that patients not receiving intracameral cefuroxime were almost 5 times more likely to experience endophthalmitis as compared to patients receiving intracameral cefuroxime. The rates of endophthalmitis were 0.345% for the patients receiving no perioperative antibiotics versus 0.062 % for the patients receiving intracameral cefuroxime (1mg in 0.1ml). Shorstein et al evaluated 16264 consecutive phacoemulsification surgeries out of which 78% received a direct intracameral injection (cefuroxime in 84%, moxifloxacin in 15% and vancomycin in 1%) at the end of the surgery. The patients who received intracameral antibiotics were found to have a 13 fold lower rate of infection as compared to the patients who did not receive intracameral antibiotics.

Yu-Wai-Man et al carried out a retrospective study of more than 36000 patients who underwent cataract surgery to compare the rates of endophthalmitis between subconjunctival (50mg in 0.5ml) versus intracameral (1mg in 0.1ml) cefuroxime prophylaxis. The incidence of endophthalmitis was lower in patients who had received intracameral cefuroxime (0.046%) than in those who had received subconjunctival cefuroxime (0.139%), and this difference was statistically significant (p=0.0068).

A 10 year prospective study in Spain of over 13000 patients showed that the rate of endophthalmitis was 0.043% with intracameral cefuroxime as compared to 0.59% without it. A French study of more than 5000 patients undergoing cataract surgery found the rate of endophthalmitis in patients receiving intracameral cefuroxime (1mg in 0.1ml) to be 0.044% as compared to 1.238% in patients not receiving the drug. Similar results have been obtained in studies using intracameral cefazolin (1mg or 2.25mg per 0.1ml) at the end of cataract surgery.

An eleven year study in more than 50000 Asian patients by Tan et al reported a decrease in the rate of endophthalmitis from 0.064% to 0.010% after the addition of 1mg in 0.1ml intracameral cefazolin. It has been shown that using intracameral cefuroxime prevents 1 case of endophthalmitis for every 182 patients treated, thus providing a very favourable outcome in terms of the healthcare budget.

Although the use of intracameral cefuroxime has become a standard of care in the European countries, it is far from fully recognized worldwide. Outside Europe, only 2 studies (USA and South Africa) have reported significantly lower rates of postoperative endophthalmitis with the use of prophylactic intracameral cefuroxime. A prospective study of more than 15000 patients undergoing cataract surgery was carried out in a tertiary eye care centre in India. The aim of the study was to find out if the addition of intracameral cefuroxime to the existing endophthalmitis prophylaxis protocol resulted in any additional benefit. The study concluded that although the addition of intracameral cefuroxime reduced the rates of endophthalmitis from 0.155% to 0.090%, this decrease was not statistically significant. However the authors recommended the use of intracameral cefuroxime as it does not add significantly to the cost of surgery.

Regarding concerns over the safety of intracameral cephalosporins, no effect on central retinal thickness or endothelial cell density has been found with the use of intracameral cefazolin, cefuroxime of ceftazidime.
Cefuroxime has certain disadvantages when used intracamerally. It has limited activity against gram negative bacteria, needs to be reconstituted at the time of surgery (thus increasing the risk of toxic anterior segment syndrome) and has a time dependent action; all of which make cefuroxime a less than ideal drug for intracameral administration.\textsuperscript{46,59,60} Moxifloxacin in contrast has a wider spectrum of action, concentration dependent killing (making it more effective than cefuroxime as a bolus dose) and available commercial preparations. These considerations make intracameral moxifloxacin an attractive option.\textsuperscript{17} Numerous studies have been reported regarding the safety of intracameral moxifloxacin in various concentrations (0.1mg/0.1ml, 0.5mg/0.1ml and 250ug/0.05ml). Intracameral moxifloxacin has been found to be safe and effective for prophylaxis of endophthalmitis with no significant adverse effects on corneal endothelium and retinal thickness.\textsuperscript{3,61,62} Anijeet et al in a 11 year retrospective study of more than 16000 patients found that intracameral vancomycin (1mg in 0.1ml) reduced the incidence of endophthalmitis from 0.3\% to 0.008\%.\textsuperscript{63} Vancomycin is very effective against gram positive bacteria including methicillin resistant staphylococcus aureus (MRSA) but is ineffective against gram negative bacteria.\textsuperscript{8} There are concerns regarding intracameral vancomycin causing cystoid macular oedema and its limited microbial spectrum, that preclude its widespread use.\textsuperscript{64} It can however be reserved for use in MRSA carriers undergoing cataract surgery.\textsuperscript{8} A recent study by Rudinsky et al however documents no difference in the rate of endophthalmitis in patients with or without the administration of intracameral antibiotics (either vancomycin or moxifloxacin).\textsuperscript{65}

Subconjunctival Antibiotics

Although gentamycin has been used subconjunctivally at the end of cataract surgery, study of 1140 eyes demonstrated no protective effect of subconjunctival gentamycin injection in the prevention of post-operative endophthalmitis.\textsuperscript{66} Subconjunctival cefuroxime maintains therapeutic levels in the anterior chamber for up to 12 hours after administration of 125mg. Also, an association has been shown between the incidence of endophthalmitis and the omission of subconjunctival cefuroxime at the end of cataract surgery.\textsuperscript{67,68} As mentioned previously, Yu-Wai-Man et al have shown intracameral cefuroxime (1mg in 0.1ml) to be superior to subconjunctival cefuroxime (50mg in 0.5ml) as endophthalmitis prophylaxis.\textsuperscript{69} Rudinsky et al found no benefit of subconjunctival antibiotics (gentamycin, cefuroxime or cefazolin) in preventing endophthalmitis.\textsuperscript{65} The ESCRS guidelines on endophthalmitis prophylaxis do not encourage the use of subconjunctival antibiotics due to their questionable efficacy and the proven superiority of intracameral cefuroxime.\textsuperscript{13} Also the recent trend towards cataract surgery under topical anaesthesia makes subconjunctival antibiotic administration inconvenient.

Post-operative Antibiotics

Studies have shown that nearly all surgeons prescribe post-operative topical antibiotics.\textsuperscript{69-71} The 2014 ASCRS survey showed that almost 97\% of the members preferred to use topical antibiotics post-operatively; with 72\% of them stopping after one week and the rest continuing the topical antibiotics for several weeks post-operatively.\textsuperscript{12} However, the evidence for their use is not very convincing. It is seen that even a 3 day treatment with topical antibiotics reduces the number of positive conjunctival cultures by only 50\%,\textsuperscript{72,73} Thus a large number of bacteria still remain in the conjunctiva after topical antibiotic therapy. Topical antibiotics have not been found effective in reducing the incidence of endophthalmitis by the ESCRS endophthalmitis study group nor by Raen et al\textsuperscript{13,73} The strongest evidence in favour of the benefit of post-operative antibiotics perhaps comes from a study of more than 72000 patients by Rudinsky et al over an eight year period. Although all patients in this study received post-operative topical antibiotics, the authors found a statistically significant (p=0.029) decrease in the rate of endophthalmitis when moxifloxacin was used (0.01\%) as compared to when any one of the other antibiotics was used (0.04\%) (ciprofloxacin, ofloxacin, gatifloxacin, polymyxin and tobramycin).\textsuperscript{66} A recent meta-analysis of antibiotic prophylaxis of post cataract surgery endophthalmitis however, did not find any evidence favouring the use of post-operative antibiotics and hence the authors did not recommend this measure.\textsuperscript{4}

Conclusion

After considering all the available evidence, it is seen that there is no proven role for systemic or topical antibiotics, antibiotics in the irrigating solution or subconjunctival antibiotics in the prevention of post cataract surgery endophthalmitis. Amongst topical antibiotics, moxifloxacin is the only drug which has been associated with reduction in post-operative endophthalmitis but conclusive evidence is still lacking. Although strong evidence from European studies demonstrates a benefit of intracameral cefuroxime, Indian studies have not shown a significant difference. Yet the cost-benefit ratio and the overwhelming European evidence advocate the use of intracameral cefuroxime at the end of cataract surgery. Intracameral moxifloxacin offers the benefit of available commercial preparations, a broader spectrum of action and better bacterial killing over cefuroxime. Also, the high incidence of endophthalmitis due to gram negative organisms in the Indian scenario may justify its use. However till date no randomised control trial has proven the efficacy of intracameral moxifloxacin in preventing endophthalmitis after cataract surgery. Yet it remains an attractive alternative to cefuroxime. The use of povidone iodine in concentrations of 1\%, 5\% and 10\% used pre-operatively as topical drops or as irrigating fluid for the fornices has been shown to reduce rates of post-operative endophthalmitis. Thus in view of existing evidence, we feel that pre-operative use of povidone iodine and the use of intracameral cefuroxime at the conclusion of cataract surgery remain the two most important steps in preventing post-operative endophthalmitis and hence need to be practiced.
Intracameral moxifloxacin may be considered as an alternative to cefuroxime. Although pre and post-operative systemic or topical antibiotics, subconjunctival antibiotics and antibiotics in the irrigating solution have not been proven to decrease post-operative endophthalmitis, they have not been shown to be detrimental and hence surgeons may consider their use according to personal preferences and a cost-benefit analysis of their healthcare system.

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