Cataract surgery is the most commonly performed surgical procedure in the world, estimated at more than 20 to 25 million in number annually.1 With the aging of the population, the volume will continue to rise.2 Although there have been advances in technology, techniques, and training to increase the safety and efficacy of cataract surgery, there has not been a commensurate evolution in the prophylaxis of infectious postoperative endophthalmitis and the treatment of postoperative inflammation.

The incidence of infectious postoperative endophthalmitis is low, ranging from 0.04% to 0.36%,3,4 but, because of its devastating sight-threatening potential, constant vigilance and motivation are needed to further minimize its occurrence. Additionally, postoperative cystoid macular edema (CME) persists as a significant cause of suboptimal visual recovery, and this is particularly important given the increasing population of diabetic patients.5

Globally, there has been growing interest in and acceptance of intracameral, transzonular, and pars plana alternatives to topical drops in the treatment of postoperative cataract patients.6,7 However, adoption of these so-called dropless approaches has been slow in some areas. This article reviews the roadblocks to the acceptance of intracameral antibiotics and steroids in the cataract surgery setting.

ATTITUDES ON ANTIBIOTICS

Practice patterns for antibiotic prophylaxis vary from country to country. In the United States, the most common method of infectious postoperative endophthalmitis prophylaxis is perioperative topical antibiotics, usually consisting of a fourth-generation fluoroquinolone prescribed 1 to 3 days preoperatively and resumed immediately postoperatively for at least 1 week.6,8

Practitioners in the United States, Canada, Europe, Latin America, South America, Mexico, Australia, Asia, and Africa responded to a 2014 American Society of Cataract and Refractive Surgery (ASCRS) member survey. Fifteen percent of ASCRS members (n=1,147) responded. The survey found that, at the conclusion of surgery, 69% of respondents reported instilling a topical antibiotic, and 36% said they were injecting an intracameral antibiotic, up from 14% in the 2007 ASCRS member survey. The percentages totaled more than 100% because some surgeons used multiple methods of drug delivery. Among US respondents only, 30% said they were injecting an intracameral antibiotic at the end of surgery, in contrast with 70% of European respondents.6

One factor that may help explain this difference is the availability of intracameral cefuroxime powder 50 mg (Aprokam/Aprok/Prokam; Théa), which was approved by the European Medicines Agency in 2012 and is available in 24 European countries and Canada but not the United States. This single-dose unit of cefuroxime powder is reconstituted in 5 mL of sodium chloride 0.9%; 0.1 mL (cefuroxime 1.0 mg) is injected into the anterior chamber at the end of surgery.

Among US respondents only, 53% said they believe the US FDA should approve Aprokam based on European clinical trials and usage. In 2014, 75% of respondents stated that it was important to have a commercially available antibiotic approved for intracameral use, compared with 54% in 2007; 50% of those not using this route expressed concern about the risks of non–commercially prepared antibiotics, including the risks of mixing or compounding errors leading to toxic anterior segment syndrome (TASS) and contamination.

FACTORS INFLUENCING ADOPTION: INTRACAMERAL ANTIBIOTICS AND STEROIDS

Practice patterns for intracameral drug delivery vary from country to country. AT A GLANCE

- Interest in and acceptance of intracameral, transzonular, and pars plana alternatives to topical drops has grown, but adoption has been slow in some areas.
- Concerns with use of intracameral antibiotics and steroids are mitigated in some regions by national regulatory and professional society support of alternative routes of drug delivery.
THE CASE FOR INTRACAMERAL DRUG DELIVERY

The question of how best to deliver perioperative medications has become increasingly relevant, as there is more strong evidence supporting direct intracameral antibiotic injections than any other method of antibiotic prophylaxis. More than 1.3 million units of Aprokam have been used worldwide without significant incidence of reported adverse events. Globally, there appears to be consensus on the importance of direct intracameral antibiotics, but the major barrier to its use, particularly in the United States, is the lack of a commercially available formulation.

Although topical antibiotics can reach intraocular therapeutic levels when frequently applied, only intracameral antibiotics achieve suprathreshold antibiotic levels for an extended period. Intracameral antibiotics reach concentrations several times higher than the concentration needed to kill 90% of most bacterial isolates. This is in contrast to subconjunctival and topical antibiotics, which may not produce high enough aqueous concentrations to kill the most common causative organisms, coagulase-negative staphylococci. Additionally, intracameral injection achieves an instantaneously high concentration of antibiotic in the anterior chamber.

The strong evidence in support of direct intracameral antibiotic at the conclusion of surgery also raises the question of whether perioperative topical antibiotics can be eliminated. Both the landmark 2007 European Society of Cataract and Refractive Surgeons (ESCRS) endophthalmitis study and a 2013 Kaiser Permanente study found borderline additional effectiveness when topical antibiotics were combined with intracameral antibiotics at the conclusion of surgery.

The 2007 ESCRs study found that the use of direct intracameral cefuroxime at the conclusion of surgery reduced the incidence of infectious postoperative endophthalmitis fivefold (from 0.34% to 0.07%). The results were so striking that recruitment of additional patients was stopped, as the study’s data monitoring committee advised that it would be unethical to withhold the use of prophylactic intracameral cefuroxime. To date, this is the only large (16,603 patients) prospective, multicenter, randomized controlled trial to evaluate direct intracameral antibiotic injection. This study determined that the use of topical antibiotics perioperatively did not have a significant impact on the rate of infectious postoperative endophthalmitis when intracameral cefuroxime was used.

Comparable results were found in a similarly large study by Shorstein et al in 2013. Shorstein’s group at Kaiser Permanente in Northern California reviewed 16,624 cataract surgeries over three time periods based on increasing adoption of intracameral injection at the end of surgery. (Cefuroxime was the first-line choice; if the patient was allergic to this agent, then moxifloxacin or vancomycin was used.) This retrospective time-trend study from 2007 through 2011 found a 22-fold decline in infectious postoperative endophthalmitis with the increasing use, from 11% to 100%, of intracameral antibiotics. The authors also documented a low incidence of endophthalmitis (0.049%) with use of intracameral antibiotics alone in the absence of preoperative or postoperative antibiotic drops. This was similar to the 0.045% rate reported in a study in Sweden, in which 95% of 225,471 patients received intracameral cefuroxime without a postoperative topical antibiotic.

A study in Utah found that intracameral moxifloxacin without postoperative topical antibiotics after cataract surgery was safe and effective. Out of 222 eyes, 131 received a topical antibiotic and 91 received an intracameral antibiotic only. No case of endophthalmitis occurred in either group.

Most recently, Herrinton et al and the Kaiser Permanente group published a large retrospective, observational, longitudinal cohort study to examine the effects of topical and intracameral antibiotics on the risk of infectious postoperative endophthalmitis. They identified 215 cases of infectious postoperative endophthalmitis out of 315,246 procedures (0.07%) from 2005 to 2012. In this study, intracameral antibiotics (cefuroxime or moxifloxacin) were more effective than topical antibiotics alone (0.04% vs 0.07%), and topical antibiotics were not shown to add to the effectiveness of an intracameral regimen. Because of this, the authors are considering the exclusive use of intracameral antibiotic and elimination of topical antibiotics.

On top of minimizing the incidence of infectious postoperative endophthalmitis, intracameral antibiotic use may be advantageous in other ways: reduced eye drop burden on the patient, leading to quality of life improvement and reduction of self-inflicted contamination and injury; decreased cost for postoperative eye drops; decreased antibiotic resistance resulting from improper usage; and decreased ocular surface toxicity.

GLOBAL VARIATIONS IN PRACTICE PATTERNS

Although intracameral cefuroxime is commercially available in Europe and recommended by the ESCRs and by French, Scottish, and Canadian practice guidelines, practice patterns still vary throughout Europe. A 2013 survey of 479 surgeons in the United Kingdom, Spain, Sweden, Italy, Germany, Netherlands, Belgium, France, and Poland found no uniformity of antibiotic product use prior to, during, or after surgery and no standardization in regard to antiinflammatory drugs and antisepsis immediately prior to incision.
Geographic differences in microorganism distributions and priorities of antibiotic prophylaxis affect surgeon practice.

Sweden has the longest experience with intracameral cefuroxime; use of intracameral without additional perioperative topical antibiotic has become standard practice there. Similarly, Spain now almost universally uses intracameral cefuroxime. In contrast, in Germany intracameral cefuroxime is injected in less than half of cases, and in the Netherlands its use is reserved for high-risk patients such as those with diabetes or history of eye infection. Although the limits of this study included its survey method and its sponsorship by Théa (the manufacturer of Aprokam), it still provides valuable information on attitudes and highlights the variability of practice patterns among countries, even those with access to a European Medicines Agency–approved, single-use intracameral agent.

According to a 2009 member survey of the United Kingdom and Ireland Society of Cataract and Refractive Surgeons (UKISCRS), 55% of respondents used intracameral cefuroxime. Almost half of these injecting surgeons reported switching to this method in response to the landmark ESCRs 2007 study. Like the American Academy of Ophthalmology (AAO), the Royal College of Ophthalmologists (RCO) leaves details of antibiotic use to the surgeon’s discretion.

A 2007 Australian survey found just 1% of surgeons using intracameral antibiotics; 80% used preoperative topical antibiotics and 95% postoperative topical antibiotics. By 2012, with a commercial preparation of intracameral cefazolin available, a massive change in practice pattern occurred, with 84.4% of surveyed surgeons reporting use of intracameral antibiotics.

DIFFERENT BUGS, DIFFERENT DRUGS

Geographic differences in microorganism distributions and priorities of antibiotic prophylaxis can also affect surgeon practices. In 2013, a retrospective survey cohort study of 19 clinics in Japan showed that intracameral moxifloxacin decreased the risk of infectious postoperative endophthalmitis threefold, and, in more than 18,000 cases, a dose of 500 µg/mL or less did not result in severe complications such as TASS or corneal endothelial cell loss. Prior to this study, in a 2012 survey, only 1% of surgeons in Japan used intracameral administration of antibiotic. Moxifloxacin was of particular interest in Japan because of its effectiveness against Enterococcus faecalis, which is associated with a poor prognosis and accounts for about 20% of cases of infectious postoperative endophthalmitis in Japan. This is in contrast to the United States and Europe, where coagulase-negative staphylococci are most prevalent.

US surgeons frequently use fourth-generation fluoroquinolones for prophylaxis, whereas, in France, these are reserved for the treatment of known severe infection. In a similar way, the US Centers for Disease Control and the AAO discourage the prophylactic use of vancomycin, in order to preserve its effectiveness against methicillin-resistant Staphylococcus aureus.

Commercial cefuroxime is largely unavailable outside Europe. Aravind Eye Hospital has an affiliated pharmaceutical company, Aurolab, which manufactures unit packages of 0.1 mL moxifloxacin 0.5% (Promox). In addition to Aurolab, since 2013, surgeons in India have had access to 4 Quin PFS (Entod Pharmaceuticals), a commercially available formulation of intracameral moxifloxacin (0.5 mL prefilled moxifloxacin 0.5% syringe).

FACTORS SLOWING ADOPTION

In the United States, the absence of commercially available intracameral cefuroxime favors the use of moxifloxacin 0.5% ophthalmic solution (Vigamox; Alcon), as this commercially available topical agent does not require dilution or compounding; it is supplied as a sterile isotonic solution, with pH near 6.8 and osmolality of 290 mOsm/kg, making it compatible with intraocular tissues. Moxifloxacin is also self-preserved, containing no benzalkonium chloride or other preservatives known to have toxic effects on the corneal epithelium. Although Vigamox can be safely used straight out of the bottle for intracameral delivery, accidental substitution of Vigamox with Moxeza (moxifloxacin 0.5% ophthalmic solution; Alcon) has been associated with TASS due to differences in inactive ingredients.

Recent problems have increased concerns about use of compounded products. In Florida, an outbreak of endophthalmitis occurred among patients who had injections of intravitreal bevacizumab prepared in a compounding pharmacy. A Turkish hospital had eight cases of Fusarium endophthalmitis following use of intracameral cefuroxime prepared in the operating room. Another Turkish study found 17 patients with TASS linked to cefuroxime; all patients responded to intensive topical corticosteroids.

An incorrect dilution at a Finnish hospital resulted in a series of 16 patients receiving intracameral cefuroxime at 50 to 100 times the recommended dose of 1 mg/0.1 mL. Eight of the 16 eyes experienced severe, permanent visual loss. There are two case reports of anaphylactic reaction following the administration of intracameral cefuroxime during cataract surgery. Both patients had a known penicillin allergy, and cross-reactivity with the cephalosporin cefuroxime occurred.

Wong et al reported an intracameral cefuroxime compounding error, in which 9 mg of cefuroxime was administered to 13 eyes of 11 patients. This resulted in acute macular edema in six eyes, which resolved within 1 week without further adverse consequences.
Recently, there was a report of 11 eyes with hemorrhagic occlusive retinal vasculitis possibly associated with intracameral vancomycin use after cataract surgery. Nicholson et al. were the first to report four eyes in two patients with severe bilateral ischemic retinal vasculitis after rapidly sequential and otherwise uneventful phacoemulsification. Authors of both papers suggested that a delayed immune reaction to vancomycin was the cause. The ASCRS Cataract Clinical Committee and the American Society of Retina Specialists (ASRS) have developed a joint task force and registry to further explore this rare but potentially devastating condition.

Arguments that resistance can be bred by the routine prophylactic use of intracameral cefuroxime or moxifloxacin may be countered by noting that a single dose of highly concentrated drug is delivered into a confined space. By contrast, with topical therapy, there are the variables of corneal absorption, aqueous concentration, and less reliable dosing of topical antibiotics in the hands of patients. Intracameral vancomycin is currently reserved for about 1% of patients who are allergic to penicillin, cephalosporin, and a fluoroquinolone.

The preferred antibiotic for intracameral use tends to vary according to geographic region and perspective, as described earlier. The Kaiser Permanente group uses compounded cefuroxime as its first-line agent, followed by moxifloxacin and vancomycin to accommodate patient allergy contraindications. This group did not find a difference in effectiveness between cefuroxime and moxifloxacin in 315,246 cases.

The anterior chamber is able to clear some microorganisms, but, when they move posteriorly, they tend to grow in the vitreous, which may provide a protective matrix; a more posterior delivery of antibiotic might address this. One concern with the transzonal injection approach is the possibility of disrupting the anterior hyaloid face, with resulting retinal tears or detachments. From the patient’s perspective, intracameral delivery of a corticosteroid suspension, such as triamcinolone, can cause a few days to weeks of blurring and floaters from the deposits, but advances in formulation are addressing this. With the pars plana approach, there is a track record of safety and efficacy for the treatment of macular degeneration, infectious postoperative endophthalmitis, and other diseases. Intracameral, transzonal, and pars plana approaches to prophylaxis are now available with formulations provided by compounding companies such as Imprimis Pharmaceuticals and Ocular Science; these warrant further clinical study.

ANTINFAMMARY DELIVERY

Intracameral delivery of corticosteroids in cataract surgery is not new. In 2005, Gills and Gills analyzed 608 eyes and reported using up to 3 mg of intracameral triamcinolone with safety and success in the reduction of postoperative inflammation. This approach obviated the need for postoperative corticosteroid drops for patients receiving a dose of 2.8 mg or more. At doses of 1.8 mg or higher, no CME occurred. These practitioners delivered the triamcinolone through the anterior chamber but facilitated flow through the zonules by aiming the cannula posteriorly. In 2009, Chang et al. reported that 0.4 mg intracameral dexamethasone was safe and efficacious when given at the end of surgery in conjunction with standard postoperative corticosteroid drops; this retrospective study included 91 patients with and without glaucoma who were undergoing phacoemulsification. The authors did not find a significant increase in postoperative IOP in dexamethasone-treated glaucoma patients.

When injected into the anterior chamber, neither dexamethasone nor triamcinolone acetone has been associated with ocular hypertension. This is likely due to the rapid turnover of aqueous volume and the short half-life of intracameral dexamethasone. By contrast, ocular hypertension has been noted when triamcinolone acetone is injected sub-Tenon capsule or intravitreally, yielding a sustained duration of action. Studies in pediatric cataract surgery patients have not shown an increased risk for glaucoma with the use of intracameral dexamethasone or triamcinolone acetone.

CONCLUSION

Major concerns with the use of intracameral drug delivery for cataract surgery remain include the lack of a commercially available and approved antibiotic for intracameral use in some markets; the lack of national regulatory and professional society support of alternative routes of drug delivery; reports of delayed adverse sequelae, such as hemorrhagic occlusive retinal vasculitis, possibly associated with intracameral vancomycin; the risk of disrupting the anterior hyaloid face, with resultant retinal tears and or detachments; and ocular hypertension resulting from direct injection of a steroid. Additionally, the potential for blur and floaters from steroid deposits after surgery is concerning in these times of high patient expectations. These concerns are mitigated in some regions by national regulatory and professional society support of alternative routes of drug delivery.

Around the world, cataract surgery is one of the most frequently performed surgical procedures, with an astounding success rate. New developments occur regularly in surgical techniques and IOLs, continually improving patients’ visual outcomes. Postoperative endophthalmitis, while uncommon, remains the most serious potential complication of cataract surgery, but strategies for its prevention differ between the United States and Europe.

ENDOPHTHALMITIS PROPHYLAXIS

In 2004, the incidence of endophthalmitis in the United States was estimated to range from 0.06% to 0.20%. Over time, surgical methods have evolved to prevent endophthalmitis, including the use of a povidone-iodine scrub prior to cataract surgery, appropriate surgical draping, and the use of an antibiotic following surgery. Historically, physicians prescribed topical antibiotic drops one to four times daily for several weeks after surgery. However, increasing data are showing that intracameral antibiotics are more effective than topical antibiotics for preventing endophthalmitis.

In 2007, a landmark study by the European Society of Cataract and Refractive Surgeons (ESCRS) was published, showing a fivefold reduction in the risk of postoperative endophthalmitis, from 0.345% to 0.049%, when intracameral cefuroxime was used as prophylaxis instead of topical antibiotics. This study and several others were impetus for the ESCRs to change its official guidelines on the prevention and treatment of endophthalmitis after cataract surgery to include the use of intracameral cefuroxime. The European ophthalmic industry, in response, developed Aprokam (cefuroxime 50 mg; Théa Pharmaceuticals). Aprokam received approval from the European Medicines Agency (EMA) in 2012. Its availability is likely a significant factor in European surgeons’ almost total adoption of intracameral rather than topical antibiotics as prophylaxis for endophthalmitis after cataract surgery.

In the United States, the course of practice patterns has not been the same. Following the European study, another study published in 2013 by a large US health system evaluated the change in postcataract endophthalmitis rates in relation to the adoption of intracameral injection of cefuroximine, moxifloxacin, or vancomycin at the end of surgery. A total of 16,264 cataract surgeries were performed during three time periods—2007 to 2008, 2009 to 2010, and 2011—during which the adoption of intracameral antibiotic injections steadily increased. Endophthalmitis rates for the respective periods were 0.313%, 0.143%, and 0.014%. Numerous studies have followed, and the efficacy of intracameral antibiotics as prophylaxis for endophthalmitis was recognized in the American Academy of Ophthalmology’s (AAO) Preferred Practice Pattern for adult cataract surgery in 2011.

However, according to the American Society of Cataract and Refractive Surgery (ASCRS) annual survey, by 2014, only 20% to 30% of US surgeons were using intracameral injections of antibiotics. Despite high interest, most surgeons continue to rely on topical fourth-generation fluoroquinolones.
EDITORIAL SPOTLIGHT

REGULATION AND REIMBURSEMENT

Although the data are convincing that intracameral antibiotics are better than topical antibiotics for endophthalmitis prophylaxis, there are barriers in the United States related to access and reimbursement. There is no US FDA-approved counterpart to Aprokam. Although the path to approval is clear for any company that wishes to apply for an approval, the two phase 3 clinical trials required by the FDA would cost roughly US$100 million. Despite that initial outlay, with 4 million cataract surgeries performed each year in the United States, a reasonable reimbursement of, say, US$100 per surgery would allow any company developing such a drug to obtain an adequate return on investment.

Unfortunately, there is currently no path toward even that modest level of reimbursement for this hypothetical product in the United States. The government agency that determines reimbursement for Medicare (US government-sponsored health insurance), which in turn influences the reimbursement practices of most private insurance companies, has ruled that any intraocular antibiotic injection would be bundled into the standard surgical fee for cataract surgery. Furthermore, the ruling also states that it would be illegal for patients to opt for the injection over topical antibiotics and pay for it themselves, as they do with premium IOLs. Thus, any surgeon who wants to use an intracameral injection of antibiotics has to cover the cost out of the surgical fees already paid.

OFF-LABEL DRUGS

With the lack of an FDA-approved pharmaceutical, some physicians have been opting to buy an antibiotic and draw it out on their own, but most continue to use topical drops. One compounding pharmacy, Imprimis Pharmaceuticals, has stepped in to fill the void. A government-regulated pharmacy, Imprimis has created patented combination drugs that combine preservative-free antibiotics with the anti-inflammatory medications commonly prescribed after cataract surgery.

TriMoxi (triamcinolone 3 mg and moxifloxacin 0.2 mg) and TriMoxiVanc (triamcinolone 3 mg, moxifloxacin 0.2 mg, and vancomycin 2 mg) use a carrier adjuvant to bind the particles together to create a well-distributed micronized particle suspension that is stable at room temperature. Intracameral moxifloxacin has a broad spectrum of antibacterial activity against both gram-positive and gram-negative organisms and has a half-life of more than 1 hour. Several studies have found it to be as effective as intracameral cefturoxime in the prevention of endophthalmitis.

Data presented at the 2014 ASCRS meeting included a retrospective chart review of 2,300 consecutive eyes that received a transzonular injection of TriMoxi after cataract surgery. Nineteen percent of patients had diabetes, and 5% had an epiretinal membrane; thus, 19% of the overall patient population received supplemental topical NSAIDs after surgery. There were no cases of endophthalmitis, and only 2.5% of patients (n=40) developed inflammation, which was defined as patients complaining of pain and/or photophobia accompanied by any cell and/or flare or by asymptomatic iritis with greater than 1+ cell/flare.

Of nearly 200,000 patient-specific doses of TriMoxi shipped to more than 500 doctors by the company, there have been only two known cases of endophthalmitis, both of which occurred several weeks after surgery in patients with dementia who reportedly engaged in frequent eye rubbing.

There are some differences with this approach, compared with the European standard of care. First, TriMoxi and TriMoxiVanc address inflammation and cystoid macular edema as well as endophthalmitis with a single injection, eliminating or greatly reducing the number of post-surgical drops necessary. Second, the injection is placed intravitreally versus intracamerally. This makes intuitive sense, as the posterior segment is where endophthalmitis would colonize and where cystoid macular edema occurs. Third, this remains an option with no reimbursement coverage, so surgeons using the so-called dropless technique must continue to cover the cost, a fact that hampers universal adoption. At US$20 per prescription, it is a manageable cost for something that I believe to be a great benefit to patients.
CONCLUSION

I feel it would be in the interest of patients, physicians, and the health care system as a whole to find a path to reimbursement for injectable prophylaxis at the time of surgery, as has been done in Europe. If not reimbursement, then allowing patients the option to pay for the injection out of pocket would help spur greater adoption of intravitreal antibiotics.

As an executive member of Cataract Surgeons for Improved Eyemedeveyecare.org, a national membership association of ophthalmologists who are committed to the highest quality of care for our patients, I will continue to provide my patients with access to innovative, cost-effective, and practical ophthalmology solutions while lobbying our national health care system to do the same.


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