Improving Postsurgical Outcomes: Perioperative Antibiotic and Anti-inflammatory Use

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Compared with many other medical specialties, ocular surgeons are hampered by the paucity of evidence-based literature which prevents determining the optimum approach to perioperative antimicrobial prophylaxis. This is particularly unfortunate, because postoperative endophthalmitis is a potential complication of every cataract surgery. Therefore, practitioners are forced to rely on an empirical approach that lacks consensus in a setting where antibiotic resistance among the pathogens is increasing.

Endophthalmitis is rare following uncomplicated phacoemulsification, with reported incidences ranging between 1 in 3,000 and 1 in 7,000. However, each case has the potential to be visually devastating. Large series have shown that endophthalmitis can occur despite the use of prophylactic and perioperative antibiotics, and cases can occur where no in vitro resistance to the antibiotics being used is observed. Data from animal and clinical studies indicate that an intact posterior capsule is an effective barrier that reduces the rate of endophthalmitis between 4-fold and 14-fold. Factors that increase the risk of infection include diabetes, immune deficiency, preoperative external eye infections, previous ocular surgery, and wound abnormalities. The most common sources of these organisms are endogenous lid and conjunctival flora. Infections are only rarely acquired from contaminated instruments, solutions, the IOLs, or airborne contaminants.

Three-fourths of conjunctival cultures are positive without prophylaxis. While it may be possible to reduce the colony-forming units on the ocular surface with povidone-iodine and topical fluoroquinolones, it is not possible to completely sterilize the ocular surface. Povidone-iodine is effective at reducing the bacterial

### Table 1. Fluoroquinolone Resistance Patterns of Conjunctival Bacteria Isolated Preoperatively

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of Strains</th>
<th>Resistant Strains, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LFX</td>
</tr>
<tr>
<td>CNS</td>
<td>62</td>
<td>24 (38.7)</td>
</tr>
<tr>
<td>MS CNS</td>
<td>30</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>MR CNS</td>
<td>32</td>
<td>22 (68.8)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>5</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>MSSA</td>
<td>4</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>MRSA</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td><em>Corynebacterium</em></td>
<td>14</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td><em>Propionibacterium acne</em></td>
<td>68</td>
<td>0</td>
</tr>
</tbody>
</table>

KEY: GFX — gatifloxacin, LFX — levofloxacin, MR CNS — methicillin-resistant coagulase-negative *Staphylococcus*, MS CNS — methicillin-sensitive coagulase-negative *Staphylococcus*, MRSA — methicillin-resistant *Staphylococcus aureus*, MSSA — methicillin-sensitive *Staphylococcus aureus*

Table 2. Antibiotic Sensitivities in 6 Eyes with MRSA Endophthalmitis

<table>
<thead>
<tr>
<th>Case</th>
<th>Ciprofloxacin</th>
<th>Ofloxacin</th>
<th>Levofloxacin</th>
<th>Gatifloxacin</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R/S</td>
<td>MIC</td>
<td>R/S</td>
<td>MIC</td>
<td>R/S</td>
</tr>
<tr>
<td>1</td>
<td>R</td>
<td>≥4</td>
<td>—</td>
<td>—</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>—</td>
<td>R</td>
<td>kb</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>&gt;2</td>
<td>—</td>
<td>—</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>&gt;2</td>
<td>—</td>
<td>—</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>≥4</td>
<td>R</td>
<td>kb</td>
<td>R</td>
</tr>
</tbody>
</table>

KEY: kb — Kirby Bauer testing, MIC — minimum inhibitory concentration, R — resistant, S — sensitive

load when it is applied preoperatively and perioperatively. However, despite the use of povidone-iodine and antibiotics, bacteria are introduced into the eye in 43% of routine phacoemulsification procedures, which have been shown in some cases to correlate with prior conjunctival cultures.

In endophthalmitis cases, the anterior chamber may be culture-positive with a negative vitreous culture, and the reverse can also occur; that is, the vitreous culture is positive with a negative anterior chamber culture. The anterior chamber has defensins and is inherently capable of clearing microbes, while the vitreous is not as efficient. Therefore, the anterior chamber culture is a poor predictor of the infection status of the vitreous.

Development of Fluoroquinolone Resistance

Methicillin-resistant Staphylococcus aureus (MRSA) is becoming increasingly prevalent in ocular cultures. In one study analyzing data from 1994 to 2003, MRSA underwent an approximate 10-fold increase (4% to 43% of S aureus isolates; P = .001) in patients with conjunctivitis. Although reference is often made only to methicillin-resistant organisms, many bacteria have become multi-drug resistant. For example, a subset of organisms is resistant to both methicillin and fluoroquinolones. DNA gyrase (topoisomerase II) and topoisomerase IV are the 2 principal enzymes involved in bacterial replication. DNA gyrase catalyzes supercoiling and uncoiling of the double helical prokaryotic DNA, and topoisomerase IV is involved in breaking the duplicated DNA of replicated bacterial DNA to form daughter cells. Fluoroquinolones target these enzymes, forming a stabilized drug:enzyme:cleaved DNA complex, which leads to unrepaired lethal breaks in the double stranded DNA. If these enzymes undergo a genetic mutation, limiting quinolone binding, the fluoroquinolone is incapable of inhibiting them and bacterial replication proceeds normally. However, newer fluoroquinolones target both of these enzymes, reducing the likelihood that the organism will develop resistance, as it would have to undergo 2 mutations.

A study of preoperative conjunctival swabs obtained from cataract patients revealed significant resistance to fluoroquinolones (Table 1, page 11). Approximately one-half and two-thirds of methicillin-resistant coagulase-negative Staphylococcus strains were also resistant to gatifloxacin and levofloxacin, respectively. As shown in this and other studies, there was also evidence of fluoroquinolone resistance in some strains that were methicillin-sensitive.

In the landmark Endophthalmitis Vitrectomy Study performed in the early 1990s, only 6 of 323 (1.9%) isolated organisms were MRSA. In a more recent series of data from 2003-2006, 6 of 33 cases (18.2%) of culture-positive endophthalmitis were caused by MRSA. This represents nearly a 10-fold increase in MRSA-induced acute endophthalmitis compared with the study conducted 10 years earlier. The 6 eyes had been given fluoroquinolone antibiotics prophylactically 2 or 3 days before surgery. All were vancomycin- and gentamicin-sensitive. However, resistance to fluoroquinolones was demonstrated in these cases (Table 2).

Besifloxacin is a novel fluoroquinolone approved by the FDA in June 2009 for the treatment of bacterial conjunctivitis. In a recent study comparing the potency of besifloxacin ophthalmic suspension 0.6% with other
fluoroquinolones, besifloxacin had an MIC<sub>90</sub> (minimum inhibitory concentration required to inhibit the growth of 90% of the organisms) of 2 μg/mL and 4 μg/mL against MSSA and MRSA, respectively, and 1 μg/mL and 4 μg/mL against susceptible and resistant Staphylococcus epidermidis. All comparator agents had an MIC<sub>90</sub> of at least 8 μg/mL. Additional data will be forthcoming as besifloxacin receives more usage in this setting.

**Endophthalmitis Prophylaxis**

When topical antibiotics are applied, the aqueous humor concentrations achieved decreased in order from moxifloxacin > gatifloxacin > besifloxacin. Concentrations are sensitive to the dosing regimen, and data on the persistence and required levels to achieve bacterial inhibition are currently unavailable.

**Intracameral antibiotics**

Some surgeons have used intracameral moxifloxacin 0.1%, indicated for the treatment of bacterial conjunctivitis, off-label for endophthalmitis prophylaxis. An increase in cystoid macular edema (CME) on optical coherence tomography (OCT) or stromal edema has not been reported following this use. However, efficacy is not established. Moxifloxacin is detected in the vitreous 2 hours following topical dosing with 0.11 μg/mL, and it is assumed that intracameral concentrations are higher. However, effective antibiotic concentrations and the relevant duration of effective concentrations intracameral are not known.

The European Society of Cataract & Refractive Surgeons (ESCRS) Endophthalmitis Study showed that the use of an intracameral antibiotic, cefuroxime, reduced the odds of endophthalmitis by almost 6-fold. The rate of infectious endophthalmitis was 0.07% in patients treated with intracameral cefuroxime compared to 0.34% in control patients (OR 5.85; P = .005).

Standard prophylactic practice includes reducing the number of bacteria colonizing the lids and ocular surface preoperatively with topical fluoroquinolones and using lid scrubs and other lid hygiene practices. Povidone-iodine should be applied to the ocular surface preoperatively. Off-label use of an intracameral antibiotic such as moxifloxacin can be considered. The prophylactic use of "big gun" therapeutic antimicrobials, such as vancomycin, should be avoided due to the emergence of vancomycin-resistant enterococcal endophthalmitis.

**Postoperative Inflammation**

The stress of ocular surgery increases the production of prostaglandins and other inflammatory mediators, breaking down the blood-ocular barrier, increasing perifoveal capillary permeability, and leading to the accumulation of intraretinal fluid. Classic features of CME include late petaloid staining seen with fluorescein angiography and macular thickening seen with OCT 4 to 6 weeks postoperatively.

**Inflammation and surgical technique**

Comparing cataract surgery methodologies, angiographic CME occurs following 50% to 70% of intracapsular cataract extractions (ICCE) compared to 20% to 30% following extracapsular cataract extractions (ECCE) or phacoemulsification. Following phacoemulsification, clinically significant CME with visual acuity of less than 20/40 occurs in less than 1% of cases. However, complicated phacoemulsification, where the capsule is ruptured with accompanying vitreous loss, iris trauma, or intraocular hemorrhage, clinically significant CME can occur in up to 20% of cases. A randomized trial that used slit lamp grading and flare meter readings to compare inflammation after phacoemulsification to that after ECCE showed that phacoemulsification produced significantly less inflammation, which was of shorter duration. A return to baseline occurred in 1 month in the phacoemulsification group compared to 2 months in the ECCE group.

Postoperative pseudophakic CME, also known as Irvine-Gass syndrome, is the primary cause of decreased vision following uncomplicated cataract surgery. A retrospective review of 139,759 Medicare beneficiaries following cataract surgery demonstrated an incidence of 1.95%. There is a further increased risk for CME in patients with diabetes, uveitis, ocular vascular or cardiovascular disease, epiretinal membranes, vitreoretinal interface membranes, or retinitis pigmentosa.

**Corticosteroid and NSAID mechanism of action**

Surgical trauma releases cell membrane phospholipids, and phospholipase A<sub>2</sub>, a key enzyme involved in the release of these phospholipids from the cell membrane, also catalyzes the conversion of the phospholipids to arachidonic acid. This initial step is blocked by corticosteroids. Later in the pathway the cyclo-oxygenase (COX) enzymes convert arachidonic acid to prostaglandins. This step is blocked by NSAIDs. Therefore, these 2 drug classes are complementary; that is, they block the inflammatory cascade in 2 different locations (Figure, page 14).

**Combination treatment with NSAIDs and corticosteroids**

The goals of treatment with topical NSAIDs are management of postoperative inflammation following cataract surgery, prevention and treatment of postoperative CME, prevention and treatment of intraoperative
miosis, and reduction of pain and photophobia following keratorefractive surgery. Several studies suggest that NSAIDs and corticosteroids may show synergy in preventing and treating ocular inflammation. Visually significant CME occurred less frequently in cataract patients treated with nepafenac and corticosteroids (0/210; 0%) than in those treated with corticosteroids alone (5/240; 2.1%; P = .0354). A randomized trial compared 4 days daily prednisolone acetate 1% (n = 278) with prednisolone 1% plus ketorolac 0.4% (n = 268), given for approximately 4 weeks postoperatively. Compared with steroid-only patients, those in the steroid/NSAID group had less clinical CME (0 vs. 5 cases, P = .032), OCT evidence of definite or probable CME (0 vs. 6 patients, P = .018) and possible CME (5 vs. 15 patients, P = .037). In addition, more patients treated with steroid-only had macular thickening >10 μm (49% vs. 26%, P < .001) compared with patients treated with both ketorolac and corticosteroid. Patients with <10 μm retinal thickening had significantly greater contrast sensitivity at 6, 12, and 18 cycles per degree compared to those who had greater postoperative thickening, indicating that better vision resulted when the drugs were used in combination. Additional data supporting the comparative benefit of using both NSAIDs and steroids were provided by a study showing that in patients with acute CME, ketorolac plus corticosteroid compared to either agent alone was more likely to result in 2 lines of vision improvement and faster time to resolution. In that study, 4 of 8 (50%) patients randomized to prednisolone, 6 of 9 (67%) patients on ketorolac only, and 8 of 9 (89%) patients treated with a combination achieved at least a 2-line improvement in visual acuity. Average improvement within groups was 1.1, 1.6, and 3.8 lines, respectively.

**Dosing regimens**

NSAID dosing regimens are very important, and pre-dosing provides several benefits. In a 4-group randomized controlled trial enrolling 100 patients, pupil size maintenance was improved with 1-day preoperative ketorolac dosing compared with placebo or ketorolac given 1-hour before phacoemulsification (P < .01). Furthermore, giving ketorolac for 3 days preoperatively provided significantly better pupil size maintenance than 1-day pre-dosing (P < .01). Patients treated 3- and 1-day preoperatively with ketorolac had reduced surgical time, phacoemulsification time and energy, and endothelial cell loss. Furthermore, these patients had improved visual acuity. NSAIDs do not have an effect on pre-existing ocular prostaglandins; therefore, pre-dosing 3 days before surgery may deplete the endogenous supply, enhancing NSAID effectiveness. In this study, none of the patients who received ketorolac 0.4% for 1 or 3 days preoperatively developed CME, compared with 12% of patients in the placebo group and 4% in the group who received ketorolac 1-hour preoperatively.

**Adverse effects of topical NSAIDs and steroids**

When using ocular corticosteroids, their possible adverse effects should be considered. In general, corticosteroids can cause delayed wound healing and increased susceptibility to infection. In addition, they can increase IOP. Common adverse effects of NSAIDs include burning, stinging, delayed wound healing, corneal erosions, corneal thinning, ulceration, and perforation. Sight-threatening adverse effects are greater in patients with complicated cataract, corneal denervation, corneal epithelial defects, diabetes, ocular surface disease (including dry eye syndrome), rheumatoid arthritis, and repeat ocular surgery. When NSAIDs are used too frequently or in patients with epithelial defects, they have been associated with corneal melting.

Utilization of a "soft" steroid such as loteprednol could be taken into consideration. As a "soft" steroid, loteprednol is inactivated when unbound. Naturally occurring esterases metabolize corticosteroids such as
loteprednol that have with an ester group instead of a ketone group at C-20. These characteristics are believed to minimize adverse events.

A study performed several years ago compared the effects of loteprednol with prednisolone acetate 1% on IOP. Mean IOP in the loteprednol group was increased 4.1 mm Hg from baseline at 6 weeks, which was within the normal range and not significantly different from baseline. Mean IOP in patients in the prednisolone group increased significantly from baseline by 5.9, 7.7, and 9.0 mm Hg on days 14, 28, and 42, respectively (P < .05 for all time points). The hypertensive effect of prednisolone may have been underestimated due to protocol-required discontinuation of subjects with significant IOP elevation. Loteprednol use was associated with a lower case incidence of clinically significant IOP elevation (≥ 10 mm Hg) compared to prednisolone.

A recent study of 30 corneal transplant patients who were switched from prednisolone acetate 1.0% to loteprednol etabonate 0.5% in response to a secondary increase in IOP showed successful reduction in IOP without concomitant signs of allograft rejection. Loteprednol has less potent anti-inflammatory activity than prednisolone acetate, however, due to its metabolism by esterases.

In June 2008, the FDA approved difluprednate 0.05% emulsion for the treatment of inflammation and pain associated with ocular surgery. Difluprednate is fluorinated at both C6 and C9 to increase potency. In a multicenter placebo-controlled trial that enrolled 438 patients, difluprednate was administered starting 1 day after cataract surgery 2 or 4 times daily in inflamed eyes for 14 days followed by a 14-day tapering-off period. Treatment was followed by a 7-day safety evaluation. Difluprednate reduced intraocular inflammation and pain safely and effectively compared to placebo. A second study randomized 121 patients 2:1 to difluprednate or placebo given twice daily starting 1 day preoperatively and continuing for 16 days, followed by a 14-day tapering period. Clinical signs of inflammation, ocular pain and discomfort, IOP, and adverse events were assessed. Compared with placebo, difluprednate was significantly effective at decreasing postoperative inflammation and pain. A clinically significant increase in IOP (defined as ≥ 21 mm Hg and ≥ 10 mm Hg from baseline) occurred in 3% and 3.7% of difluprednate patients in these 2 studies, respectively, compared with 1% and 0% of patients in the placebo groups. This reversible IOP increase is similar to that observed with other topical steroids. Therefore, IOP should be monitored carefully in all patients treated with steroids.

The prevalence of dry eye syndrome and rosacea increases with age. Therefore, these conditions are common in many ocular surgery patients. A cross-sectional study of 39,876 female health care professionals revealed that dry eye syndrome was present in 5.7% of women ≥ 50 years of age, increasing to 9.8% of women ≥ 75 years of age. The age-adjusted prevalence of dry eye syndrome in women at least 50 years of age was 7.8%, or 3.23 million women in the United States. When dry eye syndrome is present, the resultant tear hyperosmolarity induces pro-inflammatory mediators, which can exacerbate inflammation following cataract surgery. Therefore, dry eye syndrome should be treated preoperatively.

In conclusion, prospective, randomized, masked studies demonstrate a reduction in the incidence of CME and ocular inflammation with the perioperative use of topical NSAIDs and corticosteroids. The effect of the 2 medications appears to be synergistic, as they work at different points in the inflammatory cascade. Other inflammatory conditions prevalent in the cataract population, such as dry eye syndrome and rosacea, should be treated. CME and capsular fibrosis can have late onsets; therefore, 6 to 8 weeks of treatment with a topical NSAID and a "soft" steroid should be considered, particularly in patients at high risk for CME and in patients electing premium IOL implantation.

References

Full references are available at www.OSNSuperSite.com. Click on the Education Lab.