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Reducing the impact of cataract surgical stress by mitigating inflammation and reducing ultrasound energy

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Terry Kim, MD

Reducing the impact of cataract surgery stress

by Terry Kim, MD

Eliminating or reducing the risk of postop inflammation is key to improving patient satisfaction

Low-to-moderate inflammation after cataract surgery can significantly impact patient comfort.[1] Postop pain was the most significant predictor of patient dissatisfaction, and postop pain was associated with low ratings of the quality of the surgical experience.

The 2013 ASCRS Clinical Survey, which included responses from more than 1,000 ASCRS members, found respondents "strongly agree" that postop inflammation can impact variability in visual acuity and quality results (29%), and visual recovery time is adversely impacted when postop inflammation is present (42%).[2] The percentage of respondents who "agree" with the statements is similar. Results were similar for 2014 (see Table 1). Further, the 2013 results found more than half of respondents noted using both nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to block the inflammatory cascade is warranted after cataract surgery. Yet in 2014, 47% of respondents said they do not preload with NSAIDs, and only 40% use both NSAIDs and steroids on postop day 1.[3]

My personal preference when planning for an uncomplicated cataract surgery includes the use of both a corticosteroid and an NSAID on every patient. As I operate at 2 different facilities, my preop and postop treatment regimen differs based on the facility. At the university setting, I prescribe moxifloxacin 0.5% and nepafenac 0.1% prior to dilating drops the day of surgery, and moxifloxacin 0.5% three times daily for 1 week, prednisolone acetate 1% three times daily with a weekly taper, and 0.1% nepafenac three times daily until the bottle is empty. At the ambulatory surgery center, I prescribe besifloxacin 0.6% and bromfenac 0.07% prior to dilating drops the day of surgery, and besifloxacin 0.6% twice daily for 1 week, loteprednol gel 0.5% twice daily for 3 weeks, and bromfenac 0.07% once daily until the bottle is empty.

Today's cataract patient expects excellent vision on postop day 1 (20/20 or better); delivering on these expectations requires excellent surgical skills as well as a highly effective regimen to facilitate healing and decrease postop inflammation.[4]

For example, numerous NSAIDs have been approved for the treatment of pain and inflammation after cataract surgery,[5–10] and although an off-label indication in the U.S.,

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Percentage of respondents who "strongly agree" or "agree" that low-to-moderate inflammation after cataract surgery can significantly impact …*	2013 (n=1,041)	2014 (n=1,501)
Variability in visual acuity and quality results	71% (29%)	86% (41%)
Visual recovery time	81% (42%)	90% (47%)
Patient comfort and satisfaction	83% (42%)	93% (55%)

Table 1. ASCRS Clinical Survey results
**=Percentages in parentheses represent the number of respondents who responded "strongly agree."*

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Educational Objectives
Ophthalmologists who participate in this course will:
- Identify the true impact of ocular inflammation levels on outcomes in refractive cataract surgery, including variability in visual acuity and quality results, delayed visual recovery, and patient comfort and satisfaction;
- Describe strategies to prevent edema and relieve pain by maximizing the penetration of anti-inflammatory agents into target tissues, including key vehicle parameters, dosage, interventional timing and duration, and patient adherence; and
- Discuss the clinical impact of various levels of ultrasound energy during cataract surgery and the amount of reduction available with laser cataract technology for specific types of patients.

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Sonia H. Yoo, MD

The true impact of ocular inflammation on refractive cataract surgery outcomes

by Sonia H. Yoo, MD

Inflammation-associated postoperative pain results in dissatisfied patients

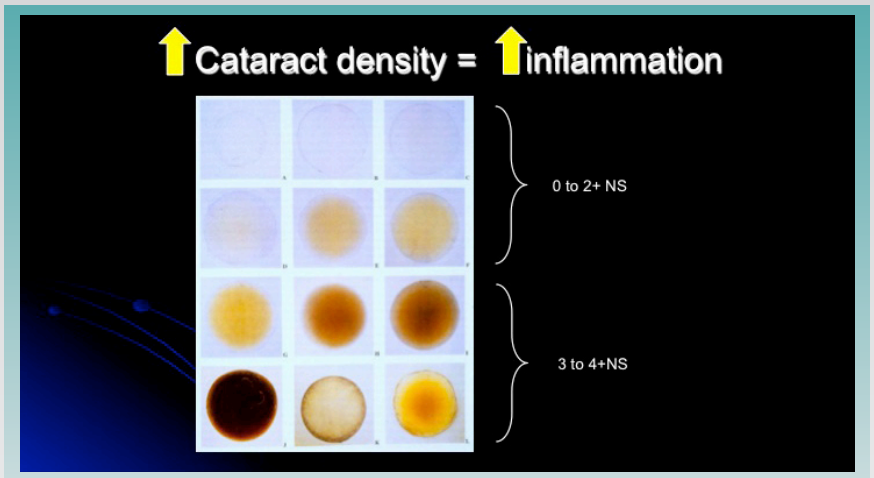

Figure 1. Cataract density, ranging in grade from 0 to 4+. As the cataract density increases from 0 (upper left corner) to 4+ (lower right corner), the risk of postoperative inflammation increases as well.

Adapted from Chylack et al., 1993[10]

The physical trauma associated with ocular surgery can induce an inflammatory response that affects the entire eye. Inflammation on the cornea generates prostaglandins (caused by initiating the arachidonic acid cascade) that activate both cyclooxygenase-1 and cyclooxygenase-2.[1] This cascade can manifest clinically as hyperemia, miosis, impaired vision, or diminished visual acuity secondary to cystoid macular edema (CME) in more severe cases.[1,2] Subjective complaints can range from pain to photophobia.[3] Phacoemulsification typically does not result in significant inflammation, but some patients are at higher risk and will experience some form of postoperative inflammation.[4,5]

For the typical cataract patient, what had been acceptable postop vision (20/40) years ago is no longer acceptable, especially in the premium IOL patient population.[3] For this group, any postop incident that can reduce visual acuity (even if transient) is considered a failure on the part of the surgeon to deliver the best care possible.

Factors influencing postop inflammation

The higher the density level of cataract, the greater the likelihood for inflammation[6] (see Figure 1). Iris pigmentation is another factor;

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a primary reason anterior segment surgeons use NSAIDs postop is for CME prophylaxis. (See Table 2 for the list of recently approved NSAIDs and steroids.)

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Drug (active ingredient, manufacturer)	Drug type	Indication	Dosing
Ilevro[8] (nepafenac 0.3%, Alcon)	NSAID	Treatment of pain and inflammation associated with cataract surgery	1 drop day before surgery, day of surgery, and 14 days postoperatively; additional drop administered 30–120 minutes before surgery
Prolensa[10] (bromfenac 0.07%, Bausch + Lomb)	NSAID	Treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery	1 drop day before surgery, day of surgery, and 14 days postoperatively
Lotemax gel[7] (loteprednol etabonate ophthalmic gel 0.5%, Bausch + Lomb)	Corticosteroid	Treatment of postoperative inflammation and pain following ocular surgery	1–2 drops 4 times daily beginning the day after surgery and continuing throughout the first 2 weeks of the postoperative period
Durezol[11] (difluprednate 0.05%, Alcon)	Corticosteroid	Treatment of inflammation and pain associated with ocular surgery; treatment of endogenous anterior uveitis	1 drop 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 postop weeks; 2 times daily for a week; then taper based on response

Table 2. Anti-inflammatory drugs, 2013

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Previous traditional cataract patient	Today's cataract patient
Retired	Working
Minimal to no driving	Independent
Not on a computer	Uses cell phone, computer, tablet
Expectation of recovery time	Needs good functional vision as quickly as possible
Needed glasses postop	Pays for premium IOL

Table 1. Changing patient needs. Patients expect cataract surgery to be "no big deal," with little pain and excellent postop day 1 vision. Any pain or reduced visual acuity equates to poor service and surgery on the part of the physician.

Source: Sonia H. Yoo, MD

patients with darker irides are more prone to postop inflammation.[7] Similarly, the younger the patient, the more likely postop inflammation will occur,[8,9] and these patients are at risk for capsular fibrosis and iritis postoperatively. From the surgical standpoint, the more balanced salt solution used, the greater the likelihood of postoperative inflammation. Longer surgical times also result in a higher likelihood of inflammation.[1,6]

Numerous comorbid conditions can directly impact the risk of increased postop inflammation,[11,12] including diabetes or autoimmune disorders, or ocular conditions such as corneal disease, inflammatory conditions, glaucoma, weakened zonules/intraoperative floppy iris syndrome, history of retinal vascular disease, or a history of trauma, to name a few.

Cystoid macular edema

The incidence of post-cataract clinical CME is 1–2%,[2,13] but the incidence of angiographic CME is much higher.[12,13] In the short term, CME leads to patient discomfort and displeasure with their vision, but if the CME does not resolve, the visual detriment could be long lasting. There is increased cost of care, as these patients necessitate more chair time and prolonged drug use.

Patient lifestyles are also changing. Today's patients actively use computers, tablets, smartphones, and pay out-of-pocket for premium technologies (see Table 1). In short, these are not patients who tolerate any kind of disruption to their daily lifestyle well. As a result, anterior segment surgeons use anti-inflammatory medications prophylactically and during the postoperative period to diminish the likelihood of CME even further.[5,14,15]

The anti-inflammatory effects of steroids are well known.[16,17] Although topical steroids seem to be more powerful than nonsteroidal anti-inflammatory drugs (NSAIDs), as the latter only inhibit cyclooxygenase, steroids do have frequent, potentially dangerous side effects. NSAIDs, on the other hand, are well known for their extraordinary safety profile.[16,17] A literature search recommended the prophylactic use of NSAIDs in combination with corticosteroids to prevent CME.[17] In this meta-analysis, the recommended treatment is one drop 4 times daily the day before surgery and continuing for 4 weeks after surgery. (And one drop every 15 minutes in the hour immediately before surgery.[17]) The preoperative treatment with NSAIDs followed by combined NSAID/steroid therapy postoperatively is considered the "standard of care" in cataract surgery.[16]

In my practice, I prefer to use a steroid (prednisolone acetate 1% or loteprednol), an antibiotic (moxifloxacin or trimethoprim/polymyxin B), and ketorolac 0.5% four times daily in week 1, with a quick taper on the steroid to 3, 2, and 1 time daily in weeks 2–4. I stop the antibiotic after 1 week, and continue to have the patient use the NSAID 4 times daily until the bottle runs out.

Postoperative pain: A continuum

Postoperative pain complaints can vary from minor discomfort to "FTS" (patient "feels the stitches") to moderate-to-severe pain. The latter groups may have borderline ocular surface disease as well.

Fung et al. evaluated 306 subjects undergoing cataract surgery to measure both pain and satisfaction levels during the immediate postoperative period (in the recovery room).[18] They found 37% of subjects reported mild-to-moderate postop pain, and 34% required oral pain medication to alleviate their symptoms. Gender and cataract density were not significant determinants of postop patient satisfaction; preoperative anxiety and postoperative pain were. Any postoperative pain was the single most significant predictor of dissatisfaction with the subject's care. The greater the postop pain, the lower the rating for quality of the surgical experience.

Summary

Given the evidence that postoperative inflammation slows visual recovery, it is our responsibility to do what we can to minimize inflammation in order to maximize postop vision and speed recovery time. We know that nonsteroidal anti-inflammatory drugs and steroids are often used together to achieve those purposes.[19,20]

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Steven J. Dell, MD

The impact of reducing or eliminating ultrasound energy on inflammation

by Steven J. Dell, MD

Figure 1. An example of a geometric shape created by a femtosecond laser. Multiple microscopic pulses form the desired ablation geometry.

Source: Bausch + Lomb

The less surgical stress that is introduced into the ocular system during surgery, the lower the risk of postop inflammation

Surgical stress on the eye begins before the first incision is ever made. Topical anesthetics, antibiotics and other topical agents begin a cascade that releases inflammatory mediators. Postoperative corneal edema is related to some aspects of the cataract procedure itself, including ultrasound time and the volume of irrigation/aspiration (I/A), but also to non-surgical factors, such as cataract density or ocular comorbidities.[1] But at its heart, postop inflammation is a direct result of the surgical stress the eye undergoes during surgery.[2] There are various techniques for lens removal that all attempt to produce a gentler surgery. Pre-slicing techniques have better outcomes than stop-and-chop techniques in terms of cumulative ultrasound, cumulative delivered energy. Divide-and-conquer takes more time and uses more energy than chopping techniques.[3–8] A 2008 clinical trial demonstrated ultrasound energy consumption (phacoemulsification time, power, and EPT) was significantly higher in a stop-and-chop group vs. the nuclear pre-slice technique. Both techniques had similar results including endothelial cell loss.[9] Further, whenever ultrasound energy is used, there is the potential for wound burn.[10]

However, Sorensen et al. found phacoemulsification-induced wound burns are inversely correlated to a surgeon's experience, and can be reduced by nucleus disassembly choice, ophthalmic viscosurgical device (OVD) choice, and by reducing or eliminating ultrasound altogether when the anterior chamber is filled with OVD.[2] OVDs can factor into the stress introduced, as exothermic dispersive OVDs create more heat production than cohesive forms.

There are 3 principal sources of corneal surgical stress introduced during cataract surgery: the incision, epithelial trauma, and endothelium loss.[2] Minimizing these will result in a gentler surgery. Pupil dilation, anesthetic drops, and commonly used povidone iodine preparations result in epithelial trauma. Endothelial cell loss is increased in eyes with shorter axial lengths and is higher with longer active phaco time. The choice between scleral tunnel or clear corneal incision affects endothelium loss as well.

Femtosecond laser-assisted cataract surgery

Femtosecond laser-assisted cataract surgery has the potential to reduce the phaco energy delivered to the eye by orders of magnitude over ultrasound, as its ability to pre-fragment or soften the lens may result in the reduction or elimination of ultrasound altogether.[11,12]

Femtosecond lasers use a tightly focused, ultra-short pulse of light that causes photodisruption by creating high energy density in whatever tissue they are trying to penetrate. Each "plasma explosion" is a few microns in diameter, which do not cause thermal damage. Geometric shapes are easily created by arranging thousands of these pulses into various shapes (see Figure 1).

Laser-assisted cataract surgery (LACS) utilizes a femtosecond laser to perform several functions in cataract surgery, including creation of the capsulotomy, entry wounds, astigmatic incisions, and lens fragmentation. In the first 3 mentioned steps, surgeons are using the laser primarily to improve the precision of what we could do manually. Lens fragmentation is unique in that it pre-softens the lens, considerably altering the conditions that are

present when we enter the eye with the phaco tip. It is prudent to urge caution when discussions about the latest femtosecond lasers occur, as surgeons are using substantial volumes of I/A through the eye to achieve some of the low phaco times. Ideally, surgeons attempt to keep disruption of other tissue and heat damage to a minimum.

See Table 1 for the currently approved devices and their respective indications.

Procedure	**Catalys Precision Laser** Abbott Medical Optics	**Femto LDV Z6** Ziemer Ophthalmic Systems AG	**LENSAR** LENSAR	**LenSx** Alcon	**Victus** Bausch + Lomb
Anterior capsulotomy	X		X	X	X
Lens fragmentation	X		X	X	X
Corneal incisions	X	X	X	X	X
Arcuate incisions	X	X	X	X	X

Table 1. Femtosecond lasers for cataract surgery: U.S. approvals as of July 31, 2014

Personal experience with LACS

I have been performing femtosecond LACS since 2010. Among the initial concerns was how these lasers would affect intraocular pressure or temperature, and whether they would increase the risk of macular edema. The literature predominantly favors LACS: LACS was found to cause less corneal swelling in the early postoperative period.[13] It was suggested LACS causes less trauma to corneal endothelial cells than standard phacoemulsification.[13] Effective phacoemulsification time is significantly reduced with LACS.[14]

Nagy et al. demonstrated reduced incidence of macular edema on optical coherence tomography as compared to standard phacoemulsification.[15] Even more recently, Conrad-Hengerer et al. found LACS does not increase the risk of macular edema[16] and does not affect cortex removal times compared to standard phaco.[17]

However, Schultz et al. found prostaglandins rise immediately after femtosecond treatment.[18] This suggests future patients may be better served if they are treated with NSAIDs to maintain mydriasis before undergoing LACS. My personal preop/postop regimen for uncomplicated patients undergoing cataract surgery involves using a topical NSAID for 2 days preop and for 4 weeks postop. Topical steroids are also used for the same duration. Topical antibiotics are used for 1 week postop.

In all LACS cases I still use some level of phaco to remove residual lens material. But any substantial reduction in phaco energy is highly beneficial for the patient and for reducing the risk of postop inflammation.

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Keith A. Walter, MD

Maximizing penetration of anti-inflammatory agents to prevent edema and relieve pain

by Keith A. Walter, MD

The importance of the vehicle used to deliver ophthalmic drugs cannot be overlooked and may play a role in both patient compliance and drug efficacy

Numerous ophthalmic medications are now being marketed in once daily formulations or in preservative-free formulations. How the medication is delivered to the target tissue (the vehicle) is possibly the second most important variable after the active ingredient. Today's newer vehicles decrease toxicity, increase solubility, increase ocular concentrations, and decrease dosing. Yet even with these advances, the majority of eye drops have less than 5 minutes of ocular surface contact time.[1]

Studies have shown that a 50 µL drop will result in only 5% of the original dose reaching the target tissue.[1,2] During that 5 minutes, tearing and blinking, tear film turnover, conjunctival and scleral absorption, and corneal absorption can disrupt the delivery of that drug.[1–4] A substantial obstacle in drug delivery is ensuring the maximal drug concentration is achieved at the desired site of action.[5] (See Figure 1.)

The role of the vehicle

Achieving sufficient corneal penetration and prolonged contact time with the corneal tissue can be accomplished by increasing the effective dose, increasing the active drug concentration, improving the molecular design (increasing lipophilicity and solubility), or increasing the frequency of instillation.[1,5–7] Opting to increase the number of drops a patient must instill daily is not optimal and has been shown to decrease patient compliance.[8]

Increased lipophilicity will result in a soluble compound that can more easily penetrate the cornea.[9]

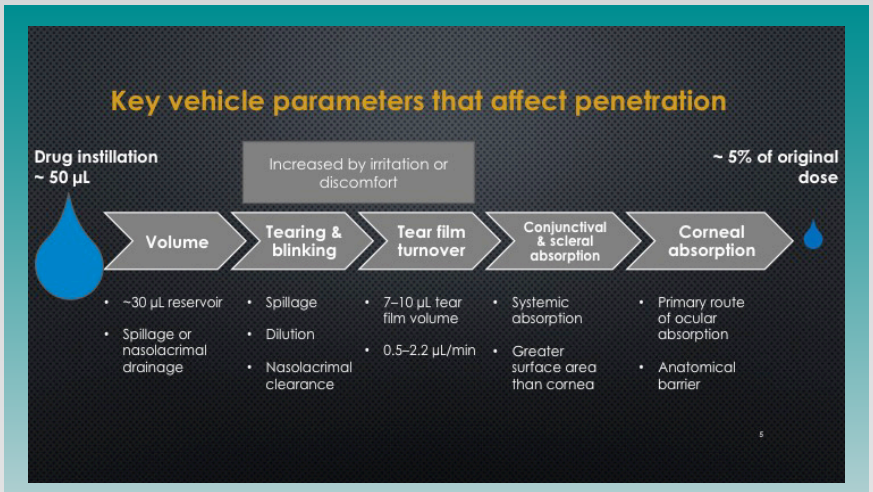

Figure 1. Key vehicle parameters that affect penetration. Numerous factors can adversely impact the amount of active ingredient that penetrates the ocular surface to reach the target tissue area.

Image adapted from Bausch + Lomb

Both bromfenac and nepafenac (two well-known nonsteroidal anti-inflammatory drugs, or NSAIDs) have unique chemical structures that facilitate penetration through cell membranes. Bromfenac is a highly lipophilic molecule that rapidly penetrates to produce early and sustained drug levels in all ocular tissues. It manifests in a rapid reduction of postsurgical inflammation and pain.[9] Nepafenac is not very lipophilic, but as a prodrug it can cross the cornea more rapidly.

Nepafenac 0.3% utilizes a new product formulation with a higher viscosity realized by the introduction of guar gum. It also features a reduced particle size and a more physiological pH (7.4).[10] The topical corticosteroid loteprednol gel 0.5% uses mucoadhesive technology; it has been engineered to adhere to the ocular surface. This adaptive technology allows the agent to start as a gel and as the patient blinks, the force of the blink alters the composition to its liquid form.[11] Lipid emulsion increases bioavailability and provides uniform medication in the most recent difluprednate formulation.[12] A benefit of this technology is that it remains in suspension, eliminating the need for patients to shake the bottle before instillation.

Polycarbophil USP is a polymer that provides the gel structure to the formulation to prevent sedimentation. It also functions as a mucoadhesive and viscoelastic suspending agent. From a clinical perspective, the new non-settling formulation delivers consistent, full doses to the ocular surface for reliable drug delivery and subsequent clinical effect. It is currently being used in loteprednol gel and DuraSite drug delivery vehicles. In a rabbit study, the administration of azithromycin ophthalmic solution 1% in DuraSite resulted in 18-fold higher maximum concentrations (Cmax) in rabbit superior bulbar conjunctiva than 1% azithromycin aqueous formulation (without DuraSite drug delivery vehicle).[13]

Not all vehicles are the same. New products must undergo animal studies, clinical studies, and bioavailability analyses, costs spiral into the hundreds of millions, and it may take up to 12 years to bring a single new entity to market.[14] In both Canada and the U.S., generic formulations must demonstrate similar bioequivalence to the original drug and show comparable absorption.[15] However, generic manufacturers can vary the nonactive ingredients, bottle design, and drop volume. Drop size is directly related to the outer orifice diameters and can vary widely from name brand to generic, resulting in highly variable drop volume.[15]

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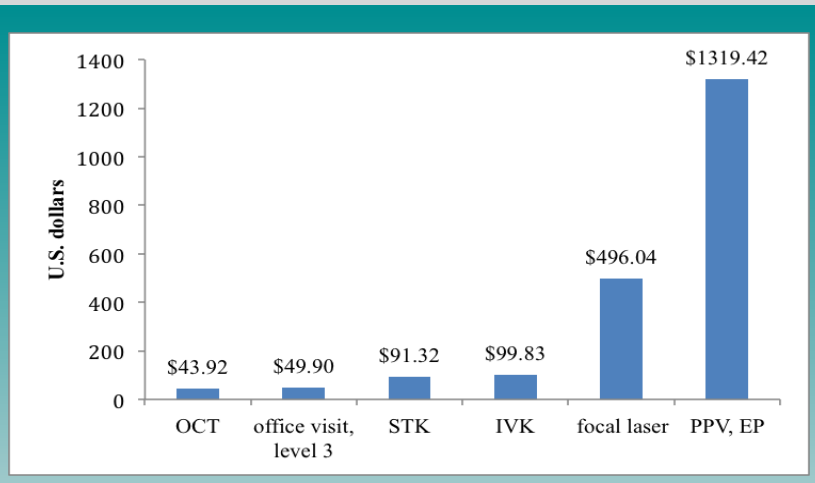

Figure 2. Medicare allowable payments. Medicare allowable payments (cost in U.S. dollars, North Carolina 2014 Revised Medicare Part B Fee Schedule) for services related to the diagnosis and treatment of CME. STK = sub-Tenon's triamcinolone; IVK = intravitreal triamcinolone; PPV = pars plana vitrectomy; EP = epiretinal membrane peel

Dosing therapy for maximum effect

Claxton reviewed 76 compliance studies that measured dosing through electronic monitoring. Mean dose-taking compliance was 71%±17% (range 34%–97%) and declined as the number of daily doses increased: 1 dose = 79%±14%, 2 doses = 69%±15%, 3 doses = 65%±16%, 4 doses = 51%±20% (P<0.001 among dose schedules). Compliance was significantly higher for once-daily versus 3-times-daily (P=0.008), once-daily versus 4-times-daily (P<0.001), and twice daily versus 4-times-daily regimens (P=0.001); however, there were no significant differences in compliance between once-daily and twice-daily regimens or between twice-daily and 3-times-daily regimens. In the subset of 14 studies that reported dose-timing results, mean dose-timing compliance was 59%±24%; more frequent dosing was associated with lower compliance rates.[16]

Patient compliance in the real world

The science behind these medications and their ophthalmic delivery is moot if patients do not adhere to the treatment regimen. Real world noncompliance is relatively high.[17–19] In one study of 500 patients in Canada, Kholdebarin et al. found an overall 27.9% noncompliance with ocular therapeutics: 28.8% contaminated the bottle tip and 33.8% demonstrated improper technique.[17] Winfield et al. found 69% of patients would refuse to tell their doctor about problems with drop administration even when directly asked.[19] Although the majority of patient compliance studies are concentrated on chronic illnesses such as glaucoma, it has been noted that treatment duration of under 5 years increased patient-reported noncompliance.[17]

Avoiding cystoid macular edema

In today's environment, nepafenac and bromfenac are indicated for once-daily use, which should improve compliance and, therefore, reduce postoperative events,[18] including cystoid macular edema (CME).[20–22]

At our center, we evaluated the last 42 cases of clinically proven CME with optical coherence tomography. Follow-up was 1 year from time of detection. Our goal was to determine how easily treated CME is, the expense associated with treatment (see Figure 2), and the time to resolution. At last follow-up, only 14% had best corrected visual acuity (BCVA) of 20/20 or better, 26% were 20/40 or worse, and 1 patient was 20/100. We also found 31% progressed to a permanent epiretinal membrane.

At Wake Forest, our prophylactic treatment regimen includes prescribing an NSAID 2 days before cataract surgery and having patients continue for 30 days postop. Since implementing this regimen, our incidence of CME is about 1 in 1,000. We are currently evaluating NSAIDs alone (without the concomitant use of a steroid postop). To date:

- 1 case in 1,300 when bromfenac 0.07% was used
- 2 cases in 2,000 when bromfenac 0.09% was used
- Ongoing analysis with nepafenac 0.3% alone

All our patients have had good refractive outcomes.

NSAIDs have been well established at reducing inflammation and decreasing postop pain. We are now finding they are also capable of preventing CME; none of the currently marketed NSAIDs are approved in the U.S. for CME prophylaxis.

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CME Questions (Circle the correct answer)

1. **Inflammation on the cornea generates prostaglandins; this inflammatory cascade can manifest clinically as:**
   a. Hyperemia
   b. Miosis
   c. Impaired vision
   d. CME
   e. All of the above

2. **Which patients have less likelihood of inflammation?**
   a. Diabetic patients
   b. Older patients
   c. Patients with high density level of cataract
   d. Patients with darker irides
   e. Younger patients

3. **According to Fung et al., any postoperative pain was the single most significant predictor of dissatisfaction with the subject's care.**
   a. True
   b. False

4. **Which of the following is NOT a principal source of corneal surgical stress introduced during cataract surgery?**
   a. The incision
   b. Endothelium loss
   c. Epithelial trauma
   d. Pupillary constriction

5. **Which of the following is NOT an optimal way for a topical eye drop to achieve corneal penetration and prolonged contact time with the corneal tissue?**
   a. Increasing the active drug concentration
   b. Increasing the frequency of instillation
   c. Increasing lipophilicity
   d. Increasing solubility

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