

# Inflammation Control in LASIK and PRK: New Findings

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See complete CME information on page 2.

## STATEMENT OF NEED AND PROGRAM DESCRIPTION

While surface ablation procedures such as LASIK and photorefractive keratectomy (PRK) do not trigger as much inflammation as intraocular procedures, poorly controlled postoperative inflammation can still result in both short-term and long-term consequences following LASIK and PRK, including haze, diffuse lamellar keratitis, and pain. Surgeons have thus devoted considerable attention to developing effective postoperative antiinflammatory regimens, with most surgeons using a steroid following LASIK and both a steroid and a non-steroidal antiinflammatory drug (NSAID) following PRK.

Strong steroids—including prednisolone acetate, dexamethasone, and difluprednate—are known to provide excellent antiinflammatory efficacy, but their use following refractive surgery has been limited by concerns about side effects associated with long-term use of these drugs. More recently, however, surgeons have begun to focus more on the risks of poorly controlled postoperative inflammation and use of strong steroids is becoming more common, at least in the immediate postoperative period. Surgeons therefore need to consider the merits of various drugs for this application, including the new drug difluprednate.

**OFF-LABEL USE STATEMENT** This work discusses off-label uses of antiinfective and antiinflammatory medications.

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**TARGET AUDIENCE** This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

## LEARNING OBJECTIVES

1. List 3 clinically relevant differences between topical prednisolone acetate 1% and topical difluprednate 0.05%.
2. State the arguments for and against using a strong steroid to control postoperative inflammation following refractive surgery.
3. List 3 non-pharmaceutical strategies to minimize inflammation following PRK.

## FACULTY AND DISCLOSURE STATEMENTS

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**COMMERCIAL SUPPORTERS** This activity is supported by an educational grant from Alcon Laboratories, Inc.

# Inflammation Control in LASIK and PRK: New Findings

Eric D. Donnenfeld, MD, and Karl G. Stonecipher, MD

While nonpenetrating corneal procedures such as LASIK and photorefractive keratectomy (PRK) generally produce less inflammation than intraocular procedures, patients can still experience serious complications if this inflammation is not adequately controlled. Among the possible consequences of post-refractive surgery inflammation are haze, scarring, diffuse lamellar keratitis (DLK), and excessive reepithelialization, all of which can lead to temporary or permanent decreases in vision.

In some cases, inflammation may lead to a persistent epithelial defect, which not only results in impaired vision but also increases the risk of infection and other undesirable sequelae. This is not to mention postoperative discomfort, which all surgeons strive to minimize, particularly in elective surgeries. In fact, because refractive surgery is an elective procedure driven largely by word of mouth from satisfied patients, any complication can be deleterious to the surgeon's success.

To prevent inflammatory complications and to increase the chance of a fast and comfortable recovery, most surgeons use one or more antiinflammatory medications to control inflammation following LASIK or PRK. While there are many such medications available—including nonsteroidal antiinflammatory drugs (NSAIDs), antihistamines, and topical cyclosporine—steroids remain the mainstay of postoperative antiinflammatory regimens.

There is debate as to which type of steroid is best, with some arguing that less potent steroids (eg, loteprednol etabonate 0.5%, fluorometholone 0.1%) have safety advantages, while others contend that strong steroids (eg, difluprednate 0.05%, prednisolone acetate 1%, dexamethasone 0.1%) quell inflammation quickly and effectively and, so, bring about a faster and more complete visual recovery. A corollary to this argument is that all steroids (including strong ones) are generally relatively safe when used for a brief period of time.

Within each group of steroids, there are also differences between specific drugs in terms of efficacy, safety, and other parameters. While most of today's steroids have been available for a decade or more (and many for as long as three decades), difluprednate is relatively new and differs from other members of its class in both the pharmacological properties of the active molecule and in its formulation as an emulsion.

## Inflammation in PRK

Surface ablation of all types requires removing a large section of the corneal epithelium, which can provoke a significant inflammatory response. The degree of acute inflammation, however, can vary widely between individuals during the early stage of wound healing.

In broad outline, the epithelial cell membrane damage of PRK has been shown to trigger the recruitment of inflammatory cells and to incite the release of prostaglandins and other inflammatory mediators, all of which contribute to the inflammatory cascade.<sup>1</sup> The degree of inflammatory response observed after PRK is related to the size of the

epithelial defect, with larger defects yielding a stronger inflammatory response (all other things being equal). However, the method of epithelium removal (eg, epithelial brush vs alcohol vs laser) does not seem to affect the amount of postoperative inflammation.<sup>2</sup>

Pain and delayed healing are common byproducts of the acute inflammatory response that follows any ocular procedure; inflammation following PRK can also cause haze. Such haze is particularly associated with removal of the epithelial basement membrane and Bowman's layer.<sup>3</sup> The haze that follows PRK appears to result from the enhanced backscattering of light from highly reflective fibroblasts recruited to the site of cell destruction.<sup>4</sup>

### Inflammation in LASIK

Because there is much less epithelial trauma in LASIK than in PRK, LASIK typically triggers a milder inflammatory response. In addition, since the thin wound at the LASIK flap margin creates a much smaller defect than the 8- or 9-mm epithelial defect associated with PRK, inflammation resolves more quickly after LASIK than after PRK.

The technology used to cut the LASIK flap may, however, affect the severity of post-LASIK inflammation, with some evidence suggesting that older femtosecond lasers are associated with more inflammation than mechanical microkeratomers. However, not all femtosecond lasers are the same in this regard—most newer femtosecond lasers are associated with less inflammation, perhaps because they cut more quickly and use lower energies.<sup>5</sup> A study that compared several femtosecond lasers to a mechanical microkeratome in rabbit eyes found no significant differences between a 60KHz femtosecond laser and the mechanical microkeratome in terms of stromal cell death, stromal cell proliferation (except for mitotic stromal cells at the flap margin), or monocyte influx at 24 hours.<sup>6</sup>

### Consequences of Inflammation

In PRK there is concern that inflammation will cause a diffuse stromal scar ("late haze"), resulting in visually significant haze. Haze can reduce visual acuity and also cause glare, halos, or starbursts. Excess epithelial regrowth, which can cause regression of the refractive effect, is also a potential consequence of postoperative inflammation.

In LASIK, the most serious concern is that poorly controlled inflammation will lead to DLK (Figure 1). DLK can vary greatly in severity; while some eyes show only a mild interface haze, a more severe inflammatory response underneath the flap can cause collagenase release, resulting in the destruction of corneal tissue and possibly corneal flattening and/or irregular astigmatism. When the inflammation of DLK becomes severe, aggressive treatment with strong topical corticosteroids every 1 to 2 hours may be the only option to quiet the inflammatory process. In the past, we prescribed hourly prednisolone acetate 1%; but due to its increased potency, we now opt for difluprednate every 2 hours. Some clinicians also recommend the use of oral corticosteroids such as prednisone 60 mg daily. For especially severe (grades 3 and 4) DLK, we lift the flap and irrigate the stromal bed as atraumatically as possible with balanced salt solution.



**FIGURE 1** An eye with grade 3 DLK responded only minimally to 5 days of hourly prednisolone acetate 1%, but resolved in 2 days after therapy with difluprednate 0.05% every 2 hours.

In addition, the post-LASIK inflammatory response can adversely affect the epithelial basement membrane, potentially impairing its ability to bind the epithelium to the corneal stroma. This can lead to microerosions or even persistent epithelial defects.

Finally, as with any procedure, inflammation following LASIK or PRK can cause postoperative discomfort. Because PRK creates a large epithelial defect, untreated patients can experience significant discomfort for several days after the procedure. Pain after LASIK is generally mild and typically resolves within the first postoperative day.

### **Steroids and NSAIDs**

Pharmacologic inflammation control has been a part of LASIK and PRK from their earliest days. In addition to preventing complications, good inflammation control maximizes patient satisfaction—an essential aspect of any elective procedure. Today more than ever, patients demand a quick and pain-free recovery, and that requires effective inflammation control.

Because corticosteroids act quickly to control the inflammatory cascade—enabling faster visual rehabilitation with less pain—these drugs play a significant role in LASIK and PRK. In addition, NSAIDs and non-medical therapies can help to control postoperative inflammation in some patients.

Following PRK, it is common practice to prescribe a corticosteroid for at least 2 weeks, and many surgeons continue the steroid for up to 3 months in order to prevent late haze formation. To minimize the risk of steroid-induced intraocular pressure (IOP) increases, less potent steroids with a higher safety profile such as loteprednol etabonate or fluorometholone may be preferred for long-term use, although a strong steroid can be used to quell inflammation during the immediate postoperative period, after which the patient can be switched to a less potent steroid.

In addition to steroids, most surgeons use an NSAID to control inflammation following PRK. NSAIDs help to keep patients comfortable and act synergistically with steroids to improve inflammation control. Because steroids and NSAIDs target different parts of the inflammatory cascade, using both types of drugs yields broader inflammation control than could be achieved by either drug alone. NSAIDs are typically withdrawn 2 to 4 days following PRK, however, because of the risk of a persistent epithelial defect.

Following LASIK, the antiinflammatory regimen consists of a topical steroid, typically used for 4 to 7 days, but no NSAID. (The steroid typically suffices to control inflammation, and pain is seldom a serious issue in LASIK.) However, it has been suggested that by reducing ocular discomfort (and, therefore, eye touching) an NSAID can minimize the formation of microstriae and other complications associated with eye rubbing after surgery.

### **Preexisting Inflammatory Conditions**

Preexisting inflammatory conditions such as ocular allergies and dry eye disease can exacerbate postoperative inflammation. Patients with acute or chronic allergy are at particular risk of developing wound-healing problems after corneal refractive surgery. For this reason, pretreatment is essential to ensure good surgical outcomes. This can include treating the allergic patient with a combination antihistamine/mast cell stabilizer, such as olopatadine or epinastine, and/or a mild steroid prior to surgery. In some cases, it may be wise to postpone surgery until allergy season has passed.

Similarly, dry eye disease should be addressed both pre- and postoperatively in order to minimize its impact on surgical outcomes—the irritation and inflammation of dry eye disease can be greatly exacerbated by surgery, with LASIK being a significant instigator of dry eye symptoms. Preoperative treatment with topical cyclosporine is often adequate

## THE PHARMACEUTICAL REGIMEN

The following is Dr. Donnemfeld's standard antiinflammatory regimen. Note that postoperative drug regimens vary between surgeons, and even between patients treated by the same surgeon, so this regimen should be modified as appropriate.

### ► For PRK

- Difluprednate 0.05% QID for 1 week, then loteprednol etabonate 0.5% tapered over 4 weeks (QID for 1 week, TID for 1 week, BID for 1 week, and QD for 1 week)
- Ketorolac tromethamine ophthalmic solution 0.45% BID for 3 days
- Oral nonsteroidal (eg, ibuprofen) 400 mg every 4 hours for 1-2 days

### ► For LASIK

- Difluprednate 0.05% every 2 hours on the day of surgery, then BID for 4 days
- 1 drop ketorolac tromethamine ophthalmic solution 0.45% at the time of surgery

to control mild to moderate dry eye disease, but the addition of a mild topical steroid such as loteprednol etabonate may be appropriate for more severe cases. As with allergic patients, it can be wise to adjust the timing of surgery. For example, winter's lower humidity levels can increase the severity of dry eye patients' symptoms, so prudence may dictate postponing surgery until spring or summer when relative humidity levels rebound. If the dry eye condition cannot be resolved preoperatively, surgery may be contraindicated.

In addition to treating patients with preexisting dry eye disease, surgeons need to be alert to dry eye that may develop after surgery, since the combination of severed nerves and postoperative inflammation can trigger dry eye symptoms in a significant fraction of patients. Often vision changes, rather than the classic symptoms of burning or gritty sensations, signal the presence of postoperative dry eye, particularly in LASIK patients. This is because cutting the LASIK flap severs corneal nerves, rendering the eye less sensitive for a period of months.<sup>7</sup> Thus, patients may not report the typical discomfort sensations of dryness; instead the dry eye becomes apparent only through visual symptoms. Treatment typically consists of topical cyclosporine and/or a topical corticosteroid, along with a good artificial tear.

### Other Antiinflammatory Treatments

Some non-drug treatments can provide antiinflammatory benefit following refractive surgery. For example, the use of a nonpreserved artificial tear or other lubricant can help reduce lid-induced irritation on blink and promote healing following both PRK and LASIK.

During PRK, application of cold packs (or a "popsicle" of balanced salt solution) can help to reduce inflammation and improve patient comfort. In addition, use of a bandage contact lens following PRK reduces inflammation by protecting the exposed corneal nerves and reducing the shear forces of the eyelid against the corneal surface, further helping to keep the eye quiet and comfortable.

### Steroid Selection

While the use of NSAIDs, antihistamines, and topical cyclosporine are highly beneficial in select patients, steroids remain the mainstay of the post-refractive sur-

gery antiinflammatory regimen. To optimize the use of these drugs, surgeons should carefully consider each patient's inflammation control needs and select the steroid (or steroids) that will best meet those needs, keeping in mind the safety profile of each of the steroids in the surgeon's armamentarium. In general, one wants to use the strongest steroid available consistent with patient safety. This will shorten recovery, reduce the chance of inflammatory complications, minimize pain, and decrease the amount of necessary drug.

Healing occurs fairly quickly following LASIK, so inflammation control is rarely needed for more than 2 weeks after this procedure. As a result, a strong steroid can be used until the postoperative inflammation resolves, after which the drug should be tapered. Because the steroid is used for only a short period of time, classic steroid side effects (such as IOP elevation, increased risk of infection, and cataract formation) are unlikely to occur. Also, since LASIK creates only a slender corneal incision around the periphery of the flap, there is rarely any danger of the steroid negatively affecting the healing process.

In PRK, the risks of strong steroids must be weighed carefully. Because PRK patients have a large epithelial defect, a strong steroid could potentially affect healing. On the other hand, these patients have more inflammation and a longer recovery period, so their need for good pain management and long-term inflammation control is greater. One compromise is to use a strong steroid during the immediate postoperative period and then switch to a weaker steroid (loteprednol etabonate or fluorometholone) for long-term inflammation control. (This should reduce the danger of IOP spikes as well.<sup>8</sup>)

### **Risk Factors for Inflammation**

Differences between patients can and should influence the decision of when to use a strong steroid. While brief (less than 2-week) use of strong steroids is generally safe in most patients, some individuals are at higher risk of complications. In particular, the chief concern with strong steroids is the possibility of IOP spikes. This risk demands especially careful monitoring when using strong steroids in patients with glaucoma or ocular hypertension. In managing such patients, surgeons may want to shorten the course of the postoperative steroid to limit the risk of side effects.

There is, perhaps, an increased risk of infection when using steroids, and, indeed, strong steroids may be contraindicated in patients with a history of recent or frequent viral infections. (Of course, the surgery itself may be contraindicated in such cases, depending on the patient's medical history.)

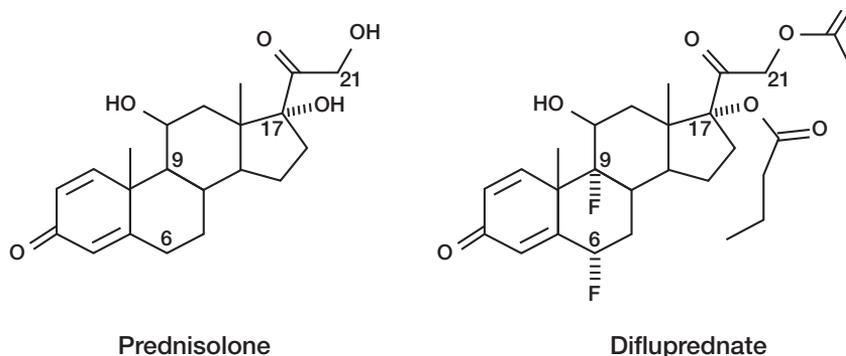
There are other patients in whom the risk of uncontrolled inflammation is the greater concern. These include patients with a history of keloids or other known predisposition to scarring. By nature, these patients are more likely to have severe postoperative inflammation following refractive surgery. Patients with a history of atopy, ocular inflammation, or corneal scarring are also at elevated risk of negative sequelae if subjected to severe inflammation. Other patients at increased risk from inflammation are patients who have developed corneal abrasions during LASIK and individuals undergoing PRK for correction of a high refractive error and/or those with larger epithelial defects.

Given this increased risk of inflammation, the antiinflammatory regimen for these patients may need to be expanded beyond what is recommended in routine cases. In addition to using stronger steroids and/or increasing the frequency of dosing, preoperative use of topical steroids and/or use of oral steroids may also be warranted. Of course, the risks associated with steroid use will increase as more aggressive antiinflammatory regimens are implemented. In some cases, the associated risks may be unacceptable and the procedure itself contraindicated.

## Increased Potency

Given the benefits of strong steroids, there is good reason to consider using one of these drugs as part of a post-refractive surgery antiinflammatory regimen. Most commercially available topical steroids are well known to ophthalmologists, as almost all of these drugs have been in use for a decade or more. The exception is difluprednate, which was approved by the Food and Drug Administration in 2008. Several times stronger than prednisolone acetate—the long-time gold standard among strong steroids—difluprednate is formulated as an emulsion rather than a suspension and is preserved with sorbic acid rather than benzalkonium chloride (BAK).

While the chemical structure of difluprednate is similar to that of prednisolone, the difluprednate molecule has been modified in several ways (Figure 2). First, difluprednate is fluorinated at both the C-6 and C-9 positions and has a butyrate ester at the C-17 position. These substitutions increase the drug's potency; and together they give difluprednate a receptor binding affinity 24 times greater than prednisolone.<sup>9</sup>



**FIGURE 2** A derivative of prednisolone acetate, difluprednate has been modified in several ways, including fluorination at the C-6 and C-9 positions, addition of a butyrate ester at the C-17 position, and the addition of an acetate ester at the C-21 position.

In addition, an acetate ester at the C-21 position increases the molecule's lipophilicity, which in turn increases tissue penetration. With esters at the C-17 and C-21 positions, difluprednate is broken down by natural esterases into inactive metabolites within the eye; as a result, little or no active drug reaches the bloodstream, and ocular side effects of the drug are limited.

On a clinical level, difluprednate achieves inflammation and pain control with less frequent dosing than prednisolone. One study of patients with anterior uveitis compared difluprednate 0.05% dosed four times a day with prednisolone acetate 1% dosed eight times a day. Though difluprednate was being used at 1/20 the concentration and was dosed half as often, it was found to be no less effective than prednisolone for controlling inflammation in these patients.<sup>10</sup>

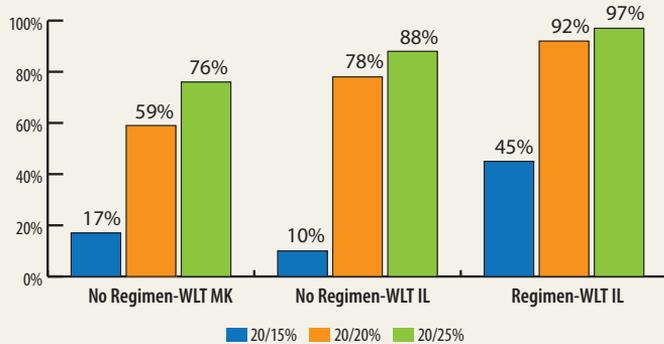
## Difluprednate in Refractive Surgery

It is widely accepted in the medical community that reducing dose frequency enhances patient compliance, and cataract and refractive surgeons are increasingly eager to simplify their postoperative drug regimens. A steroid with the strength of difluprednate enables post-refractive surgery inflammation control with twice-a-day dosing.

While steroids are not pain relievers, *per se*, difluprednate is indicated for relief of both surgical pain and inflammation. In cataract surgery patients, twice-a-day difluprednate was found to be “highly effective for managing ocular inflammation and relieving pain and discomfort postoperatively.”<sup>12</sup> Since postoperative discomfort following PRK can be

## PREOPERATIVE STEROID REGIMEN

One of us (KGS) employs a preoperative steroid regimen to control inflammation, in which a corticosteroid and antibiotic are prescribed QID for 3 days prior to surgery. He reports a significant improvement in visual results on postoperative day 1. The accompanying figure compares vision on postoperative day 1 between two groups of patients with no preoperative treatment (surgery performed with a microkeratome and an excimer laser in the first group; and with a femtosecond laser and the same excimer laser in the second group). A third group of patients was given the preoperative steroid/antibiotic regimen as described above (surgery performed with the femtosecond and excimer lasers). Note the large jump in number of patients with 20/15 vision on day 1 when the preoperative steroid regimen is used.



**FIGURE 1** The graph at right shows the influence of a preoperative regimen on postoperative day 1 vision.

significant, good pain control is essential to overall success. Even in LASIK, surgeons need to minimize discomfort to provide the quality of experience that today's refractive surgery patients expect.

### A New Formulation

We noted earlier that difluprednate's lipophilicity may enhance tissue penetration. Another consequence of its lipophilicity is that the molecule is hydrophobic and therefore cannot be dissolved in aqueous solution. However, rather than formulating the drug as a suspension in an aqueous medium (as is typical with topical corticosteroids), difluprednate is dissolved in oil droplets to form a stable emulsion.

The stability of this emulsion assures that each drop of the difluprednate formulation contains a consistent amount of drug.<sup>13</sup> Consequently, patients do not need to shake the bottle before use. In contrast, suspensions of prednisolone acetate (both generic and branded) can show extreme variations in the amount of active drug per drop, depending on how the bottle is stored and whether or not it is shaken before instillation (See Box: Emulsion vs Suspension Formulas).

Finally, topical difluprednate uses sorbic acid as a preservative, rather than BAK, removing one source of potential ocular surface toxicity.<sup>14</sup>

### Conclusion

While PRK and LASIK typically trigger less inflammation than intraocular procedures, inflammation following refractive surgery can still cause significant side effects, including haze, DLK, and pain. Since these complications can reduce postoperative visual acuity and patient satisfaction, controlling inflammation is a key component of

## EMULSION VS SUSPENSION FORMULAS

When prescribing a topical drop, the assumption is that each drop of the product delivers a consistent concentration of drug. However, this is not always the case with drugs in suspension, since how the bottle is stored and whether or not it is shaken prior to instillation can affect the amount of suspended drug contained in each drop. Even when the bottle is stored upright and shaken adequately before use, suspensions can show significant variations in the amount of drug in each drop.

In one study, the concentration of generic prednisolone acetate 1%, branded prednisolone acetate 1%, and branded difluprednate were compared under various conditions.<sup>13</sup> If the bottle was inverted and not shaken, then both suspensions showed high drug concentrations initially—up to 724% of the label claim for the generic prednisolone acetate suspension—but virtually no active drug was left by the end of the study (Figure A). If the bottle was stored upright but not shaken, then this trend was generally reversed, with low concentrations of the drug in the first few drops and higher concentrations as the bottle was depleted (Figure B).

Even when the bottle was stored upright and shaken before the drop was dispensed, the suspensions still showed variation in the dispensed concentration; the generic prednisolone acetate formulation displayed a range of 501% while the branded prednisolone acetate 1% showed a range of 261% (Figure C).

In all three scenarios, however, the difluprednate emulsion showed consistent dosing. How the bottle was stored or whether it was shaken appeared to have little to no effect on the amount of drug dispensed, with all measurements showing a difluprednate concentration near 100% of the label claim.

FIGURE A

Potency During Storage:  
Inverted, Without Shaking

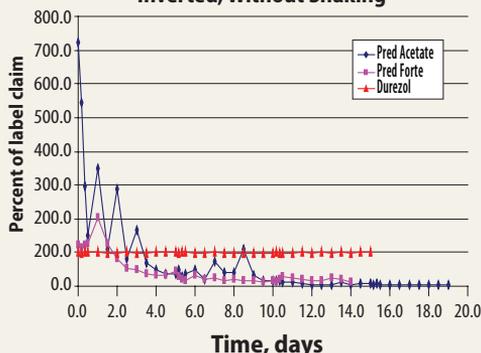


FIGURE B

Potency During Storage:  
Upright, Without Shaking

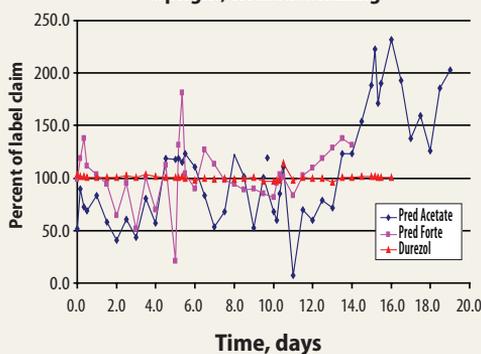
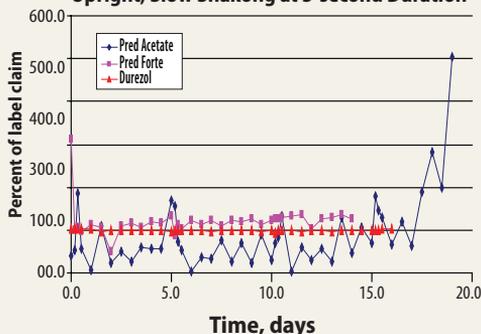


FIGURE C

Potency During Storage:  
Upright, Slow Shaking at 5-second Duration



any refractive procedure. Topical steroids are our chief means for controlling this postoperative inflammation. Steroids are routinely administered for several days following LASIK and for several weeks or months following PRK. Other antiinflammatory drugs can be used as needed where appropriate, including NSAIDs, antihistamines, mast cell stabilizers, and cyclosporine.

When selecting a steroid for inflammation control in PRK or LASIK, efficacy is a key consideration. Quelling inflammation in the least possible time allows patients to achieve a faster visual recovery and minimizes the risk of significant complications. And good inflammation control keeps patients comfortable. For these reasons, a strong steroid may be desirable following refractive surgery.

Of course, rapid effect must be weighed against safety considerations. With strong steroids, the risk of side effects is acceptable in most patients so long as the drugs are used only in the immediate postoperative period. Strong steroids must be used more cautiously, if at all, in patients at greater risk of side effects.

In the strong steroid realm, difluprednate is the first new agent to become available in almost three decades. It differs from other available strong steroids in its greater potency, emulsion formulation, and non-BAK preservative. Its potency makes it possible to use the drug twice a day rather than four times, which is convenient and may be compliance-enhancing.

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## References

1. Netto MV, Mohan RR, Bazan R, et al. Wound healing in the cornea: a review of refractive surgery complications and new prospects for therapy. *Cornea*. 2005;24(5):509-22.
2. Moller-Pedersen T, Li HF, Petroll WM, et al. Confocal microscopic characterization of wound repair after photorefractive keratectomy. *Invest Ophthalmol Vis Sci*. 1998;39:487-501.
3. Petroll WM, Vogel M, Li HF, et al. Quantification of stromal thinning, epithelial thickness, and corneal haze after photorefractive keratectomy using in vivo confocal microscopy. *Ophthalmology*. 1997;104:360-8.
4. Merayo-Llodes J, Yáñez B, Mayo A. Experimental model of corneal haze in chickens. *J Refract Surg*. 2001;17(6):696-9.
5. de Medeiros FW, Kaur H, Agrawal V, et al. Effect of femtosecond laser energy level on corneal stromal cell death and inflammation. *J Refract Surg*. 2009 Oct;25(10):869-74.
6. Netto MV, Mohan RR, Medeiros FW, et al. Femtosecond laser and microkeratome corneal flaps: comparison of stromal wound healing and inflammation. *J Refract Surg*. 2007 Sep;23(7):667-76.
7. Solomon R, Donnenfeld ED, Perry HD. The effects of LASIK on the ocular surface. *Ocul Surf*. 2004 Jan;2(1):34-44.
8. Holland EJ, Djalilian AR, Sanderson JP. Attenuation of ocular hypertension with the use of topical loteprednol etabonate 0.5% in steroid responders after corneal transplantation. *Cornea*. 2009 Dec;28(10):1139-43.
9. Buchwald P. Glucocorticoid receptor binding: a biphasic dependence on molecular size as revealed by the bilinear LinBiExp model. *Steroids*. 2008 Feb;73(2):193-208.
10. Foster CS, Davanzo R, Flynn TE, et al. Durezol (difluprednate ophthalmic emulsion 0.05%) compared with Pred Forte 1% ophthalmic suspension in the treatment of endogenous anterior uveitis. *J Ocul Pharmacol Ther*. 2010 Oct;26(5):475-83.
11. Shigemura J, Ogawa T, Yoshino A, et al. Predictors of antidepressant adherence: results of a Japanese Internet-based survey. *Psychiatry Clin Neurosci*. 2010 Apr;64(2):179-86. Epub 2010 Feb 1.
12. Smith S, Lorenz D, Peace J, et al. Difluprednate ophthalmic emulsion 0.05% (Durezol) administered two times daily for managing ocular inflammation and pain following cataract surgery. *Clin Ophthalmol*. 2010 Sep 7;4:983-91.
13. Stringer W, Bryant R. Dose uniformity of topical corticosteroid preparations: difluprednate ophthalmic emulsion 0.05% versus branded and generic prednisolone acetate ophthalmic suspension 1%. *Clin Ophthalmol*. 2010 Oct 5;4:1119-24.
14. Baudouin C, Labbé A, Liang H, et al. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res*. 2010 Jul;29(4):312-34. Epub 2010 Mar 17.

## EXAMINATION QUESTIONS: Inflammation Control in LASIK and PRK: New Findings

This CME program is sponsored by the University of Florida, College of Medicine and supported by an unrestricted educational grant from Alcon Laboratories, Inc. **Directions:** Select the one best answer to each question in the exam (Questions 1-10) and in the evaluation (Questions 11-16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this activity for a maximum of 1.0 AMA PRA Category 1 Credit™. There is no fee to participate in this activity. Or you can take the test online at <https://eval.medinfo.ufl.edu/cgi/eval.cgi?dir=candeo;form=lasik>.

- Which of the following is NOT considered a strong steroid?
  - Prednisolone acetate
  - Loteprednol etabonate
  - Difluprednate
  - Dexamethasone
- Which of the following is NOT normally considered an inflammatory complication of refractive surgery?
  - Haze
  - Diffuse lamellar keratitis
  - Pain
  - Iritis
- Which of the following would be expected to generate the least amount of inflammation?
  - PRK with a 8-mm epithelial defect
  - PRK with a 9-mm epithelial defect
  - LASIK performed with a mechanical microkeratome
  - LASIK performed with a first-generation femtosecond laser
- Which of the following are potential risks of long-term steroid use following PRK?
  - Intraocular pressure elevation
  - Increased risk of infection
  - Cataract formation
  - All of the above
- Which patients are NOT at increased risk of complications due to strong steroids?
  - Glaucoma patients
  - Individuals with ocular hypertension
  - Patients with keloids
  - Patients with a history of viral infections
- Which of the following is true of an emulsion formulation?
  - It offers a consistent drug concentration in each drop
  - It must be shaken for 1 minute prior to instillation
  - The bottle must be stored upside down
  - It must be stored in the refrigerator
- Which of the following is a NOT a common non-pharmaceutical means to reduce inflammation following PRK?
  - Bandage contact lens
  - Intraoperative cooling of the cornea
  - Artificial tears
  - Eyelid rubbing to stimulate meibum flow
- Which of the following strategies would NOT be an appropriate way to address dry eye disease in a refractive surgery candidate?
  - Pretreat the patient with topical cyclosporine
  - Postpone surgery until a time of year when relative humidity levels rebound
  - Postpone surgery until a time of year when humidity levels are low
  - Cancel surgery if the patient's dry eye cannot be resolved
- Patients may not be bothered by dry eye discomfort following LASIK because
  - Corneal sensation is reduced because corneal nerves have been cut
  - A side effect of LASIK is increased tearing
  - Postoperative pain masks the milder sensation of dry eye
  - Dry eye is a very rare complication of LASIK
- Which of the following best describes the typical antiinflammatory regimen following PRK?
  - Use of a corticosteroid only
  - Use of an NSAID only
  - Use of both steroid and NSAID
  - Use of both NSAID and cyclosporine

## EXAMINATION ANSWER SHEET: Inflammation Control in Lasik and PRK: New Findings

This CME program is sponsored by the University of Florida and Candeo Clinical/Science Communications, LLC, and supported by an unrestricted educational grant from Alcon Laboratories, Inc. Mail to: University of Florida CME Office, PO Box 100233, Gainesville, FL 32610-0233. Release date: January 2011. Expiration date: January 31, 2012.

**DIRECTIONS:** Select the one best answer for each question in the exam above (Questions 1–10). Participants must score at least 80% on the questions and complete the entire Evaluation (Questions 11–16) to receive CME credit.

ANSWERS:	
1. A B C D	6. A B C D
2. A B C D	7. A B C D
3. A B C D	8. A B C D
4. A B C D	9. A B C D
5. A B C D	10. A B C D

### EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

- Extent to which the activity met the identified
  - Objective 1: 1 2 3 4 5
  - Objective 2: 1 2 3 4 5
  - Objective 3: 1 2 3 4 5
- Rate the overall effectiveness of how the activity:
  - Related to my practice: 1 2 3 4 5
  - Will influence how I practice: 1 2 3 4 5
  - Will help me improve patient care: 1 2 3 4 5
  - Stimulated my intellectual curiosity: 1 2 3 4 5
  - Overall quality of material: 1 2 3 4 5
  - Overall met my expectations: 1 2 3 4 5
  - Avoided commercial bias/influence: 1 2 3 4 5
- Will the information presented cause you to make any changes in your practice? Yes No
- If yes, please describe: \_\_\_\_\_
- How committed are you to making these changes?
  - 1 2 3 4 5
- Are future activities on this topic important to you?
  - Yes No

If you wish to receive credit for this activity, please fill in the following information. Retain a copy for your records

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