GOING DROPLESS: SOONER THAN YOU THINK?

The stars are aligning to allow elimination of postoperative regimens for cataract surgery.

BY JOHN A. HOVANESIAN, MD

For literally hundreds of years, we have medicated the eye by means of topical therapies, including ointments and eye drops. This makes perfect sense because we have the privilege of treating a surface tissue in the eye, where we can put the medication very close to or directly on the area of interest.

POTENTIAL PROBLEMS

Despite the long history, there are problems with topical therapy.

- **No. 1: We depend upon the patient to administer the drug.** However, we know that nearly 80% of patients don't do it well.[1] And we know there's variability in how patients put drops in their eyes, even when they're instructed on how to do so effectively.
- **No. 2: Toxicity can be an issue with long-term administration.** We have all seen patients who have had chronic glaucoma therapy over many years, who have basically destroyed their limbal stem cells and have intractable iatrogenic dry eye disease (DED).
- **No. 3: Generic medications are proliferating.** For example, in the United States, prescriptions for latanoprost, the most commonly prescribed glaucoma medication, are now filled about 95% of the time with a generic formulation, according to data from IQVIA, formerly IMS Health and Quintiles. This means that products from multiple manufacturers of that drop might end up in your glaucoma patient's eye, and these different formulations can have varying toxicity.

It is likely that there will be a greater move toward generic topical medications in the future. This is a worry for physicians, who feel a loss of control over the drugs their patients are receiving.

NEW ALTERNATIVES

Clearly we need a better way to administer ocular medications, and it seems that this need is currently being answered in two key ways. This article explores some of the alternatives to topical drug delivery that are emerging or on the way.

Less-frequent administration. The first wave of *going dropless*, so to speak, took place with the emergence of several drug formulations that require fewer instillations—for example, once-daily administration instead of multiple applications per day.

This change has taken place in the area of NSAIDs, with the introduction of formulations such as Ilevro (nepafenac solution 0.3%, Alcon), which is more concentrated than the earlier version of the drug Nevanac (nepafenac solution 0.1%, Alcon).[2-4] Similarly, Prolensa (bromfenac ophthalmic solution 0.07%, Bausch + Lomb) and Bromday (bromfenac ophthalmic solution 0.09%, Ista Pharmaceuticals), labeled for once-daily use, have replaced earlier formulations calling for twice-daily administration.[4,5]

We are now seeing a similar development with topical steroids. Inveltys (loteprednol etabonate ophthalmic suspension 1%, Kala Pharmaceuticals) and Lotemax SM (loteprednol etabonate ophthalmic gel 0.38%, Bausch + Lomb) can be dosed less frequently than older 0.5% formulations of loteprednol, which called for four-times-daily dosing.[6,7]

Dropless. Then of course, some products are available that require even less frequent dosing, facilitating so-called *dropless surgery.* (For more on going dropless, see *Four Reasons to Integrate Dropless Cataract Surgery.*) This is an important development because many cataract surgery patients, unlike for example our established glaucoma or DED patients, have never used eye drops before. And yet it is crucial that they get the proper medication at this time, when their eye has been traumatized by surgery. It's going to affect their results for the rest of their lives. Further, many cataract patients are at advanced age and have systemic issues or comorbities that can make the administration of drops an extra challenge.

To address this, we now have Dextenza (dexamethasone ophthalmic insert 0.4 mg, Ocular Therapeutix), approved by the FDA in 2018 for the treatment of pain after ophthalmic surgery.[8] This product is an intracanalicular insert that is placed in the punctum and into the canaliculus. It is designed to deliver preservative-free dexamethasone to the ocular surface for up to 30 days, with a dose sufficient to address inflammation after routine cataract surgery. It then exits the nasolacrimal system without requiring removal. Another option, also approved by the FDA this past year, is Dexycu (dexamethasone intraocular suspension 9%, EyePoint Pharmaceuticals), a single-dose, sustained-release intracameral steroid for the treatment of inflammation after cataract surgery.[9]

These two products use different routes of administration to perform the same function of delivering sufficient steroid to treat inflammation in the postoperative period. Dextenza has a familiar implantation technique, with

FOUR REASONS TO INTEGRATE DROPLESS CATARACT SURGERY

BY KAMRAN M. RIAZ, MD

Efforts to minimize or even eliminate traditional postoperative topical medications after cataract surgery have gained attention over the past few years. More surgeons are interested in effective strategies to develop a truly dropless cataract surgery experience. Dropless strategies primarily involve injecting antibiotics, steroids, and/or nonsteroidal medications into the anterior chamber, intracapsular space, or the vitreous cavity.

My preferred strategy since 2014 has been to inject Tri-Moxi (triamcinolone 15 mg/mL and 1 mg/mL moxifloxacin, ImprimisRx) into the vitreous cavity with a 30-gauge needle via a pars plana approach, at a location approximately 3.5 mm posterior to the surgical limbus. The intravitreal antibiotic steroid (IVAS) injection is performed after routine and uneventful cataract surgery. Some ophthalmologists may wonder why they should consider a dropless approach when topical medications can be adjusted as needed and, perhaps more importantly, are familiar to both surgeons and patients.

ADVANTAGES

To my mind, there are four advantages of IVAS.

- **No. 1: Cost savings.** Postoperative topical therapy can range in cost from $50 to $300 per eye, but some out-of-pocket copayments are as high as $650 per eye. IVAS therapy costs $22 per vial, which is borne by the surgery center. A study cosponsored by Cataract Surgeons for Improved Eyecare (improvedeyecare.org) found that dropless therapy could save the CMS more than $7 billion and patients about $1.4 billion in out-of-pocket costs in a 10-year period.[1]
- **No. 2: Improved compliance.** Multiple studies indicate that patients can struggle to use their medications correctly.[2-4] Poor compliance is multifactorial, and injecting medication *into* the eye, as opposed to applying it *on* the eye, offers advantages.
- **No. 3: Less ocular surface damage.** Topical medications can cause and exacerbate ocular surface disease through multiple mechanisms. IVAS reduces the risk of corneal toxicity by eliminating preservative-containing topical medications that cause ocular surface damage, ranging from allergic reactions to direct epithelial toxicity. The negative effects of the preservative benzalkonium chloride are well known.
- **No. 4: Fewer calls to the office and staff.** IVAS can reduce the number of labor-hours spent by office staff talking to patients about their drug regimens, obtaining prior authorizations from insurance companies, and talking to pharmacists about alternative medications if a certain topical medication is not covered by insurance. On a personal note, I have had two incidents when a pharmacist replaced a noncovered topical NSAID with topical proparacaine without consulting me.

TABLE. PRELIMINARY ALGORITHM FOR IVAS INJECTIONS

Risk Factor	Point Value	Risk Factor	Point Value	Risk Factor	Point Value
PDR in past 6 months	4	Active wet AMD (or in past 6 months)	2	LCS	2
NPDR in past 6 months	3	Dry AMD	1	Standard phaco	0
Mild to moderate NPDR	2	Young age < 55 years	1	History of retinal surgery (PPV)	1
Injection history for DME	2	Older age > 55 years	0		
Diabetes	1				
Uveitis history (inactive at time of surgery)	1	Grade of cataract (3+ or more)	2		
Presence of ERM	2	Grade of Cataract (<3+)	0		

Abbreviations: PDR, proliferative diabetic retinopathy; AMD, age-related macular degeneration; LCS, laser cataract surgery; NPDR, nonproliferative diabetic retinopathy; PPV, pars plana vitrectomy; DME, diabetic macular edema; ERM, epiretinal membrane

DISADVANTAGES

Admittedly, IVAS therapy is not without potential limitations and risks.

- **No. 1: Concerns about compounding pharmacies.** There has been significant concern that triamcinolone-moxifloxacin injections prepared by 503A pharmacies can cause endophthalmitis.[5] It is vital for any surgeon choosing to use IVAS to understand the difference between a 503A and 503B pharmacy and to use only medications from 503B pharmacies for intraocular injection. I have and will only use Tri-Moxi.
- **No. 2: Complaints from patients.** Patients may report minor pain, floaters, and subconjunctival hemorrhages in the immediate postoperative period. It is important to discuss the possibility of these phenomena with patients prior to cataract surgery, especially if they have chosen to receive a premium IOL and if they have certain postoperative visual expectations.
- **No. 3: Continued inflammation.** This is probably the greatest concern with IVAS therapy, because some patients demonstrate continued inflammation after surgery. It is likely that patients with proinflammatory ocular pathologies such as diabetic retinopathy, uveitis, and epiretinal membranes; those who have undergone laser cataract surgery; and those with dense cataracts or wet age-related macular degeneration will require supplemental topical antiinflammatory medications.
- **No. 4: Catastrophe.** A joint task force formed by the ASCRS and ASRS reported a strong

association between hemorrhagic occlusive retinal vasculitis and the use of intraocular vancomycin.[6] Since this statement was issued, most surgeons have stopped using vancomycin, and no cases of hemorrhagic occlusive retinal vasculitis have been reported with a triamcinolone-moxifloxacin combination only. ImprimisRx no longer makes Tri-Moxi-Vanc.

WHEN TO SUPPLEMENT

Some patients, based on risk factors, will require supplemental topical antiinflammatory medications after an IVAS injection. Based on the risk factors outlined in the Table, I propose stratifying cataract surgery patients into three categories:

1. Low Risk (0–4 points): Can safely receive IVAS without supplemental topical antiinflammatory medications;
2. Medium Risk (5–7 points): Can receive IVAS, but surgeon should strongly consider supplemental topical antiinflammatory medications; and
3. High Risk (7+ points): Can receive IVAS but must also receive supplemental topical antiinflammatory medications.

In my current practice with IVAS, I give all diabetic patients topical NSAID medications. For patients at medium-risk, I prescribe either a twice-daily topical steroid (loteprednol) or a topical NSAID (bromfenac administered daily or ketorolac administered three times daily) for 6 weeks. For patients at high-risk, I prescribe a twice-daily topical steroid and a topical NSAID, either bromfenac daily or ketorolac three times a day, depending on insurance coverage, for 6 weeks.

CONCLUSION

We are far away from truly dropless cataract surgery, but current IVAS products provide surgeons with an opportunity to customize their injection approach. At present, IVAS therapy as a standalone intervention may not be sufficient to control postoperative inflammation in certain patient populations. Some risk factors have been identified, but more research is needed to further optimize patient outcomes.

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placement in the punctum. It is visible after insertion and easily removed by flushing it out of the punctum. It also provides a beneficial ocular surface effect by increasing the tear lake (bit.ly/0619Hovanesian). Dexycu, placed inside the eye, is delivered closer to the target organs. There is a learning curve for the injection technique, however, which requires getting the product behind the iris in the ciliary sulcus (bit.ly/0619Hovanesian1).

Both products performed well in comparison with placebo in clinical trials for FDA approval.[8,9] These products spare the surface of the eye from the effects of topical preservatives and provide good antiinflammatory effect. IOP spikes with these nontopical steroids were no higher than with placebo in studies for both products,[2,3] so they appear to be both safe and effective.

PASS-THROUGH

In clinical use, most investigators and physicians who have been using the commercial products discussed in this article feel that they are comparable to topical steroids in controlling inflammation. Some physicians are, however, concerned about the payment for these products because they have pass-through reimbursement status. This means that the product is covered for the patient and free to the physician, which is a positive. By statute, the pass-through reimbursement is at the high level of more than $400 for each drug.

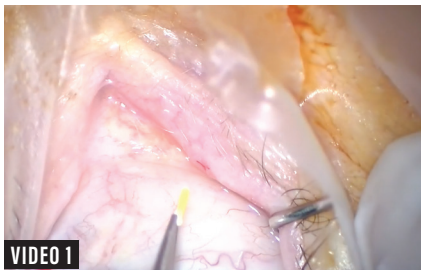
Physicians bristle at this high reimbursement level, but this is a temporary phenomenon. Pass-through status lasts only 3 years, and then companies will have to determine a new method of reimbursement. This arrangement, guaranteeing high reimbursement levels for the initial years of a product, helps manufacturers to bring innovative products to market. (For more on pass-through reimbursement, see "A Primer on Pass-Through Status," by Lisa M. Nijm, MD, JD, pg 33.)

A FLUID APPROACH

Some physicians are suggesting that a topical NSAID may not be needed after surgery if Omidria (phenylephrine 1%/ketorolac 3% intraocular solution, Omeros) is used in the infusion fluid.[10] The argument for this approach is that the high and very localized dosing of ketorolac that results from its presence in the irrigation fluid saturates cellular receptors and provides adequate NSAID treatment for at least the early postoperative period.

WATCH IT NOW

DEXTENZA INJECTION TECHNIQUE



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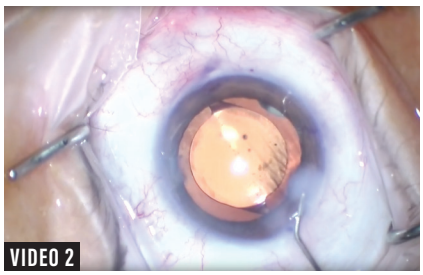
DEXECYU INJECTION TECHNIQUE



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For diabetic patients or those who have epiretinal membranes or certain other conditions that merit longer-term NSAID treatment, topical therapy with drops may be appropriate even after they have received this intraoperative infusion. But for routine cases, it may be that we don't need anything more than Omidria plus either Dexycu or Dextenza to obtain all the antiinflammatory effect that the eye needs.

ANTIBIOTIC CHANGE COMING

So far in this article we have been addressing only the antiinflammatory aspect of topical postoperative therapy. The other important component, of course, is antibiotic prophylaxis. It is very clear that the standard of care in this regard in the United States should change. We should move toward intracameral administration of antibiotics, as our European colleagues have. But still the majority of US surgeons do not use intracameral antibiotics, according to a recent ASCRS members' survey.

The most common reason for this is that there is no FDA-approved product for intracameral antibiosis. ASCRS is pursuing a large-scale intracameral moxifloxacin study, and interested physicians can enroll at www.ascrs.org. For surgeons who want to participate, this is a good way to offer intracameral antibiotics to patients under the protection of a study protocol.

THE FUTURE IS HERE

Aside from the study, however, there are already thousands of US surgeons using off-label intracameral antibiotics from compounding pharmacies, generally with very good results, according to the ASCRS clinical survey.

In light of this, I think it's reasonable to anticipate that, within the next 5 years, we will be drop-free after cataract surgery. As I mentioned, there are already many surgeons using intracameral antibiotics, and if they also believe that the antiinflammatory regimen of Omidria plus either Dextenza or Dexycu is sufficient, they don't need to use drops at all right now. Within 5 years, I think the standard of care will have moved to that type of practice.

Physicians have their preferences, of course. Some more conservative physicians may be reluctant to embrace these products. But those of us who have used them know that our experience mimics what was seen in the trials. Payment barriers may be a problem, as the two pass-through products will have to become accepted by private insurance companies, even though Medicare offers a pathway. That will happen, but it will not happen instantly. ■

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OCULAR THERAPEUTIX RECEIVES PASS-THROUGH PAYMENT STATUS, C-CODE FOR DEXTENZA

Dextenza (dexamethasone ophthalmic insert, Ocular Therapeutix) received transitional pass-through payment status and a new reimbursement code, C9048, effective July 1.

"With sample product available and insertion training sessions already underway, the receipt of the C-code is another important step in the commercial launch of Dextenza," Anthony Mattessich, Ocular Therapeutix President and Chief Executive Officer, said in a news release.

The formal receipt of the C-code facilitates the reimbursement of Dextenza until potential CMS approval of a J-code becomes effective. In May, the company announced that the CMS had included Dextenza on its list of products that have been preliminarily recommended for a new dedicated Healthcare Common Procedure Coding System J-code, which, if granted, would become effective January 1. A J-code represents a permanent product code that could be used across settings of care.