

Improving the Success of Filtering Surgery

Which drugs should be avoided? The simple answer is all of them.

BY GEOFFREY T. EMERICK, MD

Most ophthalmic medications adversely affect the ocular surface and have the potential to reduce the success rate of glaucoma filtering surgery. The main culprits appear to be preservatives, most commonly benzalkonium chloride (BAK). In general, the more BAK that an eye receives, the worse the condition of the conjunctiva and the greater the risk of failure. Other important considerations include ocular allergy or toxicity caused by the glaucoma medication itself and drug-induced conjunctival cicatrization (pseudopemphigoid) in susceptible individuals. This article discusses these issues and expands on a thorough review of the impact of glaucoma medications on surgical success that was presented in an earlier issue of *Glaucoma Today*.¹

EFFECTS OF LONG-TERM TREATMENT

The ideal patient undergoing glaucoma filtering surgery would have normal lid position, an absence of blepharitis, a normal tear film, healthy noninflamed conjunctiva without scarring, and normal aqueous composition. Unfortunately, by the time they undergo surgery, few patients

fit this description. The normal ocular surface is frequently damaged by long-term treatment with topical glaucoma medications. Often used in quantity and over many years, topical medications may significantly reduce the success rate of filtering surgery.²⁻⁵

Conjunctival inflammation and scarring decrease filtration surgery success rates.⁶ Any preserved topical medication, including most glaucoma medications as well as artificial tears, causes an increase in myofibroblast proliferation.⁷ Eyes treated long term with topical glaucoma medications show a decrease in conjunctival goblet cells and an increase in macrophages, fibroblasts, lymphocytes, and mast cells.⁸ Moreover, research has directly associated conjunctival metaplasia with the number of glaucoma medications.⁹

Several studies^{2,6} have demonstrated that the cumulative duration of topical treatment is a significant risk factor for the failure of filtering surgery. Thus, several medications used for a shorter period of time may be as damaging as one used for a longer period. Similarly, drugs requiring b.i.d., t.i.d., or q.i.d. dosing likely cause greater damage than those dosed q.d.

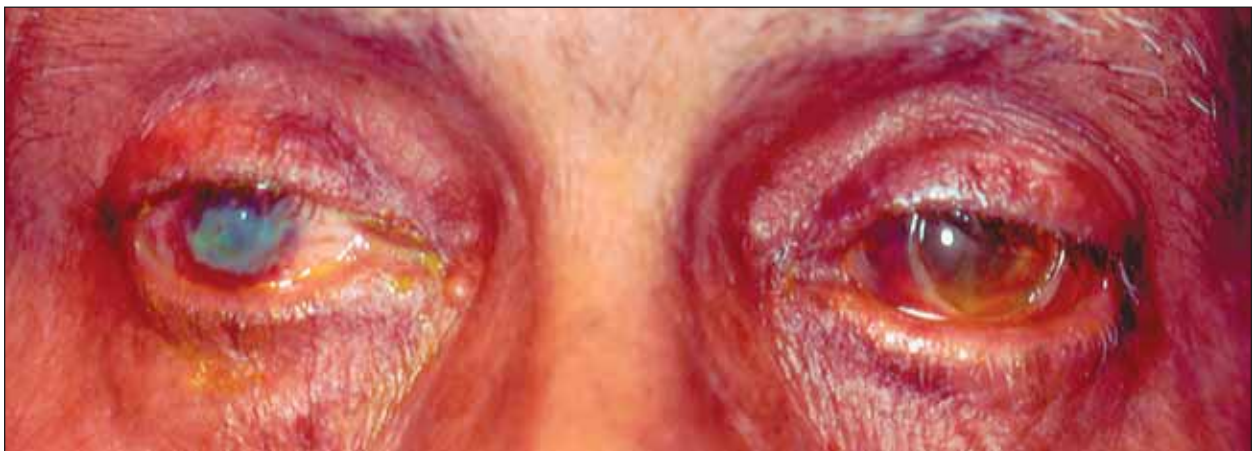


Figure 1. This 67-year-old male had severe, drug-induced, cicatricial conjunctivitis secondary to long-term pilocarpine use and required a limbal stem-cell transplant in his left eye.

TABLE 1. BAK CONCENTRATIONS OF COMMONLY USED GLAUCOMA MEDICATIONS

Generic Name	Brand Name (Manufacturer)	BAK Concentration
Brinzolamide	Azopt (Alcon Laboratories, Inc.)	0.01%
Dorzolamide	Trusopt (Merck & Co, Inc.)	0.0075%
Betaxolol	Betoptic-S (Alcon Laboratories, Inc.)	0.01%
Carteolol	Ocupress (Novartis Ophthalmics, Inc.)	0.005%
Levobunolol	Betagan (Allergan, Inc.)	0.004%
Metipranolol	Optipranolol (Bausch & Lomb)	0.004%
Timolol	Timoptic (Merck & Co, Inc.) Betimol (Santen, Inc.)	0.01%
Timolol/dorzolamide	Cosopt (Merck & Co, Inc.)	0.0075%
Brimonidine	Generic	0.005%
Unoprostone	Rescula (Novartis Ophthalmics, Inc.)	0.015%
Bimatoprost	Lumigan (Allergan, Inc.)	0.005%
Latanoprost	Xalatan (Pfizer Inc.)	0.02%
Travoprost	Travatan (Alcon Laboratories, Inc.)	0.015%
Timolol	Timoptic XE (Merck & Co, Inc.) Timolol GFS (Falcon Pharmaceuticals)	Benzododecinium bromide 0.012%
Timolol	Timoptic Ocudose (Merck & Co., Inc.)	Preservative-free
Brimonidine	Alphagan-P (Allergan, Inc.)	Purite

PRESERVATIVES

Quaternary Ammonium Compounds

Drugs that have higher concentrations of BAK may be more damaging than those using other preservatives. Of topical carbonic anhydrase inhibitors, dorzolamide alone or in combination with timolol has the lowest concentration of BAK (Table 1). Among beta-blockers, levobunolol and metipranolol have the lowest concentrations of BAK, as does bimatoprost among prostaglandin analogs. Timolol in a gel-forming solution is preserved with benzododecinium bromide. Like BAK, it is a quaternary ammonium compound and has toxic effects on the conjunctiva.¹⁰

In animal models, most preservatives cause corneal and conjunctival damage, including epithelial alterations, keratinization, and inflammatory infiltrates at the limbus and within the conjunctival stroma and epithelium. A study investigating the toxicity mechanisms of 10 currently used ophthalmic preservatives in vitro found a significant decrease in conjunctival cell membrane integrity with both BAK and benzododecinium bromide at con-

centrations of 0.005% and higher.¹¹ These quaternary ammonium compounds also induced the production of superoxide anions, which may play an important role in the tissue damage induced by preservatives. In the study, an apoptotic mechanism appeared to be present at low concentrations of quaternary ammoniums, whereas a necrotic process appeared at higher concentrations.

Used in most glaucoma medications, BAK has been implicated as one of the major causes of conjunctival inflammation in eyes undergoing long-term treatment. In one study,¹² the conjunctivae of 24 out of 26 patients receiving treatment with two or more BAK-preserved drugs for at least 1 year had abnormal inflammatory markers, fibroblastic markers, or both. By contrast, 19 of 30 conjunctivae in patients treated with a beta-blocker for more than

1 year and one of five eyes that underwent primary surgery possessed these markers. In rats receiving topical solutions bilaterally for 1 month, preserved timolol and BAK alone produced similar degrees of inflammatory infiltrates, whereas preservative-free timolol did not cause increased inflammation compared with controls.¹²

Alternatives

Of commonly used, commercially available glaucoma medications, only two are not preserved with quaternary ammonium compounds. Alphagan-P (Allergan, Inc., Irvine, CA) is preserved with Purite, a stabilized oxychloro complex. Additionally, timolol (Merck & Co., Inc., West Point, PA) is available without preservatives in unit-dose dispensers. Other glaucoma medications such as pilocarpine are available in nonpreserved formulations through independent pharmacies.

No published studies on the conjunctival effects of Purite are available, but a presentation by Noecker et al indicated that it may be less toxic than other preserva-

tives.¹³ In the study, investigators performed conjunctival biopsies on patients using latanoprost and timolol as well as BAK- and Purite-preserved bimatoprost. Inflammatory cell counts were higher in patients using latanoprost or timolol compared with those using bimatoprost. There was no significant difference between the BAK- and Purite-preserved bimatoprost groups, although only three Purite-treated patients were studied. The investigators explained this finding by noting the lower concentration of BAK in brimonidine relative to latanoprost or timolol, but further studies on the toxicity of Purite are clearly needed.

CONJUNCTIVAL HYPEREMIA, ALLERGY, AND TOXICITY

It may be reasonable to avoid medications that cause conjunctival hyperemia, although no data exist to suggest that hyperemia alone reduces surgical success rates. Physicians should, however, be alert for potentially subtle signs of allergy or ocular toxicity in patients. Allergies are possible with all glaucoma medications, although incidences differ. For example, beta-blockers can cause conjunctival hyperemia, punctate epithelial erosions, and dry eye symptoms. Some patients may develop allergic blepharoconjunctivitis.¹⁴ Epinephrine and dipivefrin commonly cause reactive hyperemia and follicular conjunctivitis. With long-term treatment, these agents often result in allergic blepharoconjunctivitis. Apraclonidine is also associated with a high allergy/toxicity rate, as great as 50% in some series.¹⁵

Brimonidine 0.2% has a significantly lower allergy/toxicity rate than apraclonidine, and the rate with brimonidine-Purite 0.15% is even lower. A 12-month study using t.i.d. dosing found a 15.7% incidence of allergic conjunctivitis with brimonidine 0.2% and a 9.2% incidence with brimonidine-Purite 0.15%.¹⁶ The incidence of conjunctival hyperemia was 25.6% and 18.2%, respectively—also statistically significant.

Topical carbonic anhydrase inhibitors have an allergy rate of approximately 10%, and true allergy to the prostaglandin analogs appears to be relatively low, in the range of 1% to 3%, according to the package inserts for latanoprost, travoprost, and bimatoprost. Prostaglandin hyperemia rates, on the other hand, are quite high. One 12-week study reported hyperemia rates of 47%, 58%, and 68% with latanoprost, travoprost, and bimatoprost, respectively.¹⁷ Although based on anecdotal reports, there is some concern that conjunctival hyperemia may predispose eyes to bleeding at the time of surgery. I have not found this problem to be significant and have been able to control bleeding with careful surgical technique. There is no evidence that hyperemia alone decreases surgical success rates.

DRUG-INDUCED CONJUNCTIVAL CICATRIZATION

Also called *pseudopemphigoid*, drug-induced conjunctival cicatrization (Figure 1) is usually identical in appearance to true pemphigoid. Several drugs, including beta-blockers, have been associated with the condition, but miotics are implicated most often.

Early findings include only a chronic papillary conjunctivitis, mostly in the inferior fornix. Later, there is a foreshortening of the inferior fornix, a flattening of the conjunctival folds, and a thickening and vascularization of the conjunctiva. Progression of the condition leads to subepithelial fibrosis, occlusion of the puncta, symblepharon formation, and trichiasis. Drug-induced conjunctival cicatrization seems to occur only in susceptible individuals and usually after many years of treatment with topical medications. The average time between starting glaucoma medications and the first symptoms of drug-induced conjunctival cicatrization is 11 to 15 years.¹⁸ Treatment is difficult, and the management of glaucoma in these patients may require a glaucoma drainage implant.

PREOPERATIVE TREATMENT

Many surgeons advocate discontinuing some or all of patients' glaucoma medications prior to filtering surgery. Traditional teaching advises at least halting miotics prior to surgery and discontinuing long-acting agents such as echothiophate 2 weeks preoperatively. The reasoning is that these agents can increase postoperative inflammation, promote the breakdown of the blood-aqueous barrier, and cause a forward rotation of the ciliary body and lens-iris diaphragm, thereby increasing the risk of anterior chamber shallowing. This issue is less important, because the use of miotics is now rare, although many experienced surgeons do not discontinue miotics prior to surgery. Many practitioners, myself included, administer pilocarpine immediately prior to surgery in order to induce miosis and facilitate the creation of a basal iridectomy. The use of antimetabolites as well as postoperative atropine and corticosteroids reduces the importance of all these concerns.

Some physicians advocate discontinuing other glaucoma agents, such as aqueous suppressants, prior to surgery in order to reduce the risk of hypotony due to aqueous hyposecretion in the postoperative period. The use of laser suture lysis or releasable sutures partly addresses this concern, because the surgeon can titrate pressure while aqueous production returns to "normal" in the days or weeks after surgery. I do not typically stop any glaucoma medications preoperatively, because I am concerned about even a short-term increase in IOP as well as a theoretically increased risk of choroidal hemorrhage with a larger drop in IOP at the time of surgery.

THE BOTTOM LINE

The practical implications of the data presented in this article are as follows. First, the eye is in its best condition for successful glaucoma surgery prior to receiving any drops. Second, if drops (including artificial tears) are used, then the less preservative they contain, the better (Purite may be an exception). Third, because the cumulative effect of preservatives seems to be important, once-daily dosing is preferable. Fourth, preservative-free formulations are a good, if impractical, alternative. Finally, laser trabeculoplasty is a good, practical alternative to adding more medications.

The reality is that many patients will undergo surgery after many years' treatment with numerous drops. The use of antimetabolites has significantly improved the success rate of filtering surgery in these patients. □

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