

Background Information: Inflammation and Pain Associated with Ocular Surgery

There are more than 5 million ophthalmic surgeries performed each year in the United States. Due to the high prevalence of cataracts among the aging population, cataract extraction and installation of an artificial lens are the most frequently performed eye surgeries¹, with an estimated 3 million cataract surgeries occurring per year in the U.S.

Postoperative Inflammation and Pain

The most common sequelae arising after cataract and other ocular surgeries are persistent inflammation, pain, elevation in intraocular pressure (IOP), infection, swelling of the retina and retinal detachment.

Postoperative inflammation is a common occurrence following ophthalmic surgical procedures, including cataract surgery. Symptoms of postoperative inflammation include²:

- Swelling and redness for as long as 4 to 6 weeks after surgery
- Decrease in visual acuity, sometimes caused by cystoid macular edema (CME)
- Ocular pain
- Crusting of the eyelashes upon awakening
- Bloody tears for 12 to 24 hours after surgery

Inflammation after cataract or other ophthalmic surgery begins with tissue injury when the surgical incision is made. This incision triggers the inflammatory cascade, which begins with activation of phospholipase A-2. Phospholipids in the cell membranes are broken down into arachidonic acid, which is then converted to prostaglandins by cyclooxygenase or converted to hydroxy acids and leukotrienes by 5-lipoxygenase.

The degree of postoperative inflammation following cataract surgery is linked to several surgery-dependent factors such as surgical technique, intraocular lens type and patient-dependent factors such as history of inflammatory disease and degree of iris pigmentation.

Since inflammation can result in damage to ocular tissues, rapid resolution is imperative. While most postoperative inflammation lasts a relatively short time, more severe forms of inflammation can persist for a longer period. If left untreated, inflammation following ocular surgery can interfere with the patient's visual rehabilitation or lead to further complications, such as acute pain and discomfort, chronic cystoid macular edema, posterior capsule fibrosis, keratopathy, fibrin reaction, chronic uveitis, raised intraocular pressure (IOP), synechiae or secondary membrane.

Some experts believe that the recovery of visual acuity after cataract surgery directly relates to the amount and duration of postoperative inflammation³. Therefore, any steps surgeons can take to decrease either the amount of inflammation that occurs initially in the procedure or the duration that it lasts will positively impact patient outcomes.

Treatment of Postoperative Inflammation and Pain

As there is no way to predict which patients may develop inflammatory complications, anti-inflammatory eye drops, including corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), are used in the weeks after cataract surgery to help control inflammation and pain.

¹ Uhr, Barry W. History of Ophthalmology at Baylor University Medical Center. Proc (Baylor University Medical Center). 2003 October; 16(4): 435–438.

² National Institutes of Health, Clinical Center, 2008.

³ Roberts CW. Pretreatment with topical NSAIDs to decrease pain during cataract surgery. ASCRS 2003; San Francisco, CA.

Anti-infectives are also given as a routine part of care in order to prevent the occurrence of a postoperative infection^{4,5,6}.

The positive therapeutic effect on the prevention of inflammation and infection following cataract surgery with standard formulations of corticosteroids, NSAIDs and antibiotics has been documented in many clinical studies^{7,8,9,10,11,12,13,14,15,16,17,18}.

Steroids and NSAIDs intervene at different steps of the inflammatory cascade: steroids act upstream on phospholipase A-2 to stop the breakdown of phospholipids, while NSAIDs act downstream on cyclooxygenase to inhibit the conversion of arachidonic acid to prostaglandins¹⁹. Until recently, steroids have not been indicated for the treatment of postoperative pain.

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) offer several benefits after ocular surgery. Some NSAIDs can reduce patients' intra- and postoperative pain, help maintain pupillary dilation, control inflammation after surgery and inhibit the development of cystoid macular edema (CME), although inhibition of CME is not a claim in FDA-approved labeling for any NSAIDs. NSAIDs have been associated with problems that vary from corneal stinging to corneal melting.

Steroids

Corticosteroids are highly potent anti-inflammatory medications that are the standard of care in ocular inflammatory diseases. They are generally considered stronger than other options, and superior at controlling the inflammation associated with cataract surgery because they inhibit phospholipase A2 and subsequently inhibit both the cyclo-oxygenase and lipoxigenase pathways²⁰. In addition, steroids can enter the nucleus to interact with specific DNA sequences, altering production of inhibitory proteins, and thus inhibiting additional inflammatory mediator

⁴ Abel R, Abel AD. Perioperative antibiotic, steroid and nonsteroidal anti-inflammatory agents in cataract intraocular lens surgery. *Curr Opin Ophthalmol* 1997; 8: 29-32.

⁵ Jaanus SD. Prevention of postoperative infection: limits and possibilities. *Br J Ophthalmol* 1996; 80: 681-2.

⁶ Flach AJ. Topical nonsteroidal antiinflammatory drugs in ophthalmology. *Int Ophthalmol Clin* 2002; 42: 1-11.

⁷ Struck HG, Bariszlovich A. Comparison of 0.1% dexamethasone phosphate eye gel (Dexagel) and 1% prednisolone acetate eye suspension in the treatment of post-operative inflammation after cataract surgery. *Graefes Arch Clin Exp Ophthalmol* 2001 239: 737-42.

⁸ Holzer MP, Solomon KD, Sandoval HP, et al. Comparison of ketorolac tromethamine 0.5% and loteprednol etabonate 0.5% for inflammation after phacoemulsification: prospective randomized double-masked study. *J Cataract Refract Surg* 2002; 28: 93-9.

⁹ Papa V, Milazzo G, Santocono M, et al. Naproxen ophthalmic solution to manage inflammation after phacoemulsification. *J Cataract Refract Surg* 2002; 28: 321-7.

¹⁰ Solomon KD, Vroman DT, Barker D, et al. Comparison of ketorolac tromethamine 0.5% and rimexolone 1% to control inflammation after cataract extraction: prospective randomized double-masked study. *J Cataract Refract Surg* 2001; 27: 1232-7.

¹¹ Kraff MC, Martin RG, Neumann AC, et al. Efficacy of diclofenac sodium ophthalmic solution versus placebo in reducing inflammation following cataract extraction and posterior chamber lens implantation. *J Cataract Refract Surg* 1994; 20: 138-44.

¹² Othenin-Girard PH, Tritten JJ, Pittet N, et al. Dexamethasone versus diclofenac sodium eyedrops to treat inflammation after cataract surgery. *J Cataract Refract Surg* 1994; 20: 9-11.

¹³ Starr MB. Prophylactic antibiotics for ophthalmic surgery. *Surv Ophthalmol* 1983; 27: 353-73.

¹⁴ Stewart RH, Kimbrough RL, Smith JP, et al. Use of steroid/antibiotic prophylaxis in intraocular lens implantation: a double-masked study vs placebo. *Ann Ophthalmol* 1983; 15: 24-8.

¹⁵ Reddy MS, Suneetha N, Thomas RK, et al. Topical diclofenac sodium for treatment of postoperative inflammation in cataract surgery. *Indian J Ophthalmol* 2000; 48: 223-6.

¹⁶ Barraquer RI, Alvarez de Toledo JP, Montané D, et al. Fixed-dose combination of 1.1% diclofenac plus 0.3% tobramycin ophthalmic solution for inflammation after cataract surgery: a randomized, comparative, active treatment-controlled trial. *Eur J Ophthalmol* 1998; 8: 173-8.

¹⁷ Vidal R, Riu JL, Martínez C, et al. 0.1% diclofenac sodium-0.3% tobramycin eye drops (DT): efficacy and ocular distribution of diclofenac and tobramycin [abstract]. *Methods Find Exp Clin Pharmacol* 1997; 19 Suppl. A: 191.

¹⁸ Mohan N, Gupta V, Tandon R, et al. Topical ciprofloxacin-dexamethasone combination therapy after cataract surgery: randomized controlled clinical trial. *J Cataract Refract Surg* 2001; 27: 1975-8.

¹⁹ Roberts, Calvin W. M.D., The Role of NSAIDs in Cataract Surgery, *Cataract & Refractive Surgery Today*, April 2003.

²⁰ Jaanus SD, Leshner GA. Anti-Inflammatory Drugs. In: Bartlett JD, Jaanus SD, eds. *Clinical Ocular Pharmacology*. Boston: Butterworth-Heinemann, 1995:303.

production. This mechanism contributes to steroids' broad activity: Corticosteroids suppress the inflammatory response to a variety of inciting agents of a mechanical, chemical or immunological nature. They exert additional anti-inflammatory actions, including a reduction in migration of macrophages and neutrophils, decreasing vascular permeability and suppressing the action of various lymphokines²¹. They inhibit edema, cellular infiltration, capillary dilatation, fibroblastic proliferation and deposition of collagen.

While topical steroids are extremely useful in the management of intraocular inflammation, prolonged use of corticosteroids carries increased risks. Ophthalmic corticosteroids are contraindicated in most viral diseases of the cornea and conjunctiva and also in mycobacterial infection of the eye and fungal disease of ocular structures. Prolonged use of corticosteroids may result in delayed wound healing, elevated IOP resulting in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation.

Summary

Rapid resolution of postoperative ocular inflammation is imperative to avoid interference with the patient's visual rehabilitation or further complications. Anti-inflammatory eye drops, including corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), are used in the weeks after cataract surgery to help control inflammation and pain. The positive therapeutic effects of corticosteroids and NSAIDs, which target different aspects of the inflammatory cascade, have been documented in many clinical studies.

²¹ Campbell WB, Halushka PV. Lipid Derived Autocoids. In: Hardman JG, Limbird LE, eds. Goodman and Gilman's (The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw-Hill, 1990:601-33.