Pharmacologic Approaches to the Small Pupil

The popularity of direct intracameral injection of epinephrine has grown following reports of its clinical efficacy for IFIS.

BY LADAN ESPANDAR, MD, MSc, AND TERRY KIM, MD

During cataract surgery, the pupil must be sufficiently dilated to provide adequate surgical access to the cataract. Insufficient pupillary dilation can pose surgical challenges to ophthalmologists such as an obstructed view, reduced red reflex, difficult capsulorhexis, iris prolapse from wounds, risk of bleeding, increased inflammation from iris trauma, and increased risk of posterior capsular rupture and vitreous loss.[1]

ETIOLOGY

Most cataract patients are older, and aging can cause iris atrophy and a miotic pupil. The long-term use of topical miotics such as pilocarpine in glaucoma patients can cause fibrosis of the iris sphincter and poor dilation. Patients with diabetes may experience poor dilation because of autonomic dysfunction or rubeosis iridis. In pseudoexfoliation syndrome, iris dilator muscle atrophy or sphincter muscle fibrosis represent the two main mechanisms of poor dilation. Uveitis, trauma, angle-closure attacks, and prior intraocular surgery can cause iris synechiae to the anterior capsule and miosis. Finally, in intraoperative floppy iris syndrome (IFIS), miosis may be due to dilator muscle atrophy from chronic α-1A sympathetic blockade at the receptor site.[2]

Figure 1. Mydriasert in the inferior fornix.

> "Presurgical mydriasis is usually achieved by a combination of topical drops or topical gel formulations..."

INTRAOPERATIVE FLOPPY IRIS SYNDROME

IFIS was first described by Chang and Campbell in 2005 with the clinical triad of a flaccid, billowing iris; a tendency for iris prolapse through wounds; and progressive miosis. This syndrome has been linked to use of the α-1A-adrenergic receptor antagonist, tamsulosin.[3] There is a 2.3 times greater risk of complications during phacoemulsification in patients taking tamsulosin.[4] It has been shown that the use of atropine 1% twice a day for 2 to 3 days prior to surgery can prevent IFIS in patients taking tamsulosin.[5,6]

PREOPERATIVE MYDRIASIS

Presurgical mydriasis is usually achieved by a combination of topical drops or topical gel formulations, including tropicamide 1%, cyclopentolate 1%, and phenylephrine 2.5%. Preoperative use of nonsteroidal antiinflammatory drugs (NSAIDs) such as nepafenac

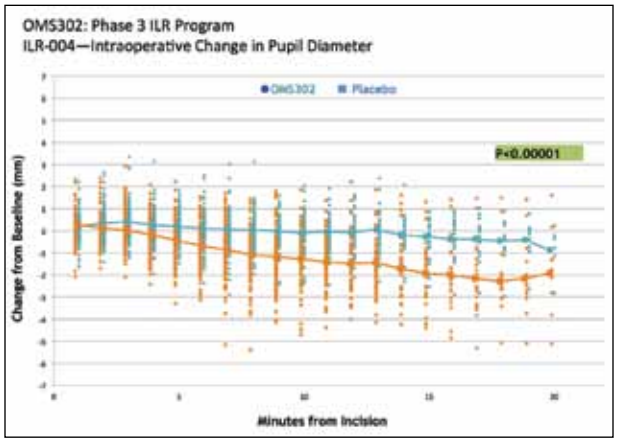

Figure 2. Omidria maintained pupillary diameter throughout the surgical procedure, whereas the placebo group demonstrated progressive pupillary constriction

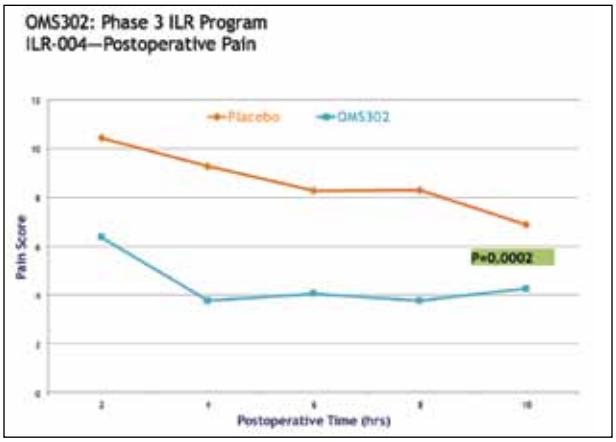

Figure 3. The mean postoperative pain reported by treatment group versus control in the Omidria trial.

0.1%, bromfenac 0.09%, and ketorolac 0.4% also contributes to the maintenance of dilation by blocking the miotic effect of prostaglandins released during cataract surgery.[7-12]

Ocular inserts represent an alternative to eye drops (ie, Mydriasert; Thea). Although not yet commercially available in the United States, this particular sustained-release insert is placed in the inferior conjunctival fornix a maximum of 2 hours before surgery and contains 0.28 mg of tropicamide and 5.4 mg of phenylephrine HCl (Figure 1).

INTRAOPERATIVE MYDRIASIS

Although adding epinephrine to the irrigating solution during cataract surgery has been a common practice for decades, direct intracameral injection of the drug has grown in popularity following published reports of its clinical efficacy for IFIS.[13-15] Intracameral epinephrine is commonly used off label to dilate and stabilize the pupil intraoperatively. In the United States, 1:1,000 epinephrine (preserved and nonpreserved) has been commercially available from several different manufacturers. Since the first report of increased risk of toxic anterior segment syndrome after using preserved epinephrine,[16] at least a 36% reduction in the use of preserved epinephrine has been reported.[17] Preservative-free 1:1000 (1 mg/mL) epinephrine comes in two forms—with and without 0.1% bisulfite as a stabilizing agent. Bisulfite improves the stability of the solution by delaying oxidation of the active substance. Previous studies have shown that undiluted epinephrine containing 0.1% bisulfite can cause corneal decompensation secondary to endothelial toxicity.[18,19] Based on these findings, many clinicians have only used preservative-free, bisulfite-free commercial preparations of epinephrine for direct intracameral injection.[20]

During the past year in the United States, there has been a nationwide shortage of bisulfite-free epinephrine. The American Society of Cararact and Refractive Surgery (ASCRS) Cataract Clinical Committee and the ASCRS Toxic Anterior Segment Syndrome Task Force have suggested that 1:1,000 epinephrine containing bisulfate appears to be safe when diluted at least 1:4 in balanced salt solution[21] (BSS or BSS Plus; both from Alcon Laboratories, Inc). Furthermore, adding bisulfite-containing epinephrine to a 500-mL BSS irrigation bottle (off label) should not cause corneal endothelial toxicity because of the significant dilution.

However, shortages of even bisulfite-containing 1:1,000 epinephrine are now being reported in the United States. Several publications report the safety and efficacy of nonpreserved 1.5% intracameral phenylephrine for both IFIS prevention and routine surgical mydriasis[22-25] without a significant reduction in endothelial cell counts.[25] Preservative-free phenylephrine 2.5% (Minims) is only commercially available in Canada and Europe. Because these preparations still contain bisulfite, a 1:4 dilution with BSS, BSS Plus, or preservative-free lidocaine is also recommended. Some cataract surgeons are using preservative-free and bisulfite-free intracameral phenylephrine 1.5% prepared by compounding pharmacies due to the lack of a commercial source in the United States. Because of the increasing scrutiny and regulation of drugs obtained from compounding pharmacies, it is recommended to request a "certificate of sterility" from the compounding pharmacy for any new intracameral preparation. The pharmacy should be accredited by the Pharmacy Compounding Accreditation Board.[26]

Omeros Corporation has developed a new preservative- and bisulfite-free proprietary combination of phenylephrine HCL and ketorolac tromethamine (Omidria) designed to be added to standard irrigation solution to maintain intraoperative mydriasis during cataract surgery. It provides a consistent, low concentration of both components during surgery and maintains a steady-state concentration directly at the targeted receptors and enzymes to maintain intraoperative mydriasis, prevent intraoperative miosis, and reduce postoperative pain. In randomized, double-masked, vehicle-controlled (phase 2) or placebo-controlled (phase 3) multicenter clinical trials in which all subjects received standard preoperative topical mydriatic and anesthetic agents, Omidria was superior to placebo/vehicle in maintenance of intraoperative mydriasis and was superior to placebo/vehicle, ketorolac alone, and phenylephrine alone in the prevention of intraoperative miosis (data on file with Omeros Corporation). It was also superior to placebo/vehicle in the reduction of acute postoperative pain and was well tolerated (Figures 2 and 3). Omidria is currently under review for marketing approval by both the FDA and the European Medicines Agency with a commercial launch planned for 2014. ■

Ladan Espandar, MD, MSc, is a cornea fellow at Duke University Eye Center in Durham, North Carolina. She acknowledged no financial interest in the products or companies mentioned herein. Dr. Espandar may be reached at ladan.espandar@duke.edu.

Terry Kim, MD, is a professor of ophthalmology at Duke University Eye Center in Durham, North Carolina. He is a consultant to Omerus. Dr. Kim may be reached at (919) 681-3568;terry.kim@duke.edu.

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