

The clinical utility of new combination phenylephrine/ketorolac injection in cataract surgery

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Abstract: The maintenance of mydriasis throughout cataract extraction surgery and the control of ocular inflammation are crucial for successful surgical outcomes. The development of miosis during cataract surgery compromises the visualization of the surgical field and working space for surgeons. This may lead to complications that include posterior capsular tear and associated vitreous loss, longer surgical time, and postoperative inflammation. Postoperative inflammation is often uncomfortable and frustrating for patients. It causes pain, redness, and photophobia. This compromises the best-uncorrected vision following surgery and often leads to multiple clinic visits. This article examines the literature published on the current treatments used to manage mydriasis, pain, and inflammation in cataract extraction surgery. Combination phenylephrine/ketorolac injection offers an exciting new class of medication for use in cataract surgery. With the recent approval of Omidria™ (combination of phenylephrine 1% and ketorolac 0.3%) by the US Food and Drug Administration (FDA) for intraocular use, we review the clinical utility of this new combination injection in cataract surgery. PubMed, MEDLINE, and conference proceedings were searched for the relevant literature using a combination of the following search terms: cataract extraction surgery, pupil dilation (mydriasis), miosis, phenylephrine, ketorolac, Omidria™, intracameral mydriatic. Relevant articles were reviewed and their references checked for further relevant literature. All abstracts were reviewed and full texts retrieved where available.

Keywords: cataract extraction surgery, ketorolac, mydriasis, miosis, Omidria™, phenylephrine

Introduction

Cataract extraction surgery remains the most commonly performed eye surgery by ophthalmologists (due to the prevalence of cataracts).¹ Cataracts remains a leading cause of visual impairment worldwide. The prevalence of cataract increases with age.² Therefore, with increasing life expectancy, the demand for cataract surgery is set to increase and increase. The treatment of this condition requires the removal of the lens and replacement with an intraocular lens (IOL).

With the continued development of surgical techniques and equipment to improve outcomes, developments in ocular medications used in cataract surgery remain just as important.

The maintenance of mydriasis throughout surgery and the control of ocular inflammation are crucial for successful surgical outcomes.

The maintenance of mydriasis is required throughout surgery to allow better visualization of the surgical field and a greater working space within the center of the eye. Complications that occur when miosis develops include posterior capsular tear and associated vitreous loss,³ longer surgical time, and postoperative inflammation.⁴

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Currently, the muscarinic antagonists cyclopentolate and tropicamide, and α -adrenoceptor agonist phenylephrine ensure mydriasis.⁵

Cataract extraction is associated with postoperative inflammation and the degree of inflammation is linked to factors such as surgical technique, degree of iris pigmentation, and IOL type. Persistent inflammation is related to the development of cystoid macular edema, corneal edema, and increases in intraocular pressure.⁴ Topical steroidal and non-steroidal drops are used before and after surgery for pain management and to reduce postoperative inflammation.⁶ Topical non-steroidal drops have also been found to maintain mydriasis during cataract surgery.⁷

The use of multiple preoperative drops is known to cause dissatisfaction among preoperative staff. It is also time consuming and may lead to delays in patients reaching the operating room. The continued pressure on theatre time and increasing patient numbers have provided the driving force for the development of new therapies to improve this process.

In this review, we will examine the current medications used for mydriasis, and pain management in cataract surgery and the clinical utility of new combination phenylephrine/ketorolac injection in cataract surgery.

Pupil dilation in cataract surgery

Preoperative treatments

Pupil dilation for cataract surgery may be achieved by topical mydriatic drops, phenylephrine 2.5% (the α adrenoceptor agonist), cyclopentolate 1%, and tropicamide 1% (muscarinic antagonists).

The pupillary muscle of the iris comprises a sphincter muscle and dilator muscle. The sphincter muscle is innervated by parasympathetic nerves and the latter by sympathetic nerves. Therefore, blocking of the parasympathetic pathway by muscarinic antagonists leads to mydriasis, as does stimulation of the sympathetic fibers by phenylephrine.

Guzek et al in a prospective study of extra ocular surgery complications found that the incidence of posterior capsular rupture was reduced by half when mydriasis is greater than 6 mm.⁸

Phenylephrine

Formulations include 2.5%, 5%, and 10%. This can be administered topically and by intracameral injection (at a different dose) to achieve mydriasis. Phenylephrine can cause cardiovascular adverse effects (increases in both systolic and diastolic blood pressure and changes in heart rate) in the elderly⁹ and neonates.¹⁰ Duffin et al found that a 10% viscous solution of phenylephrine was more effective than

a 2.5% aqueous solution of phenylephrine in maintaining mydriasis during extra capsular cataract surgery. Mean blood pressure elevations were not higher in the group receiving 10% compared with 2.5%.¹¹ Similar findings were found by Yospaiboon et al during topical administration of 2.5% vs 10% phenylephrine eye drops for pupillary dilation. Again with no significant difference in mean blood pressure between the two groups.¹² However, a recent systemic review and meta analysis by Stavert et al concluded that higher concentrations of phenylephrine (10% vs 2.5%) lead to changes in blood pressure and heart rate that are short lived.¹³

Muscarinic antagonists

Tropicamide blocks the acetylcholine in the parasympathetic pathway to the sphincter muscle leading to mydriasis. Systemic side effects of muscarinic antagonists include dry mouth, tachycardia, and headache.⁵ Other drugs within this family include atropine and cyclopentolate. Narváez et al found that the addition of one drop atropine, 1% three times a day, a day before administration of standard preoperative dilating drops for cataract surgery, resulted in a smaller dilated pupil diameter than administration of standard preoperative drops alone.¹⁴ The study found no benefit to adding atropine 1% before administration of standard preoperative drops and that the same findings applied to eyes with light or dark irides.

Steroidal and non-steroidal anti-inflammatory drops

Miosis during cataract surgery is in part related to the increased production of prostaglandins (PGs) during cataract surgery. Steroids and non-steroidal anti-inflammatory drops (NSAIDs) have their effect by their ability to block PG synthesis.¹⁵ Zanetti et al found that the preoperative use of topical anti-inflammatory prednisolone acetate, ketorolac tromethamine (KE), and nepafenac was effective in maintenance of intraoperative mydriasis during cataract surgery compared with placebo.¹⁶

Hence, the preoperative routine of drop administration (for pupil dilation) for cataract surgery has changed little despite topical treatments being slow to penetrate through the cornea¹⁷ (a maximum mydriatic effect for cyclopentolate is 30 minutes), often making the waiting time for the pupil to dilate much longer than the cataract surgery itself. Also, the initially good mydriatic effect tends to wear off during surgery. These disadvantages of topical mydriatics have enabled alternative regimens to be continually examined.

Intraoperative treatments

Intracameral mydriatics

Lundberg and Behndig compared intracameral injection of mydriatics with conventional topical mydriatics (in phacoemulsification cataract surgery) in a randomized double blind study.¹⁸ The topical group received three drops each of cyclopentolate 1% and phenylephrine 10% at 15-minute intervals (and 150 μ L of preservative-free lidocaine hydrochloride 1% [Xylocaine®]). The intracameral group was given placebo eye drops at the same intervals as in the topical group and 150 μ L of a preservative-free mixture of cyclopentolate 0.1%, phenylephrine 1.5%, and Xylocaine 1%. Within the intracameral group mydriasis reached 95% of its final value within 20 seconds. However, pupils were smaller than in the topical group, but did not contract intraoperatively as they did in the topical group.

This study found intracameral mydriatics to be a rapid, effective, and a safe alternative to topical mydriatics. The doses of cyclopentolate and phenylephrine in the topical group were 6.2 and 4.3 times greater, respectively, than in the intracameral group (calculations based on a drop size of 37 μ L). This lower dose they felt may reduce the risk of cardiovascular side effects (increases in both systolic and diastolic blood pressure and changes in heart rate) associated in patients with hypertension and heart conditions or pediatric cases.

Intracameral phenylephrine has also been used for prophylaxis against intraoperative floppy iris syndrome (IFIS). Chang and Campbell in 2005 first described the clinical triad of IFIS during cataract surgery in patients on tamsulosin (a systemic α_1 adrenergic receptor antagonist). It is characterized by billowing and flaccid iris stroma, increased occurrence of iris stroma prolapse and pupillary miosis during cataract surgery. Chang and Campbell found in a prospective case series the incidence of IFIS in tamsulosin-treated patients to be 93.8%.¹⁹ Gurbaxani and Packard found intracameral phenylephrine (0.25 mL of minims phenylephrine hydrochloride, 2.5% mixed with 1.0 mL balanced salt solution and approximately 0.5–1.0 mL was then injected into the anterior chamber) to be a highly efficient measure for the prophylaxis against IFIS in patients on tamsulosin (α_1 adrenoceptor antagonist).²⁰

In the preoperative evaluation, there is currently no reliable way to predict which patients will demonstrate IFIS. Casuccio et al found that for a pupil of 7.0 mm or smaller, the risk of IFIS existed regardless of α_1 adrenoceptor antagonist treatment.²¹

Nikeghbali et al found that the injection of 0.2–0.3 mL of preservative-free 1% lidocaine into the anterior chamber is a safe and effective way to induce pupil dilation for phacoemulsification cataract surgery method without using any preoperative or intraoperative mydriatics (no epinephrine was added to the irrigating solution). The mean pupil diameter was significantly greater than the baseline measurement. No further mydriatics were needed up to the end of the operations and no negative effects on the surgical performance were noted.²²

Myers and Shugar compared the efficacy of a solution of epinephrine 0.0025% and lidocaine 0.75% in fortified balanced salt solution (“epi-Shugarcaine”) and cyclopentolate 0.1%, phenylephrine 1.5%, and lidocaine 1% given intracamerally during cataract surgery. Both treatment groups received topical tropicamide. The pupils were statistically significantly larger with the epi-Shugarcaine group 1 minute after instillation and at the end of the procedure.²³

Other devices

Mydriatic cocktail-soaked wick,²⁴ Beehler pupil dilator, nylon iris hooks, pupillary rings (Perfect Pupil, Graether 2000, Morcher Pupil Dilator),²⁵ Malyugin Ring, and Mydriaser® (Spectrum Théa Pharmaceuticals Limited, Cheshire, UK)²⁶ are several alternative methods to maintain pupil dilation. However, they can be complex, add further time and cost to cataract extraction operations, and lead to sphincter damage or rupture, leaving the pupil atonic or misshapen.²⁷

Pain management in cataract surgery

Preoperative drops for cataract surgery can also include diclofenac 0.1% a NSAID. Trauma to ocular tissue during surgery activates phospholipase A2,²⁸ the precursor for arachidonic acid metabolites. Arachidonic acid metabolites act as a substrate for the cyclo-oxygenase (COX) pathways leading to the production of PGs E and F in aqueous humour. The effects of endogenous PGs are postoperative inflammation, miosis during surgery, conjunctival hyperemia, and changes in intraocular pressure.²⁸

NSAIDs work by inhibiting the COX pathway and hence the biosynthesis of PGs.

They are used to manage ocular inflammation, pain, and cystoid macular edema secondary to cataract surgery.^{29,30} Miosis during cataract surgery is in part related to the increased production of PGs during cataract surgery. Hence, NSAIDs are effective in maintenance of intraoperative mydriasis by their ability to block PG synthesis.^{15,31}

NSAIDs and steroid drops are also used perioperatively and continued postoperatively for post op inflammation and pain control.³² Topical NSAIDs have the advantage of avoiding the undesirable effects of topical corticosteroids, such as steroid induced raised intraocular pressure, cataract formation, and increased infection risk due to decreased immunological response.³¹

A prospective study to evaluate postoperative pain following cataract surgery reported 1/3 of patients had ocular pain during the first 4 postoperative hours and 1/4 of these patients reported moderate to severe pain.³³ With surgical centers use of postoperative pain assessments to be measures of clinical outcomes, pain management remains a primary concern for surgeons.³⁴ Intracameral lidocaine was found to relieve intraoperative discomfort caused by iris movement or manipulation.³⁵ A low pain score was reported in patients following combined topical and intracameral anesthesia during cataract surgery.³⁶

The clinical utility of new combination phenylephrine/ketorolac injection in cataract surgery

A Phase III study was conducted to evaluate the effect of phenylephrine/ketorolac injection (OMS302) on intraoperative pupil diameter and early postoperative ocular pain when administered during IOL replacement surgery.³⁷

OMS302 is a bisulfite-free and preservative-free drug that contains 60.75 mM phenylephrine hydrochloride (an α_1 adrenergic receptor agonist) and 11.25 mM KE (a non-selective COX 1/2 inhibitor) formulated in 20 mM sodium citrate buffer. Phenylephrine hydrochloride is expected to maintain intraoperative mydriasis and KE aid in mydriasis and reduce postoperative pain.

A multicenter, randomized, parallel-group, double-masked, and placebo-controlled study was conducted at 15 centers in the USA and the Netherlands. Four milliliters of OMS302 or placebo (20 mM sodium citrate buffer) were added to 500 mL of standard balanced saline irrigation solution used during the lens replacement surgery. In all, 204 patients received the placebo and 202 received OMS302. All patients received standardized preoperative topical treatments: Vigamox antibiotic, one drop of phenylephrine hydrochloride 2.5%, and one drop of tropicamide 1% at 30 minutes, 15 minutes, and 5 minutes prior to surgery.

Change in pupil diameter over time (from surgical baseline to the end of surgical procedure) and early postoperative pain were the two co-primary efficacy endpoints.

OMS302 prevented miosis in patients with pupil diameter ≥ 6 mm at completion of cortical clean up 95.9%

Table 1 Adverse reactions with Omidria™

Eye irritation (1%–10%)
Posterior capsular opacification (1%–10%)
Increased intraocular pressure (1%–10%)
Anterior chamber inflammation (24%)

vs 77.0% in the placebo group and those with pupil diameter < 6 mm at any time during surgery was 9.2% vs 38.0%.

The clinical study³⁷ found that OMS302 was superior to placebo in maintaining mydriasis during the surgical procedure. Patients in the placebo group experienced steady pupil constriction after initiation of the procedure compared with OMS302 patients who did not.

OMS302 was superior to placebo in reducing early postoperative pain. OMS302 was well tolerated and no unexpected adverse events associated. However, slightly more OMS302-treated patients experienced increased intraocular pressure. The majority of cases resolved within a few days of onset and was considered not to be a treatment effect.

Omidria™

Omidria™ (OMS302) (Omeros Corporation, Seattle, WA, USA), combination of phenylephrine 1% and ketorolac 0.3%, was approved by the US Food and Drug Administration (FDA) in May 2014.³⁸ It is the only FDA-approved product for intraocular use during cataract surgery to prevent intraoperative miosis and reduce postoperative pain. The adverse reactions with Omidria™ are listed in Table 1.

Conclusion

The maintenance of mydriasis throughout cataract surgery is critical because miosis increases the risk of injury to intraocular structures and can prolong surgical time. Currently, preoperative drops cyclopentolate, tropicamide, and phenylephrine are used to achieve this. However, the use of multiple perioperative drops is known to cause dissatisfaction among perioperative staff and is time consuming leading to delays in patients reaching the operating room and the initially good mydriatic effect tends to wear off during surgery.

Intraoperatively, the occurrence of miosis has been successfully treated with intracameral drugs such as phenylephrine. However, as these medications are not licensed for this use, the difficulty in centers obtaining bisulfate-free preparations and questions still concerning their safety and side effect profile, make their use not without risk.

Ocular inflammation produces redness, pain, and photophobia and makes patients uncomfortable. Currently,

steroidal and NSAIDs are administered and continued postoperatively for post op inflammation and pain control.

Combination of phenylephrine/ketorolac injection offers an exciting new class of medication that provides a good adjunct to current treatments used in cataract surgery to maintain intraoperative mydriasis, prevents miosis, and reduces postoperative pain. Omidria™ is approved by the FDA for intraocular use during cataract surgery providing a safe intracameral alternative compared with other non-licensed treatments. The use of Omidria™ requires no modification to the current surgical procedure offering an easy addition to current treatments and surgical technique.

However, there are few peer-reviewed studies for this agent. Larger studies are needed to support its usefulness. Its use in patients with IFIS has yet to be assessed. It could however offer a safer patient experience and less stressful time for the surgeon in these patients. It does not alter the current process of the use of multiple preoperative drops for cataract surgery. Nevertheless, it provides another tool to improve surgical outcomes and a more comfortable experience for the patient.

Disclosure

The authors report no conflicts of interest in this work.

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