Review Article

Pharmacological management of intra-operative miosis during cataract surgery

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Cataract surgery requires a well-dilated and stable pupil for a good outcome. Unexpected pupillary constriction during surgery increases the risk of complication. This problem is more pronounced in children. There are now pharmacological interventions that help tackle this unforeseen happening. Our review discusses the simple and quick options available to a cataract surgeon when faced with this dilemma. As cataract surgical techniques continue to improvise and get faster, an adequate pupil size is of paramount importance. Various topical and intra-cameral drugs are used in combination to achieve mydriasis. Despite good pre-operative dilation, the pupil can be quite unpredictable during surgery. Intra-operative miosis limits the field of surgery and increases the risk of complications. For example, if the pupil size decreases from 7 mm to 6 mm, this 1 mm change in pupil diameter will lead to a decrease of 10.2 mm^2 in the area of surgical field. Making a good capsulorhexis with a small pupil can be a challenge, even for an experienced surgeon. Repeated touching of the iris increases the risk of fibrinous complications. Removal of cataract and the cortical matter becomes increasingly difficult. Intra-ocular lens implantation in the bag also requires adequate dilation. When dealing with challenging cases like lens subluxation, pseudo-exfoliation, and zonular dehiscence, a small pupil further increases the risk and adversely affects the surgical outcome. Hence, achieving and maintaining adequate mydriasis throughout surgery is essential. This review highlights the risk factors for small pupils during surgery and current management strategies.

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Pupillary dilatation plays a pivotal role in the success of cataract surgery, making it an essential step in preoperative preparation. The ease of doing cataract surgery largely depends on the view governed by pupillary dilatation. Various methods of dilating the pupil during surgery include pharmacological agents and mechanical maneuvers. Each of these methods offers unique advantages and considerations, allowing surgeons to tailor their approach based on patient characteristics and surgical requirements. Controlling pupil dynamics is very important during surgery, so one should be aware of the risk factors to effectively anticipate and address intraoperative miosis. We herein discuss the factors affecting mydriasis and various pharmacological options to dilate the pupils for cataract surgery.

Risk factors for intra-operative miosis

Pediatric age group

As cataract surgical techniques continue to improvise and get faster, an adequate pupil size is of paramount importance.[1] In children, it is more challenging to achieve and maintain mydriasis because of a weak iris dilator muscle and decreased sympathetic innervation to the iris. Compared to adults, the pediatric pupil dilates less with the same concentration of mydriatic agents. A study showed that children responded less than adults to all classes of drugs, namely, phenylephrine, cocaine, and hydroxyamphetamine.[2] This could be attributed to an immature post-synaptic apparatus with a lower number of neurons, hence releasing less norepinephrine. In this age group, the risk of poor mydriasis and intra-operative miosis is higher in those with ocular co-morbidities like rubella and anterior segment dysgenesis.[3] Conditions like Peter's anomaly, Axenfeld–Reiger syndrome, and other anterior segment dysgeneses may need multiple intra-ocular surgeries, increasing the risk of cataract. Iris hypoplasia in these cases does not let the pupil dilate adequately and may need intra-operative pharmacological or surgical intervention. The most advocated agents to counteract intra-operative miosis in children are ophthalmic viscosurgical devices.[4]

Intra-ocular inflammation

Intra-ocular inflammation occurs in conditions like uveitis, post-operative complications, and ocular trauma. In these conditions, cataracts can be secondary to inflammation or treatment with steroids. Pediatric anterior uveitis is a prevalent cause of cataracts in children.[5] By the time children start complaining of vision loss, complications like cataract, cyclitic

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Table 1: Pharmacological agents available to dilate pupil for cataract surgery

Pharmacological Agent	Dose	Mode of Use	Effectiveness	Advantages	Disadvantages	Side Effects
Phenylephrine	10% solution	Topical eye drops	Rapid onset (10-30 min)	Safe, effective, widely used	May cause mild stinging or burning, may increase blood pressure	Increased IOP, photophobia, dry mouth, headache, dizziness
Cyclopentolate	0.5% or 1% solution	Topical eye drops	Rapid onset (20-45 min)	Safe, effective, longer duration of action than phenylephrine	May cause blurred vision, photophobia, stinging, and burning	Increased IOP, agitation, delirium, tachycardia
Tropicamide	0.5% or 1% solution	Topical eye drops	Rapid onset (20-30 min)	Safe, effective, shorter duration of action than cyclopentolate	May cause mild stinging or burning, may cause blurred vision	Increased IOP, photophobia, dry mouth, headache, dizziness
Atropine	1% oint, or 2% solution	Topical	Slow onset (60-90 min)	Long duration of action, can be used preoperatively	May cause blurred vision, photophobia, stinging, and burning	Increased IOP, dry mouth, constipation, urinary retention, confusion, agitation
Epinephrine	1:10000 solution	Intracameral injection	Rapid onset (1-3 min)	Can be used in patients with poor pupillary dilation with topical agents	May cause corneal edema, increased IOP, and arrhythmia	Corneal edema, increased IOP, tachycardia
Mydriatic anesthetic premixed injection	phenylephrine hydrochloride (0.31%), tropicamide (0.02%), lidocaine hydrochloride (1%)	Intracameral injection	Rapid onset (1-3 min)	Can be used in patients with poor pupillary dilation with topical agents	May cause corneal edema, increased IOPs, and arrhythmia	Corneal edema, increased IOP, tachycardia

membrane, and band-shaped keratopathy have already occurred or started. Prolonged standing inflammation leads to multiple recalcitrant posterior synechia and iris atrophy, leading to a poorly dilating pupil. Formation of a cyclitic membrane can also restrict pupil dilation. Poorly dilating pupils and intra-operative miosis can be seen in nearly one third of uveitic patients. This further increases the duration of surgery because of the resulting inflammation and cystoid macular edema.[6]

Diabetes

Diabetes mellitus is a known risk factor for intra-operative miosis. In a diabetic patient, even with pre-operative mydriasis comparable to that of a non-diabetic individual, chances of intra-operative miosis are very high. This is mostly because of the altered autonomic system in a person with diabetes. Failure of the pupil to dilate in darkness in some diabetic patients is also because of neuropathy of the sympathetic innervation.[7] This can prolong the duration and complication rates of surgery. Macular edema is the most common post-operative complication. Also, worsening of diabetic macular edema adversely affects post-operative vision. Therefore, it is advisable that an experienced surgeon should do cataract surgery with minimum intra-operative manoeuvrability.[8,9]

Oral alpha-1 adrenergic antagonists

Alpha-1 adrenergic antagonists like tamsulosin, doxazocin, terazosin, prazocin, and so on are commonly prescribed for benign prostate hypertrophy and bladder neck dysfunctional disorders in older males. Prazocin is also used in the management of scorpion bites. These drugs are also prescribed for women for hypertension and urine disorders. Earlier, alpha-1 adrenergic antagonists were contraindicated in children; now, they are proven safe and efficacious in medical expulsive treatment for urolithiasis.[10,11] These drugs act on alpha-1 adrenergic receptors, which are also present on the iris dilator muscle. Hence, they cause blockage of alpha-1 adrenergic receptors on dilator pupillae and prevent complete dilation of pupil, leading to intra-operative floppy iris syndrome. Apart from inadequate mydriasis, bellowing of iris also makes the surgery difficult. Tamsulosin is most notorious for causing this side effect. A bigger concern is that the adverse effect of these drugs on mydriasis is not dependent on duration of use of these drugs. Hence, any amount of drug can cause intra-operative floppy iris.[12,13]

Use of oral and systemic miotics

Oral and systemic miotics are generally used as anti-glaucoma medications, although their use has decreased with the introduction of newer anti-glaucoma medications. Pilocarpine is also used in the treatment of anisocoria. Thus, both the recent history and remote history of any such systemic medicines should be taken to help us prepare beforehand for cataract surgery.

Surgical factors

An increase in the duration of surgery increases the risk of intra-operative miosis. Factors like excess ultrasound energy leak, the use of lasers, and excessive tissue manipulation further increase the level of prostaglandins in the aqueous humor,

causing miosis. Intra-operative miosis is also common in cases of white cataract.[14-16]

Other risk factors

A history of previous intra-ocular surgery or trauma can cause pupillary abnormalities and injuries to the zonules that can hamper pupil dilation. Pseudo-exfoliation is also associated with poor pupil dilatation because of zonular weakening and iris atrophy.

Complications because of intra-operative miosis

Cataract surgery, especially phaco-emulsification, which is performed through small clear corneal incision, needs proper visualization. Every step is crucial, and each step can worsen upcoming steps. It is very difficult to make an appropriately sized capsulorhexis in the setting of an inadequate mydriasis. Incomplete rhexis is always at high risk of extension, leading to lens or intra-ocular lens drop in the later part of surgery. Because of a compromised surgical field for phaco-emulsification, iris can be injured with a phaco-probe, which will further instigate iris movements and bellowing. A trauma to the iris vessels can lead to hyphema, which further limits visibility. Any iris defect that occurs during surgery can lead to significant visual complaints post-operatively like uniocular diplopia, glare, and so on. Because of difficulties induced by intra-operative miosis and manoeuvres to dilate the pupil, the total duration of surgery increases, increasing intra-ocular inflammation and intra-ocular pressure (IOP).[17-19]

Post-operative IOP can also be high because of the retained lens matter or viscoelastic during surgery because of limited visualization. The risk of posterior capsular rent and cystoid macular edema is also high with increasing duration and complications in surgery.[20]

Management of intra-operative miosis

Intra-operative miosis can be managed by various surgical and medical methods. Surgical methods include dilation using the bimanual stretching technique or just the second instrument and various devices like iris hooks, malyugin rings, etc.[19,21,22] Various topical and intracameral drugs are used in combination to achieve mydriasis [Table 1]. Pharmacological methods to counteract miosis include topical, intra-cameral drugs and ophthalmic viscosurgical devices (OVDs).[23,24]

Pharmacological management of intra-operative miosis can be divided into

i. Pre-operative pharmacological management
ii. Intra-operative pharmacological management

i. Pre-operative pharmacological management

To achieve adequate mydriasis, most surgeons prescribe topical tropicamide 1.0% with phenylephrine 2.5% and cyclopentolate 1.0% three times at an interval of 20–30 min, a few hours before surgery. Tropicamide, an anticholinergic agent, causes dilation of pupil by relaxing the pupillary sphincter. Cyclopentolate and atropine both block contraction of the pupillary sphincter muscle. Phenylephrine is an alpha-1 adrenergic receptor agonist that acts on the dilator pupillae muscle and causes dilatation of the pupil. The mydriatic effects of 2.5% and 10% phenylephrine are similar, with 10% causing more side effects.[23,24] A day before surgery, topical non-steroidal anti-inflammatory drugs (NSAIDs) are also prescribed. NSAIDs act as cyclooxygenase (COX) inhibitors. COX enzyme is responsible for synthesis of prostaglandins. Prostaglandin secretion is induced by intra-ocular tissue manipulation, which further induces intra-operative miosis. Thus, NSAIDs cause inhibition of prostaglandin synthesis by inhibiting COX and prevent intra-operative miosis. NSAIDs were the first drugs to be approved by the Food and Drug Administration (FDA) for preventing intra-operative miosis. Multiple NSAIDs are proven to be effective in avoiding intra-operative miosis, with flurbiprofen being the first one to be approved. Diclofenac 0.1% and ketorolac 0.5% have also been found to be effective.[25,26] Bromfenac is also proven to prevent cystoid macular edema by reducing inflammation.[27] NSAIDs are even found to be better than topical steroids to maintain mydriasis after adult cataract surgery.[28] The dose response has been found to better if the NSAIDs are prescribed 1–3 days before scheduled surgery.[29] Studies using atropine to prevent intra-operative miosis have also been carried out without significant results.[30,31] Repeated use of dilators like atropine, cyclopentolate, and tropicamide can cause pupil fatigue and reduce mydriasis.[32]

ii. Intra-operative management of intra-operative miosis

The use of intra-cameral drugs in phaco-emulsification goes way back to 1999, when Crandall AS first described the use of intra-cameral anesthesia (lidocaine).[33] Since then, several combinations of mydriatics, anesthetics, and NSAIDs have been advocated to prevent intra-operative miosis.

Intra-operative mydriatic and anesthetic mixture

The use of intra-cameral mydriatic drugs is now a well-established practice. In 2006, Shugar JK first introduced the use of intra-cameral epinephrine for mydriasis and preventing idiopathic floppy Iris syndrome (IFIS). He described shugarcaine, an intra-cameral anesthetic mixture containing 3:1 BSS Plus and non-preserved lidocaine 4%. It was shown that with shugarcaine, iris flaccidity resolves within a few seconds and gives about 1.5 mm additional mydriasis in the next minute. He also described epi-sugarcaine as being similar to the earlier described mixture, with the addition of epinephrine to enhance the dilating effect.[34] Gupta *et al*. used an intra-cameral solution containing 0.5% lignocaine and 0.001% epinephrine, which was also proven safe and effective for providing rapid mydriasis and adequate for safe phaco-emulsification.[35] Ajay K *et al*. concluded that SICS can be performed effectively and safely using intra-cameral mydriatics only.[36] In both these studies, pre-operative dilating drops were not given. Similarly, Chiambaretta *et al*. performed two randomized studies (phase 2 and phase 3) of 139 and 591 patients, respectively. They used a combination of two mydriatics and one anesthetic and compared with a standard topical regimen. They noted that 95% of pupil dilation was achieved in 28.6 ± 4.6 s after injection of intra-cameral combination in both groups. Important to note is that in their study, the intra-operative pupil diameter remained stable in the intra-cameral combination group while decreasing in the group dilated with drops.[37] Other studies also showed similar results.[38] With intra-cameral dilators, there was documented increased intra-operative comfort for the patient and lesser post-operative pain, which further favored these preparations over drops for inducing as well as maintaining intra-operative mydriasis.[39]

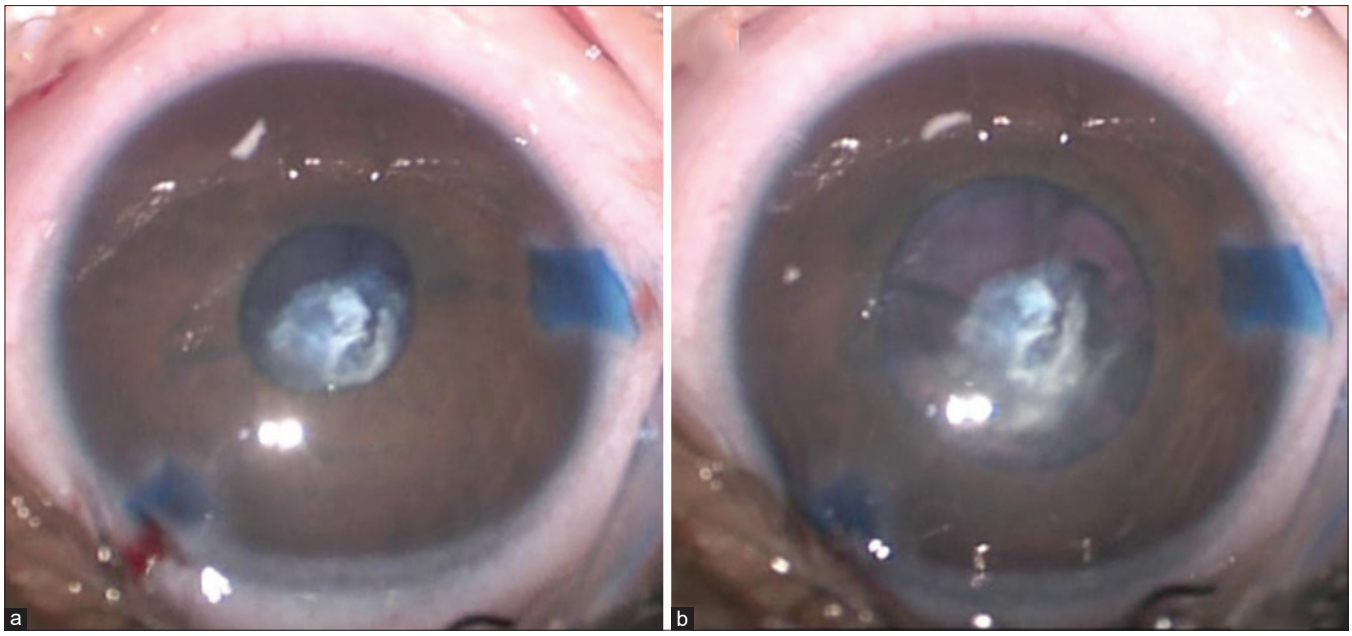

Figure 1: (a) Intraoperative pupillary constriction when drops were used to dilate pupil. (b) Intracameral adrenaline used in this patient adequately dilates the pupil during surgery

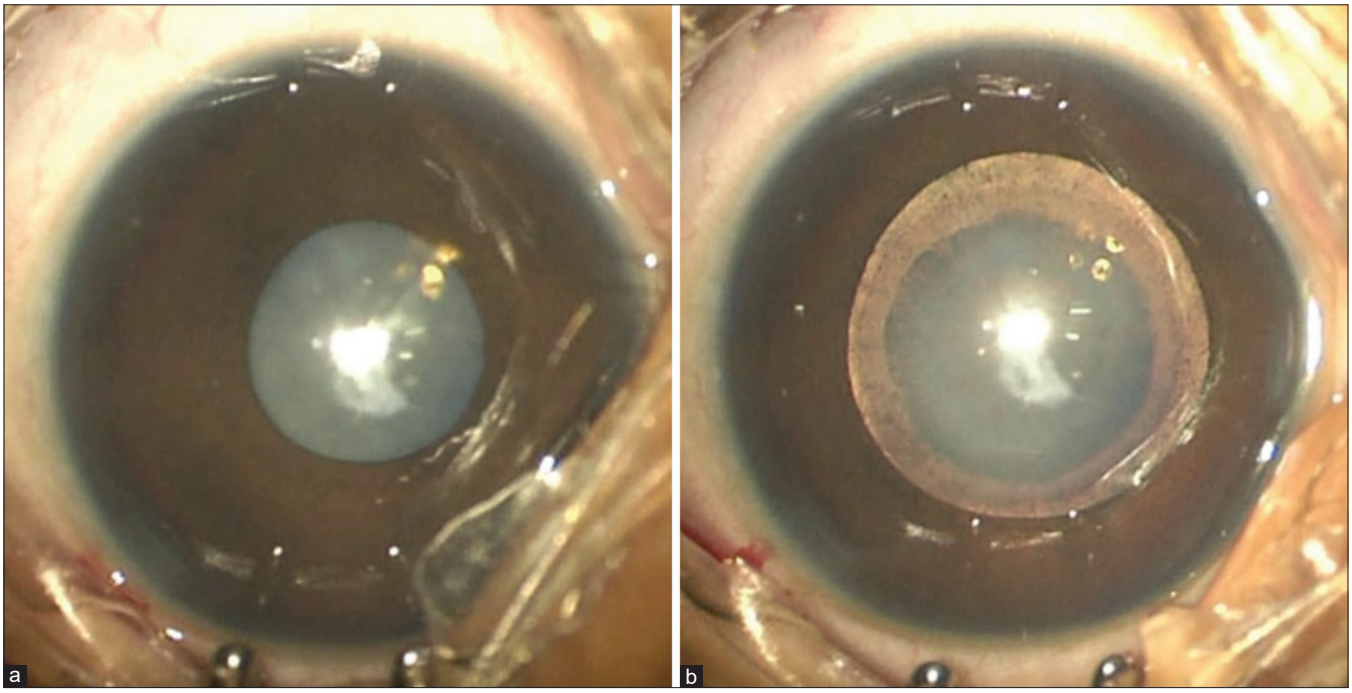

Figure 2: (a) Poor pupil dilatation with drops. (b) An intracameral injection of commercially available anesthetic mydriatic solution rescues the pupil size

Intra-operative mydriatric and NSAID mixture

Recently, the FDA approved one more drug combination, "Omidria," for intra-cameral use to prevent and manage intra-operative miosis. Omidria is a combination of phenylephrine and ketorolac. Ketorolac, a first-generation NSAID, acts by inhibition of prostaglandin synthesis by competitive blocking of the enzyme COX. It blocks prostaglandin synthesis, which is induced by surgery and manipulation. It is proven to maintain pupil dilation by preventing miosis. In FDA-reviewed clinical studies, this drug was proven to be safe and well tolerated, providing direct, continuous intra-cameral delivery of NSAID and mydriatic therapy during cataract surgery. As per two pivotal phase 3 clinical trials of 808 patients (403 with phenylephrine 1.0%, ketorolac 0.3%, and 405), the combination was proven superior to placebo for maintaining mydriasis. The combination also demonstrated the ability to maintain pupillary dilation from the beginning of the cataract surgery to the end of the case.

These studies also showed that this combination also decreased post-operative pain significantly after cataract surgery.[40] Other studies also showed decreased post-operative pain with intra-cameral anti-inflammatory agents.[41,42] Omidria was shown to not only reduce post-operative pain and prevent intra-operative miosis but also reduce the risk of cystoid macular edema after cataract surgery.[43]

According to Walter K. *et al.*, who compared phenylephrine-ketorolac combination and epinephrine for intra-operative pupil dilation in femtosecond-assisted cataract surgery, the mean surgical times and need for pupil dilation manoeuvres were significantly reduced in the phenylephrine-ketorolac group than in the epinephrine group. They concluded that by using phenylephrine and ketorolac, the intra-operative time and the need for pupil expansion devices could be reduced.[44] In a study by Rosenberg ED *et al.* done among patients of age groups of 69–76 and 76–92 years, those who received phenylephrine 1.0% and ketorolac 0.3% had significantly better uncorrected visual acuity than those receiving epinephrine on post-operative day 1.[45] In other studies, a significant reduction in the need for intra-operative use of the Malyugin ring was seen in patients receiving omidria compared to epinephrine control groups.[46,47]

Counteracting intra-operative miosis in pediatric cataract surgery

As discussed above, adequate pupillary dilation can be a challenge in pediatric cataract surgery because of poorly developed dilator muscles and reduced iris stromal rigidity. Even children can exhibit intra-operative floppy iris.[48] Pupillary dilation in children is traditionally done with atropine ointment and topical mydriatics prior to cataract surgery. Intra-operatively, high-viscosity ophthalmic viscosurgical devices and bisulfite-free epinephrine in the irrigating solution are used by many pediatric ophthalmologists.[49] It is important to note that epinephrine in the irrigating solution is an off-label use of epinephrine. It suffers from the disadvantage of having many systemic and ocular side effects. Because of the lack of FDA approval of epinephrine, there is a lack of randomized trials comparing it with other pharmacological agents. Intra-cameral adrenaline is now available, which is a very potent dilator when confronted with intra-operative miosis [Fig. 1a and 1b]. Omidria has also been shown to be safe and efficacious for counteracting miosis in children with ketorolac and decreasing pain post-operatively.[50] Most recently, an intra-cameral mydriatic-anesthetic combination has been proven to be an effective and safe way to obtain stable mydriasis in pediatric cataract surgery[51] [Fig. 2a and 2b].

Conclusion

Adequate and stable mydriasis is a prerequisite for quick and safe cataract surgery. Newer intra-cameral mydriatics help in achieving a good pupil size, which is maintained until the end of surgery. More evidence is required in terms of randomized clinical trials to know more about its efficacy.

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Conflicts of interest

There are no conflicts of interest.

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